Q.F.

Industria y Comercio

SUPERINTENDENCIA

03107407

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 03107407

54. **TÍTULO** Moduladores de receptores activados por proliferadores de peroxisomas

51. **CLASIFICACIÓN INTERNACIONAL** A61K 31/192; A61K 31/195

71. **SOLICITANTE** Eli-Lilly and Company & Ligand Pharmaceuticals, INC.

DOMICILIO Indianapolis - Indiana 46285 E.U.A. San Diego, CA 92121 EUA

74. **APODERADO** Carlos R. Olarte

22. **BOGOTÁ, D. C.,** Diciembre 05 de 2003

(FORMA P-10)

202099

PETITORIO

1

Industria y Comercio
SUPERINTENDENCIA

03 107407 00

SUPERINTENDENCIA Y COMERCIO
Radicacion : 03107407 00000000 Folios: 1641
Fecha (AMD): 2003-12-05 17:00:12 cación
Tramite : 821 PCT-PATENTE 3/9 PRES. NUCI 411 PRESENTACI
Dependencia: 2000 DIVISION DE NUEVAS SOLICITUDES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 07-07-2004.

(1) SOLICITUD DE :

[ ] Patente de Invención — [ ] Patente de Modelo de Utilidad
[ ] Capítulo I. — [X] Capítulo II.

(2) SOLICITANTE (71)

Nombre: ELI LILLY AND COMPANY Y LIGAND PHARMACEUTICALS, INC.
Dirección: Indianapolis, Indiana 46285. Estados Unidos de America.
San diego, CA 92121. Estados Unidos de America.
Nacionalidad o Domicilio:
Lugar de Constitución: Indianapolis, Estados Unidos de América.
San Diego, Estados Unidos de America.
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

(3) REPRESENTANTE APODERADO

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Dirección: World Trade Center Torre C, Calle 100 No. 8A-55 Piso 10.
Teléfono: 6386200 Fax: 6386201
E-Mail: filings@olarteraisbeck.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.782.747 Bta TP 74.295

(4) INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.
Dirección: VER PAGINA ADJUNTA.
Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) PCT (85)

Solicitud Internacional No. PCT/US02/16950 Fecha Mayo 30, 2002
Publicación Internacional No. WO 02/100813 Fecha Diciembre 19, 2002

(6) Título (54) MODULADORES DE RECEPTORES ACTIVADOS POR PROLIFERADORES DE PEROXISOMAS.

(7) Clasificación Internacional (51) A61K 31/192 ; 31/195

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	Junio 7, 2001	60/297,144

(9) Comprobante de pago No. 82,760 **Fecha** 12-11-2003

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) **ANEXOS**

2

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: BUSQUEDA INTERNACIONAL

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: _____

C.C. 74.782.747 de Btá T.P. 74.295

Instrucciones para la presentación de los anexos, ver reverso de esta página

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Estados Unidos de América
Nacionalidad : Estadounidense

4/5

SUPERINTENDENCIA Y COMERCIO

Radicacion : 03IN/4N/ 00000000 Folios: 1041

Fecha (DMA): 2003-12-05 17:00:12

Tramite : 411 PCI-PRIMI S/P PERS NACI 411 PRIMERIZO

Dependencia: 2000 DIVISION DE NUEVOS COMERCIANTES

NIT : 8001760[illegible]-2

RECIBO OFICIAL DE CAJA : 03 - 82,760
FECHA : NOVIEMBRE 12 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	11025952	12/11/2003	80,420,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

ELI LILLY AND COMPANY

Bilingüe inglés- español otorgado en Indianapolis, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Peter G. Stringer, Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company.

Todd Rokita — Secretario de Estado

Secretario de Estado de Indiana — Estado de Indiana

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América- Este documento Público
2. ha sido firmado por Catherine Michel
3. Quien ejerce funciones de Secretario de la Corte del Circuito en y para el condado Johnson
4. Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana

CERTIFICADO

5. En Indianapolis, Indiana — 6. El 22 de julio de 2003
7. Por el Secretario de Estado de Indiana — 8. No. A2003- 11279
9. Gran Sello del Estado de Indiana
10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

* Vigente desde el 1 mayo de 2003, todas las apostillas del Secretario de Estado de Indiana tienen el sello impreso electrónicamente.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, fax (317) 233-3283

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
inglés - Español - Inglés
Resolución No 2117 del 7 Oct 1987

10 NOV 2005

BOGOTA, D.C. - COLOMBIA

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañía por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson

Sello de notario público de Indiana

--

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

COMO NOTARIO ENCARGADO DE ESTE CIRCULO NOTARIAL CERTIFICO QUE ESTA FOTOCOPIA COINCIDE CON EL DOCUMENTO QUE HE TENIDO A LA VISTA.

10 NOV 2003

BOGOTÁ, D.C. - COLOMBIA
JUAN NAVARRO DE BAUTISTA
NOTARIO ONCE (11)

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

ELI LILLY AND COMPANY

domiciled in

Lilly Corporate Center, Indianapolis, Indiana 46285 US

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

ELI LILLY AND COMPANY

domiciliado en

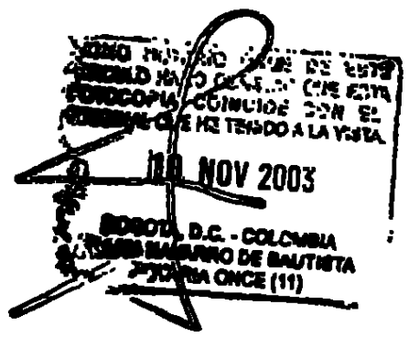
Lilly Corporate Center, Indianapolis, Indiana 46285 US

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma

Date/Fecha: 17 July 2003

City,Country/Ciudad,País: Indianapolis, Indiana, United States of America



SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. **Country: United States of America**

2. **This public document has been signed by** *Catherine Michel*

3. **acting in the capacity of circuit court clerk in & for** *Johnson* **County**

4. **and bears the seal/stamp of circuit court clerk in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**

6. **this** *Twenty-second* **day of** *July, 2003*

7. **by Secretary of State of Indiana**

8. **No. A2003-** *11279*

9. **Seal/Stamp:**

10. **Signature:**

Todd Rokita

Todd Rokita

Indiana Secretary of State

*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283

...NO NOTARIO ... DE ESTE ... HAGO CONSTAR QUE ESTA ... COPIA COINCIDE CON EL ... TENIDO A LA VISTA.

18 NOV 2003

BOGOTA, D.C. - COLOMBIA
... NAVARRO DE BAUTISTA
... ONCE (11)

OLARTE RAISBECK

OLARTE RAISBECK & FRIEDL, LTDA.
LEGAL & PROFESSIONAL SERVICES

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TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

10

Notarial Certification

On this date,
17 July 2003
The undersigned Notary Public certifies:

1. That
Peter G. Stringer
of legal age and domiciled in
7620 Castleton Farms, West Drive, Indianapolis, Indiana 46256 US
signed the foregoing document.

2. That the grantor has executed the foregoing document as Executive Director, International Patents
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY
having its principal place of business located in
Indianapolis, Indiana, United States of America
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Delegation of Authority Concerning Certain Patent Matters, executed January 20, 2003; pursuant to the authority granted to the General Counsel of the Company by the executive Committee of the Board of Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):





Catherine Michel
My Commission Expires October 21, 2008
Resident of Johnson County

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
Peter G. Stringer
mayor de edad y domiciliado
7620 Castleton Farms, West Drive, Indianapolis, Indiana 46256 US
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de

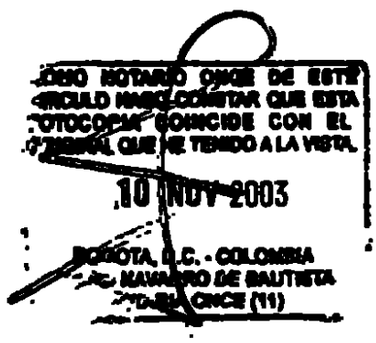
de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):



HAMILTON
BROOK
SMITH &
REYNOLDS, P.C.

PATENTS, TRADEMARKS
COPYRIGHTS & LITIGATION

530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133
TEL (978) 341-0036
FAX (978) 341-0136
www.hbsr.com

MURRIS H. HAMILTON
(1909-1994)

DAVID E. BROOK
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LEO R. REYNOLDS
JOHN L. DuPRÉ
DAVID J. BERRY
MARY LOU WAKIMURA
ALICE O. CARROLL
N. SCOTT PIERCE
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RICHARD W. WAGNER
ROBERT T. CONWAY
RODNEY D. JOHNSON
DAVID J. THEODOSAU, JR.
ANNE J. COLLINS
LISA M. TREADER
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CHRISTOPHER P. CARROLL
F. JAMES COX
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ILYA R. LAPSHUN
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* NOT ADMITTED IN MASS.

OF COUNSEL
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MICHAEL KRWSHAN
ADMINISTRATIVE DIRECTOR

BARBARA J. FORBUS
ADMINISTRATOR OF
PATENT AND
TRADEMARK PRACTICE

2003/000149.

11

24 October 2003

I hereby certify that the attached documents are true and accurate copies of : (1) the original Assignment document executed by Dawn Alisa Brooks, Alan M. Warshawsky, Chahrzad Montrose-Rafezadeh, Anne Reifel-Miller, Lourdes Prieto, Isabel Rojo, Jose Alfredo Martin, Maria Rosario Gonzales Garcia, Alicia Torrado, Rafael Ferritto Crespo, Carlos Lamas-Peteira and Maria Martin-Ortega Finger, to Eli Lilly and Company, which was forwarded to the United States Receiving Office for recordation on 08 September 2003 in connection with International Application PCT/US02/16950, filed 30 May 2002; and (2) the original Assignment document executed by Robert J. Ardecky, to Ligand Pharmaceuticals Incorporated, which was forwarded to the United States Receiving Office for recordation on 08 September 2003 in connection with International Application No. PCT/US02/16950, filed 30 May 2002.

Ellen S. Porras
Notary Public

My Commission Expires: 19 December 2008

@PFDesktop\::ODMA/MHODMA/iManage;428653;1

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Director of the U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies)

1) Dawn Alisa Brooks
2) Alan M. Warshawsky
3) Chahrzad Montrose-Rafezadeh
4) Anne Reifel-Miller
5) Lourdes Prieto

Additional name(s) of conveying party(ies) attached? [X] Yes [ ] No

2. Name and address of receiving party(ies)

Name: Eli Lilly and Company

Internal Address:

Street Address: Lilly Corporate Center

City: Indianapolis State: Indiana ZIP: 46285

Additional name(s) & address(es) attached? [ ] Yes [X] No

3. Nature of conveyance:

[X] Assignment [ ] Merger

[ ] Security Agreement [ ] Change of Name

[ ] Other

Execution Date: 1) 07/14/03 2) 07/11/03 3) 07/11/03
4) 06/24/03 5) 07/08/03 6) 07/10/03
7) 07/14/03 8) 07/08/03 9) 07/08/03
10) 07/08/03 11) 07/09/03 12) 07/08/03

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
PCT/US02/16950

B. Patent No.(s)

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Steven G. Davis, Esq.

Internal Address:

Hamilton, Brook, Smith & Reynolds, P.C.

Street Address: 530 Virginia Road, P.O. Box 9133

City: Concord State: MA ZIP: 01742-9133

6. Total number of applications and patents involved: [1]

7. Total Fee (37 C.F.R. 3.41)..... $ 40.00

[X] Enclosed

[X] Authorized to charge any deficiencies or credit any overpayment to deposit account

[ ] Authorized to be charged to deposit account

8. Deposit account number:

08-0380

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Steven G. Davis — Name of Person Signing

Signature

September 8 2003 — Date

Total number of pages including cover sheet, attachments, and document: [10]

Docket No.: 2947.1007-002

"Recordation Form Cover Sheet - Page 2"

The following information is a continuation of Box1:

Names of additional inventors:

6) Isabel Rojo
7) Jose Alfredo Martin
8) Maria Rosario Gonzales Garcia
9) Alicia Torrado
10) Rafael Ferritto Crespo
11) Carlos Lamas-Peteira
12) Maria Martin-Ortega Finger

Docket No. 2947.1007-002

Multi-Joint

ASSIGNMENT

WHEREAS, we, **Dawn Alisa Brooks, Alan M. Warshawsky, Chahrzad Montrose-Rafezadeh, Anne Reifel-Miller, Lourdes Prieto, Isabel Rojo, Jose Alfredo Martin, Maria Rosario Gonzales Garcia, Alicia Torrado, Rafael Ferritto Crespo, Carlos Lamas-Peteira** and **Maria Martin-Ortega Finger**, together with co-inventor **Robert J. Ardecky**, have invented a certain improvement in **Modulators of Peroxisome Proliferator Activated Receptors** described in an International Patent Application filed pursuant to the Patent Cooperation Treaty and which designates the United States, the specification of which:

[ ] is being executed on even date herewith and is about to be filed in the United States Patent Office;

[X] was filed on **May 30, 2002** as International Application No. **PCT/US02/16950;**

[ ] was patented under U.S. Patent No. [ ] on [ ].

WHEREAS, **Eli Lilly and Company** (hereinafter "ASSIGNEE"), a corporation organized and existing under the laws of the **State of Indiana**, and having a usual place of business at **Lilly Corporate Center, Indianapolis, Indiana 46285**, desires to acquire an interest therein in accordance with agreements duly entered into with us;

NOW, THEREFORE, to all whom it may concern be it known that for and in consideration of said agreements and of other good and valuable consideration, the receipt of which is hereby acknowledged, we have sold, assigned and transferred and by these presents do hereby sell, assign and transfer unto said ASSIGNEE, its successors, assigns and legal representatives, our entire right, title and interest in and throughout the United States of America, its territories and all foreign countries, in and to said invention as described in said International Patent Application, together with our entire right, title and interest in and to said International Patent Application and such Letters Patent as may issue thereon; said invention, International Patent Application and Letters Patent to be held and enjoyed by said ASSIGNEE for its own use and behalf and for its successors, assigns and legal representatives, to the full end of the term for which said Letters Patent may be granted as fully and entirely as the same would have been held by us had this assignment and sale not been made; we hereby convey all rights arising under or pursuant to any and all international agreements, treaties or laws relating to the protection of industrial property by filing any such International Patent Application for Letters Patent. We hereby acknowledge that this assignment, being of our entire right, title and interest in and to said invention, carries with it the right in ASSIGNEE to apply for and obtain from competent authorities in all countries of the world any and all Letters Patent by attorneys and agents of ASSIGNEE's selection and the right to procure the grant of all such Letters Patent to ASSIGNEE for its own name as assignee of the entire right, title and interest therein;

AND, we hereby further agree for ourselves and our executors and administrators to execute upon request any other lawful documents and likewise to perform any other lawful acts which may be deemed necessary to secure fully the aforesaid invention to said ASSIGNEE, its successors, assigns and legal representatives, but at its or their expense and charges, including the

execution of applications for patents in foreign countries, and the execution of substitution, reissue, divisional or continuation applications and preliminary or other statements and the giving of testimony in any interference or other proceeding in which said invention or any application or patent directed thereto may be involved;

AND, we do hereby authorize and request the Commissioner of Patents of the United States to issue such Letters Patent as shall be granted upon said International Patent Application or applications based thereon to said ASSIGNEE, its successors, assigns, and legal representatives.

IN TESTIMONY WHEREOF, we have hereunto set our hands and affixed our seals the date set forth below.

Inventor Dawn Alisa Brooks Date 7/14/2003

Dawn Alisa Brooks

Address 402 W. New York St., Apt. 307 6916 Elise Court BAB

Indianapolis, IN 46202 Indianapolis, Indiana 46220

Witness Michelle Hall

Address 3152 Chestwell Drive

Indianapolis, In. 46268

Witness

Address 7045 Bentgrass Dr.

Indianapolis, IN 46236

Inventor Alan M Warshawsky Date 7/11/03
Alan M. Warshawsky

Address 13828 Springmill Ponds Circle
Carmel, IN 46032

Witness Michelle Hall
Address 3152 Cedarwell Drive
Indianapolis, IN 46268

Witness [signature]
Address 7045 Bentgrass Drive
Indianapolis, IN 46236

Inventor _____ Date 11 July 03
Chahrzad Montrose-Rafizadeh

Address 12460 Silver Bay Circle
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Witness _____
Address 3152 Cedarwell Drive
Indianapolis, In. 46268

Witness _____
Address 7045 Bentgrass Drive
Indianapolis, IN 46236

Inventor _____ Date 24 June 03
Anne Reifel-Miller

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Witness _____
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Indianapolis, In. 46268

Witness _____
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Indianapolis, IN 46236

Inventor _____ Date July 8, 2003
Lourdes Prieto

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Witness JULIAN PRIEGO SOLER
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Witness MARTA CIFUENTES GARCIA
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Inventor _____ Date July 10, 2003
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Inventor  Date 14-7-03

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28005 Madrid, Spain

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Inventor  Date July 8, 2003

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Witness MARTA PEREZ SOMALO

Address C/ Juan Sebastian nº3 4ºC

28007 MADRID - SPAIN -

Inventor _____ Date July 8th 2003
Alicia Torrado

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Witness José Miguel Mínguez Ortega
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Witness Jaime Blanco Urgoiti
Address Doctor Pueblos 33 6°Izq 28760 Tres Cantos Madrid SPAIN

Inventor _____ Date July 8th 2003
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Inventor _____ Date July 9th, 2003
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Witness SONIA GUTIÉRREZ SANFELICIANO
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Witness JOSE A MARTINEZ PEREZ
Address C/ AVDA DE MADRID, 50, D-19
28700 S.S. DE LOS REYES MADRID (SPAIN)

Inventor _____ Date July 8th 2003
Maria Martin-Ortega Finger

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28045 Madrid, Spain

Witness JESUS BLAS BLAS
Address C/NIEBLA 3, 3°A, 28760 - TRES CANTOS (MADRID)
SPAIN

Witness CRISTINA GARCIA PAREDES
Address C/ DEL PEDREGAL Nº 10
28721 CABANILLAS DE LA SIERRA - MADRID

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Director of the U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies)

Robert J. Ardecky

Additional name(s) of conveying party(ies) attached? [ ] Yes [X] No

2. Name and address of receiving party(ies)

Name: Ligand Pharmaceuticals Incorporated

Internal Address:

Street Address: 10275 Science Center Drive

City: San Diego State: California ZIP: 92121

Additional name(s) & address(es) attached? [ ] Yes [X] No

3. Nature of conveyance:

[X] Assignment [ ] Merger

[ ] Security Agreement [ ] Change of Name

[ ] Other

Execution Date: 08/25/03

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
PCT/US02/16950

B. Patent No.(s)

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Steven G. Davis, Esq.

Internal Address:

Hamilton, Brook, Smith & Reynolds, P.C.

Street Address: 530 Virginia Road, P.O. Box 9133

City: Concord State: MA ZIP: 01742-9133

6. Total number of applications and patents involved: [1]

7. Total Fee (37 C.F.R. 3.41)..... $ 40.00

[X] Enclosed

[X] Authorized to charge any deficiencies or credit any overpayment to deposit account

[ ] Authorized to be charged to deposit account

8. Deposit account number:

08-0380

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Steven G. Davis — Name of Person Signing

Signature

September 2003 — Date

Total number of pages including cover sheet, attachments, and document: [3]

Docket No. 2947.1007-002

Multi-Joint

ASSIGNMENT

WHEREAS, I, **Robert J. Ardecky,** together with co-inventors **Dawn Alisa Brooks, Alan M. Warshawsky, Chahrzad Montrose-Rafezadeh, Anne Reifel-Miller, Lourdes Prieto, Isabel Rojo, Jose Alfredo Martin, Maria Rosario Gonzales Garcia, Alicia Torrado, Rafael Ferritto Crespo, Carlos Lamas-Peteira and Maria Martin-Ortega Finger,** have invented a certain improvement in **Modulators of Peroxisome Proliferator Activated Receptors** described in an International Patent Application filed pursuant to the Patent Cooperation Treaty and which designates the United States, the specification of which:

[ ] is being executed on even date herewith and is about to be filed in the United States Patent Office;

[X] was filed on **May 30, 2002** as Application No. **PCT/US02/16950;**

[ ] was patented under U.S. Patent No. [ ] on [ ].

WHEREAS, **Ligand Pharmaceuticals Incorporated,** (hereinafter "ASSIGNEE"), a corporation organized and existing under the laws of the **State of Delaware,** and having a usual place of business at **10275 Science Center Drive, San Diego, California 92121,** desires to acquire an interest therein in accordance with agreements duly entered into with us;

NOW, THEREFORE, to all whom it may concern be it known that for and in consideration of said agreements and of other good and valuable consideration, the receipt of which is hereby acknowledged, I have sold, assigned and transferred and by these presents do hereby sell, assign and transfer unto said ASSIGNEE, its successors, assigns and legal representatives, my entire right, title and interest in and throughout the United States of America, its territories and all foreign countries, in and to said invention as described in said International Patent Application, together with my entire right, title and interest in and to said International Patent Application and such Letters Patent as may issue thereon; said invention, International Patent Application and Letters Patent to be held and enjoyed by said ASSIGNEE for its own use and behalf and for its successors, assigns and legal representatives, to the full end of the term for which said Letters Patent may be granted as fully and entirely as the same would have been held by me had this assignment and sale not been made; I hereby convey all rights arising under or pursuant to any and all international agreements, treaties or laws relating to the protection of industrial property by filing any such International Patent Application for Letters Patent. I hereby acknowledge that this assignment, being of my entire right, title and interest in and to said invention, carries with it the right in ASSIGNEE to apply for and obtain from competent authorities in all countries of the world any and all Letters Patent by attorneys and agents of ASSIGNEE's selection and the right to procure the grant of all such Letters Patent to ASSIGNEE for its own name as assignee of the entire right, title and interest therein;

AND, I hereby further agree for myself and my executors and administrators to execute upon request any other lawful documents and likewise to perform any other lawful acts which may be deemed necessary to secure fully the aforesaid invention to said ASSIGNEE, its successors, assigns and legal representatives, but at its or their expense and charges, including the

execution of applications for patents in foreign countries, and the execution of substitution, reissue, divisional or continuation applications and preliminary or other statements and the giving of testimony in any interference or other proceeding in which said invention or any application or patent directed thereto may be involved;

AND, I do hereby authorize and request the Commissioner of Patents of the United States to issue such Letters Patent as shall be granted upon said International Patent Application or applications based thereon to said ASSIGNEE, its successors, assigns, and legal representatives.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed my seal the date set forth below.

Inventor's Signature: Robert J Ardecky

Robert J. Ardecky

State/Commonwealth

of California

County of San Diego

Then personally appeared before me the above-named **Robert J. Ardecky** and acknowledged that he executed the foregoing instrument as his free act and deed this 25th day of August, 2003.

(SEAL) Michele P. Travis Notary Public

Michele P. Travis (print name)

My Commission expires 01/01/06

MICHELE P. TRAVIS
Commission # 1333262
Notary Public - California
San Diego County
My Comm. Expires Jan 1, 2006

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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FAX: +57-1 638-6201

www.olarteraisbeck.com

INSTRUCTIONS FOR THE POWER OF ATTORNEY

FILLING OUT THE FORM CORRECTLY

1. The document has TWO (2) pages that must be filled out, the Power of Attorney itself and the Notarial Certification that accompanies it.
2. Please substitute all of the text highlighted in yellow (and only that text) with the appropriate information (or substitute it with a blank space if filled in by hand by the person signing the document).
3. We do NOT need copies of the documents you will list in point 5 of the Notarial Certification.

LEGALIZATION

The signature of the corporate official issuing the Power of Attorney should be authenticated by means of a Notarial Certification as the one enclosed herewith. The Notary's signature should then be authenticated using one of the following two procedures:

1. the Apostille; or
2. if an Apostille is not available or convenient, follow the normal chain of authentication leading to the legalization of the document by the Colombian Consul (the normal chain is that the Notary's signature is authenticated by the Country Clerk; sometimes the Consul legalizes the signature of the Clerk; other times the clerk's signature will first have to be legalized by the Secretary of the respective State).

Please do not hesitate to contact us by telephone or e-mail (filings@olarteraisbeck.com) should you have any questions.

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OLARTE RAISBECK & FRIERI, LTDA.
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TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

NAME OF THE COMPANY

domiciled in

COMPANY STREET ADDRESS

by means of these presents hereby grants to **Carlos R. Olarte, and/or Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models, Industrial Designs and Obtainer's Certificates** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

NAME OF THE COMPANY

domiciliado en

COMPANY STREET ADDRESS

por medio del presente otorga a **Carlos R. Olarte, y/o Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad, Diseños Industriales y Certificados de Obtentor** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: SIGNATURE OF THE OFFICER

Date/Fecha: DAY/MONTH (SPELL OUT)/YEAR

City,Country/Ciudad,País: CITY AND COUNTRY OF EXECUTION

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,
DATE (SPELL OUT MONTH)
The undersigned Notary Public certifies:

1. That
COMPLETE NAME OF OFFICER SIGNING POA
of legal age and domiciled in
OFFICER'S FULL STREET ADDRESS
signed the foregoing document.

2. That the grantor has executed the foregoing document as OFFICER'S TITLE of COMPANY NAME.

3. That COMPANY NAME, having its principal place of business located in CITY, STATE OR COUNTY, COUNTRY is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
LIST EACH DOCUMENT SEPARATELY, PROVIDING DATE OF EXECUTION AND ITS ORIGIN OR SOURCE (e.g. Minutes of 02 July 2003 Board Meeting, Amended Bylaws 01 February 1996)

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
mayor de edad y domiciliado
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de
de

4. Que
con sede principal ubicada en
está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):
Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)
SEAL (optional)

18

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 2947.1007002

Box No. I TITLE OF INVENTION

Modulators of Peroxisome Proliferator Activated Receptors

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
United States of America

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LIGAND PHARMACEUTICALS, INC.
10275 Science Center Drive
San Diego, California 92121
United States of America

This person is:
☒ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BROOK, David E.
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 Virginia Road, P.O. Box 9133
Concord, Massachusetts 01742-9133
United States of America

Telephone No. 978-341-0036

Facsimile No. 978-341-0136

Teleprinter No.

Agent's registration No. with the Office 22,592

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

1

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BROOKS, Dawn Alisa
6916 Elise Court
Indianapolis, Indiana 46220
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WARSHAWSKY, Alan M.
13828 Springmill Ponds Circle
Carmel, Indiana 46032
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MONTROSE-RAFEZADEH, Chahrzad
12460 Silver Bay Circle
Indianapolis, Indiana 46236
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

REIFEL-MILLER, Anne
3338 West 46th Street
Indianapolis, Indiana 46228
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PRIETO, Lourdes
C/Leopoldo Alas Clarin
n 2, 1 D, Madrid
Madrid 28035
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ROJO, Isabel
Paseo de las Acacias 22 6H
Madrid
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MARTIN, Jose Alfredo
C/Juan Duque, 9, 5-B
28005 Madrid
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GONZALES GARCIA, Maria Rosario
Pensamiento 5 1 C
28020 Madrid
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TORRADO, Alicia
C/Santiago de Compostela, 26, 9ºF
28034 Madrid
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FERRITTO CRESPO, Rafael
C/Artajona 21, 2A
Madrid
28039 Madrid
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LAMAS-PETEIRA, Carlos
C/General Yague 10, 8ºE
28020 Madrid
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MARTIN-ORTEGA FINGER, Maria
C/Frigiliana 2, B, 6ºC
28045 Madrid
SPAIN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Sheet No. ..5....

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ARDECKY, Robert J.
3461 Calle Margarita
Encinitas, California 92024
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GM Gambia	☒ NZ New Zealand
☒ AG Antigua and Barbuda	☒ HR Croatia	☒ OM Oman
☒ AL Albania	☒ HU Hungary	☒ PH Philippines
☒ AM Armenia	☒ ID Indonesia	☒ PL Poland
☒ AT Austria	☒ IL Israel	☒ PT Portugal
☒ AU Australia	☒ IN India BLACK BOX	☒ RO Romania
☒ AZ Azerbaijan	☒ IS Iceland	☒ RU Russian Federation
☒ BA Bosnia and Herzegovina	☒ JP Japan	
☒ BB Barbados	☒ KE Kenya	☒ SD Sudan
☒ BG Bulgaria	☒ KG Kyrgyzstan	☒ SE Sweden
☒ BR Brazil	☒ KP Democratic People's Republic of Korea	☒ SG Singapore
☒ BY Belarus		☒ SI Slovenia
☒ BZ Belize	☒ KR Republic of Korea	☒ SK Slovakia
☒ CA Canada	☒ KZ Kazakhstan	☒ SL Sierra Leone
☒ CH & LI Switzerland and Liechtenstein	☒ LC Saint Lucia	☒ TJ Tajikistan
☒ CN China	☒ LK Sri Lanka	☒ TM Turkmenistan
☒ CO Colombia	☒ LR Liberia	☒ TN Tunisia
☒ CR Costa Rica	☒ LS Lesotho	☒ TR Turkey
☒ CU Cuba	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☒ LU Luxembourg	
☒ DE Germany	☒ LV Latvia	☒ TZ United Republic of Tanzania
☒ DK Denmark	☒ MA Morocco	☒ UA Ukraine
☒ DM Dominica	☒ MD Republic of Moldova	☒ UG Uganda
☒ DZ Algeria		☒ US United States of America
☒ EC Ecuador	☒ MG Madagascar	
☒ EE Estonia	☒ MK The former Yugoslav Republic of Macedonia	☒ UZ Uzbekistan
☒ ES Spain		☒ VN Viet Nam
☒ FI Finland	☒ MN Mongolia	☒ YU Yugoslavia
☒ GB United Kingdom	☒ MW Malawi	☒ ZA South Africa
☒ GD Grenada	☒ MX Mexico	☒ ZM Zambia
☒ GE Georgia	☒ MZ Mozambique	☒ ZW Zimbabwe
☒ GH Ghana	☒ NO Norway	

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ Any PCT member country not listed above	☐	☐
	☐	☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

(i) *If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

(ii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

(iii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

(iv) *If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

(v) *If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

(vi) *If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

Continuation of Box No. IV

BROOK, David E., Reg. No. 22,592
SMITH, James, M., Reg. No. 28,043
REYNOLDS, Leo R., Reg. No. 20,884
WAKIMURA, Mary Lou, Reg. No. 31,804
CARROLL, Alice O., Reg. No. 33,542
PIERCE, N. Scott, Reg. No. 34,900
WENDLER, Helen E., Reg. No. 37,964
ELMORE, Carolyn S., Reg. No. 37,567
GLOVSKY, Susan G. L., Reg. No. 30,382
HOGLE, Doreen M., Reg. No. 36,361
WAGNER, Richard W., Reg. No. 34,480
CONWAY, Robert T., Reg. No. 33,859
JOHNSON, Rodney D., Reg. No. 36,558
THIBODEAU, David Jr., J., Reg. No. 31,671
COLLINS, Anne, J., Reg. No. 40,564
TREANNIE, Lisa M., Reg. No. 41,368
MEAGHER, Timothy J., Reg. No. 39,302
WISE, Richard A., Reg. No. 18,041
CRAIG, Anne I., Reg. No. 32,976
DAVIS, Steven G., Reg. No. 39,652

All of:
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 Virginia Road
P.O. Box 9133
Concord, Massachusetts 01742-9133
United States of America

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 07 June 2001 (07.06.01)	60/297,144	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* . . . .

. . . . . .

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EP . . . . . .

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	09
description (excluding sequence listing part)	:	411
claims	:	46
abstract	:	01
drawings	:	00
Sub-total number of sheets	:	467
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	467

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet w/check	:	1
2. ☐ original separate power of attorney	:	
3. ☐ original general power of attorney	:	
4. ☐ copy of general power of attorney; reference number, if any:	:	
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	
10. ☒ other *(specify)*: . *Postcard Receipt*	:	1

Figure of the drawings which should accompany the abstract: NA

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Steven G. Davis

Date: 30 May 2002

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ not received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100813 A2

(51) International Patent Classification[7]: C07C 59/68, 59/90, 59/72, 239/12, C07D 311/30, 307/91, C07C 219/10, C07D 213/30, 215/14, 295/08, C07C 217/94, A61K 31/192, 31/195, A61P 9/00, 3/04, 3/06, 3/00

(21) International Application Number: PCT/US02/16950

(22) International Filing Date: 30 May 2002 (30.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/297,144 7 June 2001 (07.06.2001) US

(71) Applicants *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BROOKS, Dawn, Alba [US/US]; 6916 Elisa Court, Indianapolis, IN 46220 (US). WARSHAWSKY, Alan, M. [US/US]; 13828 Springmill Ponds Circle, Carmel, IN 46032 (US). MONTROSE-RAFEZADEH, Cheherzad [US/US]; 12460 Silver Bay Circle, Indianapolis, IN 46236 (US). REIFEL-MILLER, Anne [US/US]; 3338 West 46th Street, Indianapolis, IN 46228 (US). PRIETO, Lourdes [ES/ES]; c/Leopoldo Alas Clarin, N2-1D, E-28035 Madrid (ES). ROJO, Isabel [ES/ES]; Paseo de las Acacias, 22-6H, E-Madrid (ES). MARTIN, Jose, Alfredo [ES/ES]; c/Juan Duque, 9-5-B, E-28005 Madrid (ES). GONZALES GARCIA, Maria, Rosario [ES/ES]; Pensamiento, 5-1C, E-28020 Madrid (ES). TORRADO, Alicia [ES/ES]; c/Santiago de Compostela, 26-9°F, E-28034 Madrid (ES). FERRITTO CRESPO, Rafael [ES/ES]; c/Artajona, 21-2A, E-28039 Madrid (ES). LAMAS-PETEIRA, Carlos [ES/ES]; c/General Yague, 10-8°E, E-28020 Madrid (ES). MARTIN-ORTEGA FINGER, Maria [ES/ES]; c/Prigiliana, 2-B, 6°C, E-28045 Madrid (ES). ARDECKY, Robert, J. [US/US]; 3461 Calle Margarita, Encinitas, CA 92024 (US).

(74) Agents: BROOK, David, E. et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

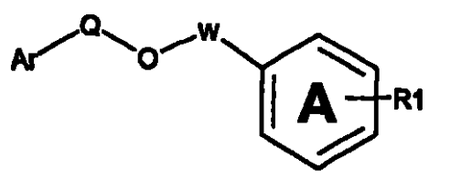
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS



(I)

(57) Abstract: Disclosed is a compound represented by Structural Formula (I): Ar is a substituted or unsubstituted aromatic group. Q is a covalent bond, $-CH_2$-or-CH_2CH_2-; W is a substituted or unsubstituted alkylene or a substituted or unsubstituted heteroalkylene linking group from two to ten atoms in length, preferably from two to seven atoms in length. Phenyl Ring A is optionally substituted with up to four substituents in addition to R_1 and W. R_1 is $(CH_2)_n$-$CH(OR_2)$-$(CH_2)_m$E, -(CH)=$C(OR_2)$-$(CH_2)_m$E, -$(CH_2)_n$-CH(Y)-$(CH_2)_m$E or (CH)=C(Y)-$(CH_2)_m$E; wherein E is $COOR_3$, C_1-C_3 alkylnitrile, carboxamide, sulfonamide, acylsulfonamide or tetrazole and wherein sulfonamide, acylsulfonamide and tetrazole are optionally substituted with one or more substituents independently selected from: C_1-C_4 alkyl, haloalkyl and aryl-C_0-4-alkyl; R_2 is H, an aliphatic group, a substituted aliphatic group, haloalkyl, an aromatic group, a substituted aromatic group, -COR_4, -$COOR_4$, -$CONR_5R_6$, -C(S)R_4, -C(S)OR_4 or C(S)NR_5R_6. R_3 is H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group. Y is O-, CH_2-, -CH_2CH_2- or CH=CH- and is bonded to a carbon atom in Phenyl Ring A that is *ortho* to R_1. R_4-R_6 are independently H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group. n and m are independently 0, 1 or 2.

WO 02/100813 A2

MODULATORS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS

RELATED APPLICATIONS

This application claims the benefit of U.S. provisional application 60/297,144, filed 07 June 2001, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

The peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor gene family that are activated by fatty acids and fatty acid metabolites. The PPARs belong to the subset of nuclear receptors that function as heterodimers with the 9-*cis* retinoic acid receptor (RXR). Three subtypes, designated PPARα, PPARγ and PPARδ, are found in species ranging from *Xenopus* to humans.

PPARα is the main subtype in the liver and has facilitated analysis of the mechanism by which peroxisome proliferators exert their pleiotropic effects. PPARα is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β-oxidation of fatty acids. PPARα is also involved with the activity of fibrates and fatty acids in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in low-density lipoprotein (LDL) cholesterol, and they are used particularly for the treatment of hypertrigiyceridemia.

PPARγ is the main subtype in adipose tissue and involved in activating the program of adipocyte differentiation. PPARγ is not involved in stimulating peroxisome proliferation in the liver. There are two isomers of PPARγ: PPARγ1 and PPARγ2, which differ only in that PPARγ2 contains an additional 28 amino acids present at the amino terminus. The DNA sequences for the PPARγ receptors are described in Elbrecht, et al., BBRC 224;431-437 (1996). Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J_2 derivatives have been identified as natural ligands for PPARγ, which also binds the anti-diabetic agents thiazolidinediones with high affinity. The physiological functions of PPARα and PPARγ in lipid and carbohydrate metabolism were uncovered once it was recognized that they were the receptors for the fibrate and glitazone drugs, repectively.

PPARα and PPARγ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as inflammatory bowel disease and other inflammation related illnesses. Such inflammation related illnesses include, but are not limited to Alzheimer's disease, Crohn's disease, rheumatoid arthritis, psoriasis, and ischemia reprofusion injury.

By contrast, PPARδ (also referred to as PPARβ and NUC1) is not reported to be receptor for any known class of drug molecules, and its role in mammalian physiology has remained undefined. The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6:1634-1641 (1992).

Diabetes is a disease in which a mammal's ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. "Type II Diabetes" or "non-insulin dependent diabetes mellitus" (NIDDM) is the form of diabetes, which is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin and hyperinsulemia results. Hyperinsulemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL (known as the "bad" cholesterol) which are risk factors in cardiovascular diseases. The constellation of symptoms which includes hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL is known as Syndrome X.

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The initial treatment for hypercholesterolemia is often a diet low in fat and cholesterol coupled with appropriate physical exercise. Drug intervention is initiated if LDL-lowering goals are not met by diet and exercise alone. It is desirable to lower elevated levels of LDL cholesterol and increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373- 381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL elevation are associated with undesirable effects, such as flushing.

There are several treatments currently available for treating diabetes mellitus but these treatments still remain unsatisfactory and have limitations. While physical exercise and reduction in dietary intake of calories will improve the diabetic condition, compliance with this approach can be poor because of sedentary lifestyles and excess food consumption, in particular high fat-containing food. Therefore, treatment with hypoglycemics, such as sulfonylureas (e.g., chlorpropamide, tolbutamide, tolazamide and acetohexamide) and biguanides (e.g. phenformin and metformin) are often necessary as the disease progresses. Sulfonylureas stimulate the β cells of the pancreas to secrete more insulin as the disease progresses. However, the response of the β cells eventually fails and treatment with insulin injections is necessary. In addition, both sulfonylurea treatment and insulin injection have the life threatening side effect of hypoglycemic coma, and thus patients using these treatments must carefully control dosage.

It has been well established that improved glycemic control in patients with diabetes (Type I and Type II) is accompanied by decreased microvascular

complications (DCCT and UKPDS). Due to difficulty in maintaining adequate glycemic control over time in patients with Type II diabetes, the use of insulin sensitizers in the therapy of Type II diabetes is growning. There is also a growing body of evidence that PPARγ agonist, insulin sensitizer, may have benefits in the treatment of Type II diabetes beyond their effects in improving glycemic control.

In the last decade a class of compounds known as thiazolidinediones (e.g. U.S. Pat. Nos. 5,089,514; 4,342,771; 4,367,234; 4,340,605; and 5,306,726) have emerged as effective antidiabetic agents that have been shown to increase the sensitivity of insulin sensitive tissues, such as skeletal muscle, liver and adipose, to insulin. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. Although thiazolidinediones have been shown to increase insulin sensitivity by binding to PPARγ receptors, this treatment also produces unwanted side effects such as weight gain and, for troglitazone, liver toxicity.

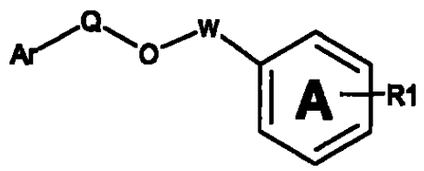
In view of the above, there exists a need for new pharmaceutical agents which modulate these receptors to prevent, treat and/or alleviate these diseases or conditions while ameliorating side effects of current treatments.

SUMMARY OF THE INVENTION

Disclosed herein are novel α-methoxy cinnamates which are modulators of peroxisome proliferator activated receptors (PPAR). Many of these novel α-methoxy cinnamates have the advantage over previously known PPAR modulators in that they selectively bind at peroxisome proliferator activated receptor modulators. Based on this discovery, methods of modulating a peroxisome proliferator activated receptor in a subject in need of such modulation, methods of treating a subject for Type II diabetes, methods of treating a subject for cardiovascular disease, methods of treating a subject for Syndrome X and methods of treating a subject with other PPAR-mediated diseases and conditions are disclosed herein.

One embodiment of the present invention is a compound represented by

Structural Formula (I):



(I).

The variables in Structural Formula (I) are defined below.

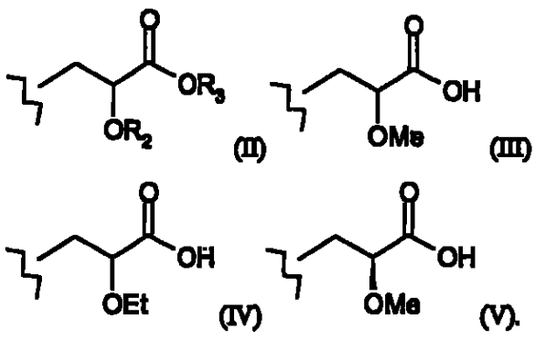
Ar is a substituted or unsubstituted aromatic group. Preferably, Ar is an unsubstituted, monosubstituted or disubstituted aromatic group.

Q is a covalent bond, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$. Preferably, Q is a covalent bond.

W is a substituted or unsubstituted alkylene group two to ten atoms in length or a substituted or unsubstituted heteroalkylene group, wherein the heteroalkylene group is an alkylene group from two to ten atoms in length in which one or more methylene groups have been replaced with a functional group selected from $-CH=CH-$, $-C\equiv C-$, $-O-$, $-CO-$, $-NR_7-$, $-NR_7CO-$, $-C(=NOH)-$, $-S-$, $-S(O)-$, $-S(O)_2-$ or $-CH(NR_7R_8)-$.

Phenyl Ring A is optionally substituted with up to four substituents in addition to R_1 and W.

R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ or $-(CH)=C(Y)-(CH_2)_mE$. E is $COOR_3$, C1-C3 -alkylnitrile, carboxamide, sulfonamide, acylsulfonamide or tetrazole and wherein sulfonamide, acylsulfonamide and tetrazole are optionally substituted with one or more substituents independently selected from: C1-C6 alkyl, C1-C6 haloalkyl and aryl-C0-4-alkyl. Preferably R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ or $-(CH)=C(Y)-(CH_2)_mCOOR_3$. More preferably R_1 is *meta* or *para* to W and is represented by Structural Formula (II), even more preferably by Structural Formulas (III) or (IV) and even more preferably by Structural Formula (V):



R_2 is -H, an aliphatic group, a substituted aliphatic group, haloalkyl, an aralkyl group, a substituted aralkyl group, an aromatic group, a substituted aromatic group, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ or $-C(S)NR_5R_6$.

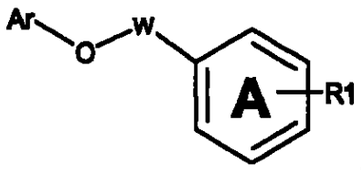
Y is –O–, $-CH_2-$, $-CH_2CH_2-$ or a –CH=CH- group that is bonded to a carbon atom in Phenyl Ring A that is *ortho* to R_1. Thus, Y, together with the two carbon atoms to which Y is bonded and the intervening carbon atoms, form a ring that is fused to Phenyl Ring A.

R_3-R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group.

n and m are independently 0, 1 or 2.

In Structural Formula (I), preferably, R_2 is a C1-C6 lower alkyl group, phenyl, benzyl or benzoyl; and R_3 is –H or a C1-C6 alkyl group (more preferably C1-C3 alkyl group).

In another embodiment, the compound of the present invention is represented by Structural Formula (VI):



(VI).

The variables in Structural Formula (VI) are defined below.

Ar is a substituted or unsubstituted aromatic group. Preferably, Ar is an unsubstituted, monosubstituted or disubstituted aromatic group.

W is a substituted or unsubstituted alkylene linking group or a substituted or unsubstituted heteroalkylene linking group from two to ten atoms in length, preferably from two to seven atoms in length.

Phenyl Ring A is optionally substituted with up to four substituents in addition to R_1.

R_1 is $-(CH_2)_n$-$CH(OR_2)$-$(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)$-$(CH_2)_mCOOR_3$, $-(CH_2)_n$-$CH(Y)$-$(CH_2)_mCOOR_3$ or $-(CH)=C(Y)$-$(CH_2)_mCOOR_3$. Preferably R_1 is *meta* or *para* to W and is represented by Structural Formula (II), more preferably by Structural Formula (III) and even more preferably by Structural Formula (IV). Structural Formulas (II)-(V) are shown above.

R_2 is -H, an aliphatic group, a substituted aliphatic group, an aryl group, a substituted aryl group, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ or $-C(S)NR_5R_6$.

Y is $-O-$, $-CH_2-$, $-CH_2CH_2-$ or $-CH=CH-$ and is bonded to a carbon atom in Phenyl Ring A that is *ortho* to R_1.

R_3-R_6 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group.

n and m are independently 0, 1 or 2.

In Structural Formula (VI), preferably, R_2 is a C1-C6 lower alkyl group, phenyl, benzyl or benzoyl; and R_3 is –H or a C1-C3 lower alkyl group.

Another embodiment of the present invention is a method of modulating a peroxisome proliferator activated receptor (PPAR). The method comprises the step of contacting the receptor with at least one of the compounds of the present invention.

Another embodiment of the present invention is a method of modulating a peroxisome proliferator activated receptor gamma in a subject in need of modulation of the peroxisome proliferator activated receptor gamma, i.e., treating a PPAR-gamma mediated disease in a subject. The method comprises the step of administering to the subject an effective amount of a compound of the present invention.

Another embodiment of the present invention is a method for lowering blood-glucose in a subject in need of such treatment. The method comprises the step of administering to the subject an effective amount of a compound of the present invention.

Another embodiment of the present invention is a method of treating a subject for hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease or other diseases where insulin resistance is a component. The method comprises the step of administering to the subject an effective amount of a compound of the present invention.

Another embodiment of the present invention is a method of treating a subject with diabetes mellitus. The method comprises the step of administering to the subject an effective amount of a compound of the present invention.

Another embodiment of the present invention is a method of treating a subject for cardiovascular disease. The method comprises the step of administering to the subject an effective amount of a compound of the present invention.

Another embodiment of the present invention is a method of treating a subject for Syndrome X. The method comprises the step of administering to the subject an effective amount of a compound of the present invention.

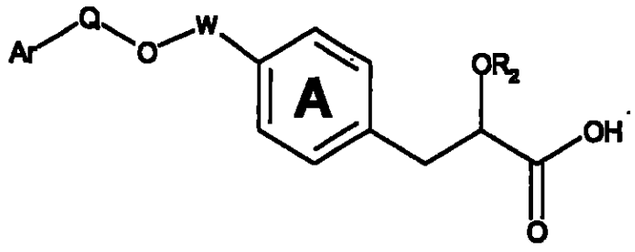
Another embodiment of the present invention is a compound of the present invention for use in therapy. The therapy can be, for example, to treat Type II diabetes, cardiovascular disease, Syndrome X or a disorder modulated by a peroxisome proliferator activated receptor.

Another embodiment of the present invention is the use of a compound of the present invention for the manufacture of a medicament for the treatment of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia

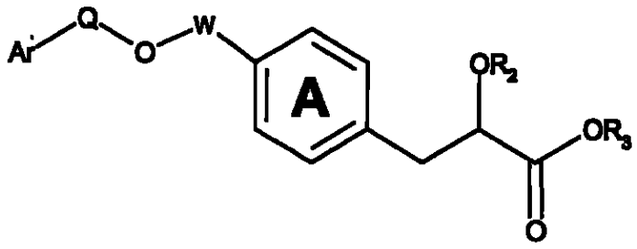
bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease or other diseases where insulin resistance is a component or other disorders modulated by a peroxisome proliferator activated receptor.

Yet another embodiment of the present invention is a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and at least one compound of the present invention.

Yet another embodiment of the present invention is a method of preparing a compound represented by Structural Formula (VII) from a starting compound represented by Structural Formula (VIII):



(VII)



(VIII).

The method comprises the step of hydrolyzing the ester group in the starting compound. Phenyl Ring A, Ar, Q, W, R_2 and R_3 are as described for Structural Formulas (I) or (VI). Q in Structural Formulas (VII) and (VIII) is preferably a covalent bond.

Yet another embodiment of the present invention is one of the novel compounds described herein, wherein the compound is radioactively labeled, i.e., comprises a radioactive isotope (e.g., ^{3}H or ^{14}C) at a specific site in the compound at level significantly greater than the natural abundance of the isotope. "Significantly

greater than natural abundance" means that the amount of isotope greater than natural abundance can be assessed by suitable means (e.g., scintillation counting). Radiolabeled, preferably tritiated, (S)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid is one example of a radiolabeled compound of the invention. Radiolabeled compounds, can be advantageously used to assess binding of test compound to PPARγ.

Yet another embodiment of the present invention is a method for determining whether a compound does or does not interact directly (e.g., binds) with PPARγ. The method comprises the step of specifically binding a radioactively labeled compound described herein to the ligand binding domain of a PPARγ receptor. The receptor is then combined with a test compound and the amount of specific binding of the radioactively labeled compound is assessed. Any decrease in the binding of the radiolabeled compound indicates that the test compound interacts directly with the peroxisome proliferator-activated receptor.

The compounds of the present invention and pharmaceutically acceptable salts, solvates and hydrates, stereoisomers thereof lower one or more of the following in mammals: glucose, insulin, triglycerides, fatty acids and/or cholesterol. They are therefore believed to be effective in treating hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease or other diseases where insulin resistance is a component or other disorders modulated by a peroxisome proliferator activated receptor.

DETAILED DESCRIPTION OF THE INVENTION

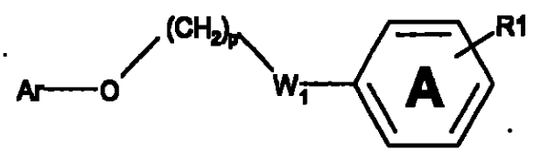
In the Schemes, Preparations and Examples below, various reagent symbols and abbreviations have the following meanings:

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	t-butoxycarbonyl

CBZ	benzyloxycarbonyl
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-dimethylamino pyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
eq.	equivalent(s)
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl
ESI-MS	electron spray ion-mass spectroscopy
Et	ethyl
EtOAc	ethyl acetate
FMOC	9-Fluorenylmethyl carbamate
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOAT:	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass
LRMS	low resolution mass
Me	methyl
Ms	methanesulfonyl
$Pd_2(dba)_3$	tris(dibenzylideneacetone) dipalladium(0)
Ph	phenyl
Phe	phenylalanine
Pr	propyl
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TBS	tertbutyldimethylsilyl
TFA	trifluoroacetic acid

TEA	triethylamine
THF	tetrahydrofuran
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
TLC	thin-layer chromatography

In one preferred embodiment, the compound of the present invention is represented by Structural Formula (IX):



(IX).

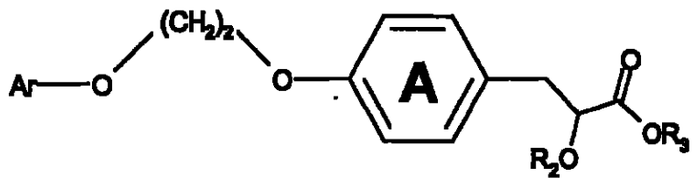
Ar, Phenyl Ring A and R_1 in Structural Formula (IX) are as defined in Structural Formulas (I) or (VI). R_1 is preferably *para* to W_1 and is represented by Structural Formula (II), more preferably Structural Formulas (III) or (IV) and even more preferably, Structural Formula (V).

p is an integer from one to nine, preferably one to four.

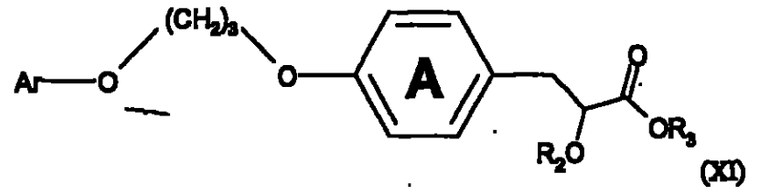
W_1 is -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- or $-CH(NR_7R_8)-$.

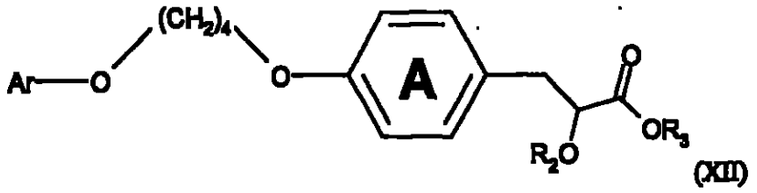
R_7 and R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group.

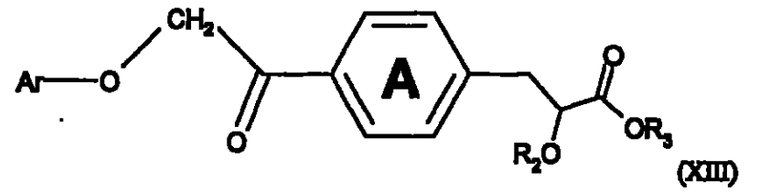
In a more preferred embodiment, the compound of the present invention is represented by a structural formula selected from Structural Formulas (X)-(XVIII):

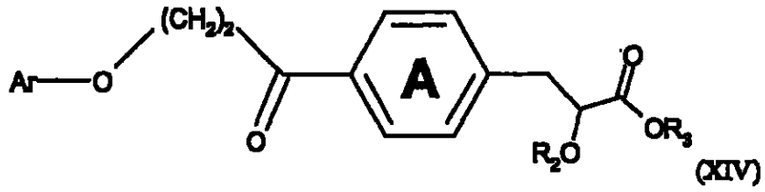


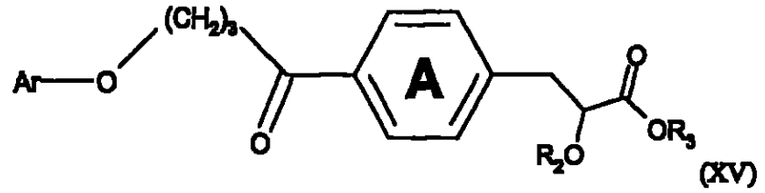
(X)

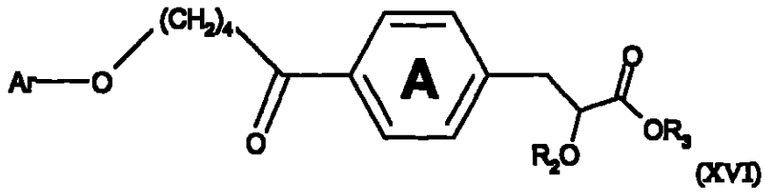

(XI)

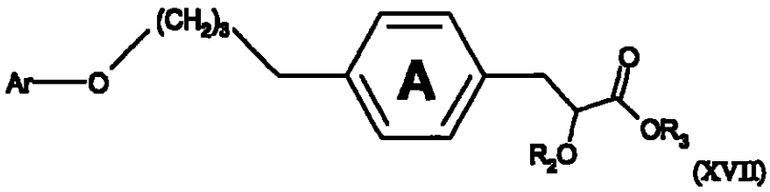

(XII)

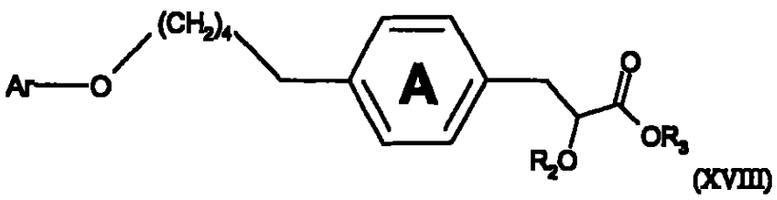

(XIII)


(XIV)

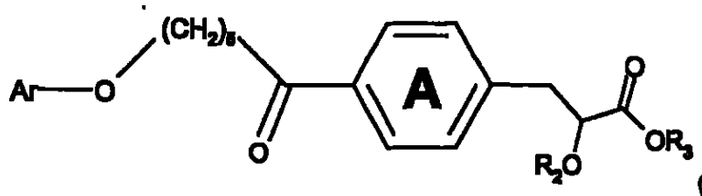

(XV)


(XVI)


(XVII)



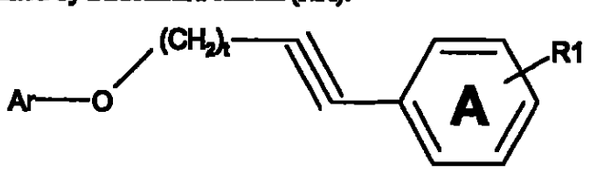
(XVIII)



(XIX).

Ar, Phenyl Ring A, R_2 and R_3 in Structural Formulas (X)-(XIX) are as described for Structural Formula (IX). Preferably, R_2 and R_3 are as described for Structural Formula (II). More preferably, $-CH_2CH(OR_2)COOR_3$ in Structural Formulas (X)-(XIX) is represented by Structural Formulas (III) or (IV) and even more preferably by Structural Formula (V).

In another preferred embodiment, the compound of the present invention is represented by Structural Formula (XX):

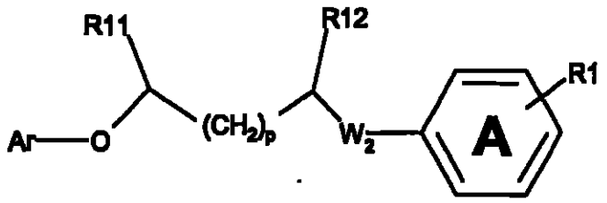


(XX).

Ar and Phenyl Ring A in Structural Formula (XX) are as described for Structural Formulas (I) or (VI) and t is an integer from 1 to about 5.

In a more preferred embodiment, R_1 in structural Formula (XX) is *para* to the carbon bonded to the alkyne group and is represented by Structural Formula (II), more preferably by Structural Formulas (III) or (IV) and even more preferably by Structural Formula (V). Preferably, t is 1, 2 or 3.

In another preferred embodiment, the compound of the present invention is represented by Structural Formula (XXI):



(XXI).

Ar and Phenyl Ring A in Structural Formula (XXI) are as described for Structural Formulas (I) or (VI).

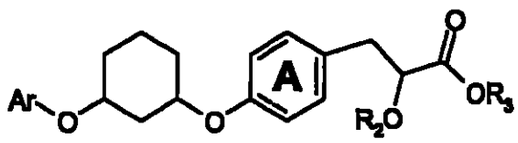
p is zero, one or two.

W_2 is -O-, -C(O)-, $-OCH_2$-, $-CH_2$-, $-NR_8$-, $-NR_8CO$-, $-NR_8CH$-, -C(=NOH)- or $-CH(NR_7R_8)$-. W_2 is preferably -O-.

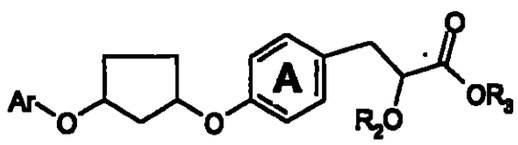
R_7 and R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group.

R_{11} and R_{12} are independently a C1-C6 alkyl group (preferably C1-C3 alkyl group), or, taken together are a substituted or unsubstituted ethylene, propylene or butylene group.

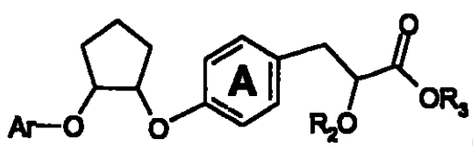
In a more preferred embodiment, the compound of the present invention is represented by a structural formula selected from Structural Formulas (XXII)-(XXVI):



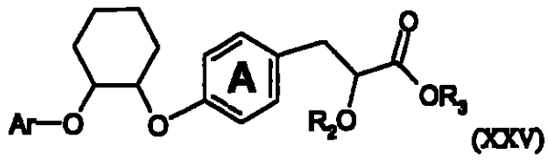
(XXII)



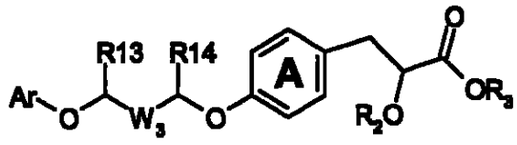
(XXIII)



(XXIV)



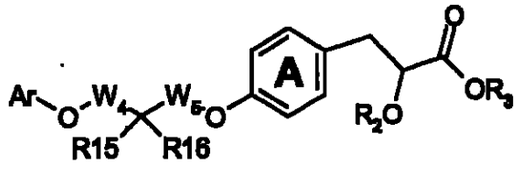
(XXV)



(XXVI).

Ar and Phenyl Ring A in Structural Formulas (XXII) - (XXVI) are as described for Structural Formula (XXI) and R_2 and R_3 in Structural Formulas (XXII)- (XXVI) are as described in Structural Formula (II). In Structural Formula (XXVI), W_3 is a covalent bond, methylene or ethylene and R_{13} and R_{14} are methyl, ethyl or propyl and are the same or different, preferably the same. Preferably, $-CH_2CH(OR_2)COOR_3$ in Structural Formulas (XXII)- (XXVI) is represented by Structural Formulas (III) or (IV), more preferably by Structural Formula (V).

In another preferred embodiment, the compound of the present invention is represented by Structural Formula (XXVII):



(XXVII).

Ar, Phenyl Ring A, R_2 and R_3 in Structural Formulas (XXVII) are as described for Structural Formulas (I) or (VI); W_4 and W_5 are independently methylene or ethylene; and R_{15} is -H and R_{16} is a C1-C6 alkyl group (preferably methyl, ethyl or propyl), or R_{15} and R_{16}, taken together, are =O or $=CH_2$. Preferably, $-CH_2CH(OR_2)COOR_3$ in Structural Formula (XXVII) is represented by Structural Formulas (III) or (IV), more preferably by Structural Formula (V).

An "aliphatic group" is non-aromatic, consists solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic. When straight chained or branched, an aliphatic group typically contains between about 1

and about 10 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an aliphatic group typically contains between about 3 and about 10 carbon atoms, more typically between about 3 and about 7 carbon atoms. Aliphatic groups are preferably C1-C10 straight chained or branched alkyl groups (i.e., completely saturated aliphatic groups), more preferably C1-C6 straight chained or branched alkyl groups. Examples include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl and *tert*-butyl.

A "haloaliphatic group" is an aliphatic group, as defined above, substituted with one or more halogen atoms.

A "haloalkyl group" is an alkyl group (i.e., a saturated aliphatic group), as defined above, substituted with one or more halogen atoms. Examples included -- CF_3, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$ and the like.

An "aralkyl group" is an alkyl group substituted with an aromatic group, preferably a phenyl group. A preferred aralkyl group is a benzyl group. Suitable aromatic groups are described below and suitable alkyl groups are described above. Suitable substituents for an aralkyl group are described below.

An "aralkenyl group" is an alkenyl group substituted with an aromatic group. An "alkenyl group" is an aliphatic group with one or more carbon carbon double bonds. Suitable aromatic groups are described below. Suitable aliphatic groups are defined above. Suitable substituents for an aralkenyl group are described below.

An "allyl group" has the formula "$-CH_2CH=CH_2$. Suitable substituents for an allyl group are described below

An "alkylene group" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer. Preferably, n is an integer from about 2 to about 10, more preferably from about 2 to about 7. A "substituted alkylene group" is an alkylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents are described below.

An "arylene" is an aromatic group in which at least two carbon atoms are bonded to moieties other than hydrogen. Suitable arylene groups are those corresponding to the aromatic groups described herein.

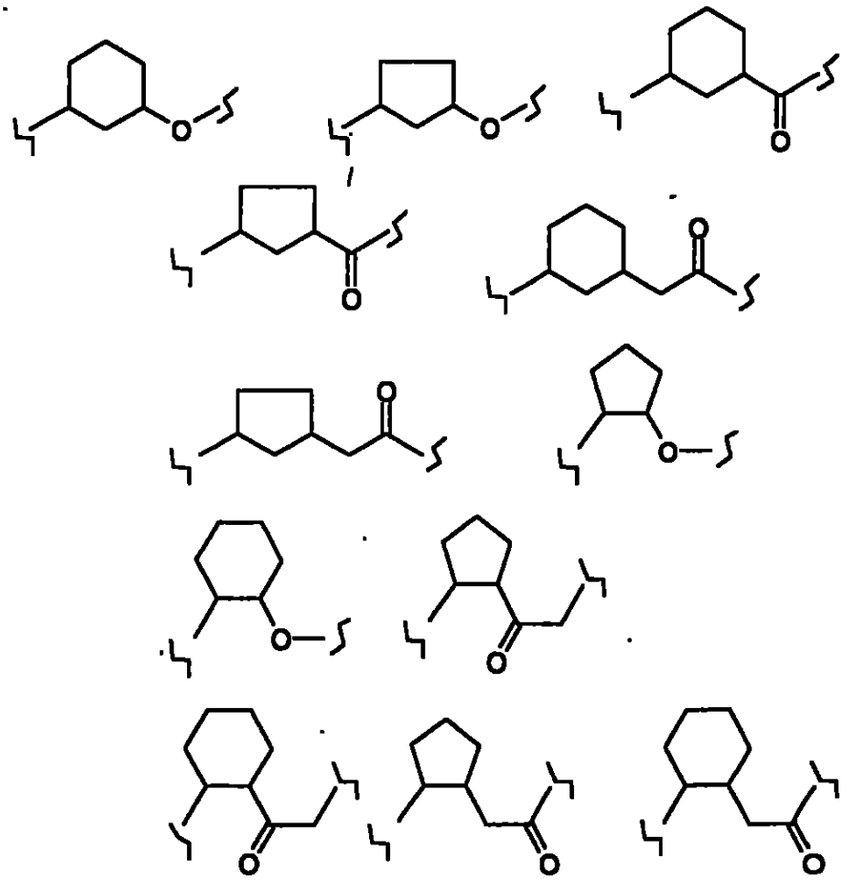
A "sulfonamide group" is represented by $-S(O)_2NH_2$. A "substituted sulfonamide group" is represented by $-S(O)_2N(R)_2$, wherein each R is independently -H, C1-C6 alkyl, C1-C6 haloalkyl or aryl-C0-C4-alkyl and at least one R is not –H.

An "acylsulfonamide group" is represented by $-S(O)_2NH-C(O)-R$ wherein R is -H or a C1-C6 alkyl group or a C1-C6 haloalkyl group. A "substituted acylsulfonamide group" is represented by $-S(O)_2NR'-C(O)R$, wherein R is –H or a C1-C6 alkyl group or C1-C6 haloalkyl group and R' is C1-C6 alkyl, C1-C6 haloalkyl or aryl-C0-C4-alkyl.

The term "heteroalkylene group" refers to an alkylene group in which one or more methylene groups have been replaced by a functional group, e.g., $-(CH_2)_p-Z-(CH_2)_q-$ wherein p is a positive integer and q is zero or a positive integer such that p + q is less than 10 and Z is a functional group. Examples of suitable functional groups include -CH=CH-, -C≡C-, -O-, -CO-, $-NR_8-$, $-NR_8CO-$, -C(=NOH)- , $-S(O)_k-$ and $-CH(NR_7R_8)-$ wherein each R_7 and each R_8 is independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group; and k is 0, 1 or 2. Preferably, a heteroalkylene group is between about 2 and 10 atoms in length. For purposes of determining the length of a heteroalkylene group, in this application a functional group is considered to be one atom. Thus, for example, $-(CH_2)_3-CO-NH-(CH_2)_2-$ is six atoms in length (five methylene carbons and a functional group); and $-(CH_2)_3-C(=NOH)-(CH_2)_2-$ is also six atoms in length (five methylene carbons and an oxime carbon). Examples of preferred heteroalkylene groups include $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-(CH_2)_4-O-$, $-CH_2-C\equiv CH-$, $-(CH_2)_2-C\equiv CH-$, $-(CH_2)_3-C\equiv CH-$, $-(CH_2)_4-C\equiv CH-$, $-(CH_2)_5-C\equiv CH-$, $-(CH_2)CO-$, $-(CH_2)_2CO-$, $-(CH_2)_3CO-$, $-(CH_2)_4CO-$, $-(CH_2)_2-C(=NOH)-$, $-(CH_2)_3-C(=NOH)-$, $-(CH_2)_4-C(=NOH)-$, $-(CH_2)_2-NR_8-$, $-(CH_2)_3-NR_8-$, $-(CH_2)_4-NR_8-$, $-(CH_2)_2-NR_8CO-$, $-(CH_2)_3-NR_8CO-$, $-(CH_2)_4-NR_8CO-$, $-(CH_2)_2-OCH_2-$, $-(CH_2)_3-OCH_2-$, $-(CH_2)_4-OCH_2-$, $-(CH_2)_2-NR_8CH_2-$, $-(CH_2)_3-NR_8CH_2-$, $-(CH_2)_4-NR_8CH_2-$, $-(CH_2)_2CH(NR_7R_8)-$, $-(CH_2)_3CH(NR_7R_8)-$ and $-(CH_2)_4-CH(NR_7R_8)-$.

56

A "substituted heteroalkylene group" is a heteroalkylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Preferred substituents include =O, =CH_2, C1-C6 alkyl and C2-C4 alkylene. When a heteroalkylene group is substituted with a C2-C4 alkylene group, the C2-C4 alkylene group together with the carbon atoms of the heteroalkylene group to which the two ends of the C2-C4 alkylene group are bonded and any intervening carbon atoms form a cycloalkyl ring. Structural Formula (XX) provides an example of a heteroalkylene group substituted with a C2-C4 alkylene group, which is represented by R_{11} and R_{12} taken together. Specifically, R_{11} and R_{12}, taken together with –CH-$(CH_2)_p$CH- can form a cycloalkyl ring. Other examples of heteroalkylene groups substituted by an alkylene are shown in the following structural formulas:



Other suitable substituents for a heteroalkylene group are described below.

A "nonaromatic heterocyclic ring" (or also refered to as a "heterocyclic ring") is a monocyclic, bicyclic, or tricyclic nonaromatic ring of 3 to14 ring atoms which are saturated or partially saturated containing carbon and from one to four heteroatoms selected from N, O or S. The term "nonaromatic heterocyclic ring " includes nitrogen-containing heterocyclic rings, which contains from one to three nitrogen atoms and optionally further contains one other heteroatom selected from O or S. Examples include morpholinyl, thiomorphonlyl, pyrrolindinyl, piperazinyl, piperidinyl, azetidinyl, azacycloheptyl, or N-phenylpiperazinyl. The term "non-aromatic heterocyclic ring" also includes non-aromatic heterocyclic rings fused to aromatic group, e.g., 1,3-benzodioxole, 4-chromanone, and phthalimide. A "non-aromatic heterocyclic ring" may be optionally substituted with a designated number of substituents, as described below.

An "aromatic group" (also refered to as an "aryl group") as used herein includes carbocyclic aromatic groups, heterocyclic aromatic groups (also refered to as "heteroaryl") and fused polycyolic aromatic ring system as defined herein.

A "carbocyclic aromatic group" is an aromatic ring of 5 to 14 carbons atoms, and includes a carbocyclic aromatic group fused with a 5-or 6-membered cycloalkyl group such as indan. Examples of carbocyclic aromatic groups include, but are not limited to, phenyl, 1-naphthyl, 2-naphyl, 1-anthracenyl, 2-anthracenyl, phenanthrenyl, fluorene, 9-fluorenone, indan and the like. A carbocyclic aromatic group is optionally substituted with a designated number of substituents, described below for aromatic groups.

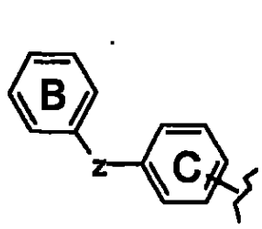
A "heterocyclic aromatic group" (or "heteroaryl") is a monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-ring atoms of carbon and from one to four heteroatoms selected from O, N, or S. Examples of heteroaryl include, but are not limted to N-imidazolyl, 2-imidazole, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyranyl, 3-pyranyl, 4-pyrazolyl, 5-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazoyl, 4-oxazoyl, 5-oxazoyl, 2-imidazolyl, isoxazoyl, pyrrolyl, pyrazinyl, and purinyl and the like.

Heterocyclic aromatic (or heteroaryl) as defined above may be optionally substituted with a designated number of substituents, as described below for aromatic groups.

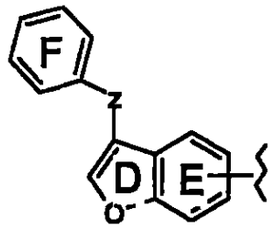
A "fused polycyclic aromatic" ring system is a carbocyclic aromatic group or heteroaryl fused with one or more other heteroaryl or nonaromatic heterocyclic ring. Examples include 2,3-dihydrobenzofuran, dibenzothiophene, dibenzofuran, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzoimidazolyl, 2-qinolinyl, 3-quinolinyl, 1-isoqinolinyl, 3-quinolinyl, 1-isoinoldyl, 3-isoindolyl, benzotriazolyl and the like. Fused polycyclic aromatic ring systems may optionally be substituted with a designated number of substituents, as described below for aromatic groups.

"Halo" refers to fluoro, chloro, bromo and iodo.

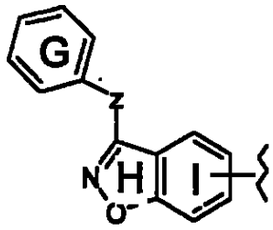
Preferred examples of suitable values for Ar in Structural Formulas (I), and (VI)-(XXVII) are shown below:



(XXVIII)



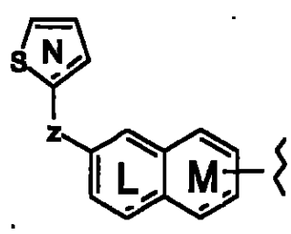
(XXIX)



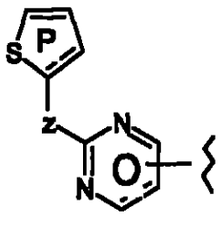
(XXX)



(XXXI)



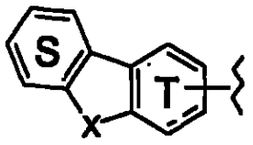
(XXXII)



(XXXIII)



(XXXIV)



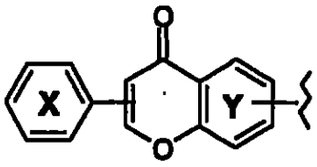
(XXXV)



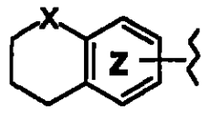
(XXXVI)



(XXXVII)



(XXXVIII)



(XXXIX)

Rings B-Z are independently substituted or unsubstituted. Other examples of suitable groups for Ar include substituted or unsubstituted benzoylnaphthyl, thienylphenyl and naphthoylphenyl. Still other examples of suitable values for Ar are found in Examples 1-379. These aromatic groups, when used as values for Ar, can be substituted or unsubstituted, as shown in Examples 1-379, or, alternatively, can contain one or more other aromatic group substituents that are described herein.

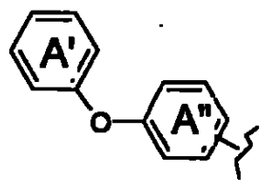
X is –O-, -S-, $-CH_2-$ or –C(O).

Z is a covalent bond, -O-, $(-CH_2)_q-$, $-CH(CH_3)(CH_2)_q-$, $-C(CH_3)_2(CH_2)_q-$, $-(CH_2)_qCH(CH_3)-$, $-(CH_2)_qC(CH_3)_2-$, $-O(CH_2)_q-$, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, $-(CH_2)_qNH-$, $-(CH_2)_qCHR_{20}-$, $-CHR_{20}(CH_2)_q-$, $-(CH_2)_qCR_{20}R_{20}-$, $-(CH_2)_qCR_{20}R_{20}-$,

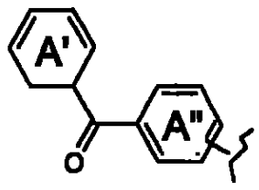
$-(CH_2)_qNR_{20}-$, $-NR_{20}(CH_2)_q-$, $-(CH_2)_qC(=NOH)-$, $-C(=NOH)(CH_2)_q-$, $-CH(OH)-(CH_2)_q-$, $-(CH_2)_q-CH(OH)-$, $-CO-(CH_2)_q-$, $-(CH_2)_q-CO-$, $-COO-(CH_2)_q-$, $-OCO-(CH_2)_q-$, $-(CH_2)_q-OCO-$, $-(CH_2)_q-COO-$, $-(CH_2)_qCO-NH-$, $-(CH_2)_qNH-CO-$, $-(CH_2)_qCONR_{20}-$, $-CONR_{20}(CH_2)_q-$, $-(CH_2)_qNR_{20}CO-$ or $-NR_{20}CO(CH_2)_q-$. Z is preferably a covalent bond, –C(=NOH), -O- or -C(O)- (more preferably -O- or -C(O)-); and q is 0, 1, 2 or 3, preferably 0 or 1.

Each R_{20} is independently a C1-C5 alkyl group or halogenated C1-C5 alkyl group.

Especially preferred values groups for Ar in Structural Formulas (I) and (VI)-(XXVII) are shown below:



(XL)



(XLI).

Phenyl Rings A' and A" are substituted or unsubstituted.

Suitable substituents for an aromatic group, including the aromatic group represented by Ar (e.g., Phenyl Rings A' and A" and Rings B-Z) and Phenyl Ring A, an aliphatic group, an alkyl group, an alkylene group, a heteroalkylene group, a non-aromatic heterocyclic group, an aralkyl group, an aralkenyl group and an allyl group are those which do not significantly diminish the activity of the compound at the Peroxisome Proliferator Activated Receptors (PPARs), e.g., decrease the activity by more than a factor of five (preferably no more than a factor of two) compared with the corresponding compound without the substituent. Examples of substituents include halogen (-Br, -Cl, -I and -F) -R, -OR, -CN, $-NO_2$, $-N(R)_2$, -COR, -COOR, $-CON(R)_2$, $-SO_kR$ (k is 0, 1 or 2) and $-NH-C(=NH)-NH_2$. Other examples include sulfonamide, acylsulfonamide, -NR-CO-R, $-OS(O)R$, $-OS(O)_2R$, cycloalkyl groups, substituted or unsubstituted non-aromatic heterocyclic groups, $-O(CH_2)_rCOOH$, $-O-O(CH_2)_r-N(R)_2$, $-O(CH_2)_r-$(cycloalkyl), $-O(CH_2)_rOH$, $-O(CH_2)_r-OSi(R)_3$ and $-(CH_2)_sCH(OR_{30})(CH_2)_tCOOR_{31}$. Each R is independently -H, an aliphatic group, a substituted aliphatic group, a halogenated aliphatic group, a benzyl group, a

substituted benzyl group, an aromatic group or a substituted aromatic group, and preferably -H, an alkyl group (e.g., a C1-C10 alkyl group), a halogenated alkyl group (e.g., a C1-C10 halogenated alkyl group), a phenyl group or a substituted phenyl group; R_{30} is a C1-C6 alkyl group or C1-C6 halogenated alkyl group, R_{31} is –H, a C1-C6 alkyl group or C1-C6 halogenated alkyl group; r is an integer from 1 to 6; a and b are independently 0, 1 or 2. An aromatic group, benzylic group, an aliphatic group, an alkyl group, an alkylene group, a heteroalkylene group, a non-aromatic heterocyclic group, aralkyl group and aralkenyl group can have more than one substituent. Other examples of suitable substituents for an aromatic group represented by Ar are those found at the corresponding position of the compounds described in the Exemplification Section.

Preferred substituents for Rings B-Z include halogen, $-R_9$, $-OR_9$, $-COR_9$, $-COOR_9$, -CN, a non-aromatic heterocyclic group, an allylic group, $-(CH_2)_aCH(OR_{30})(CH_2)_bCOOR_{31}$ or $-NR_9C(O)R_9$. R_9 is -H, an alkyl group (e.g., a C1-C10 alkyl group), cycloalkyl, a halogenated alkyl group (e.g., a C1-C10 halogenated alkyl group) or an aromatic group. R_{30}, R_{31}, a and b are as described above; preferably R_{30} is methyl or ethyl, R_{31} is $-H_3$ and a and b are one.

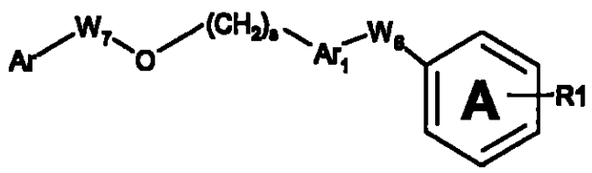
More preferably, suitable substituents for Rings B-Z include one or more groups selected from halogen, C1-C8 straight chained or branched alkyl, C1-C8 straight chained or branched halogenated alkyl (e.g., $-CF_3$), C3-C8 cycloalkyl, C1-C8 straight chained or branched alkanoyl, C1-C8 straight chained or branched alkoxy (e.g., methoxy), -Br, -F, *N*-morpholino, -COOH, -OH, -CN, or C1-C8 straight chained or branched halogenated alkoxy (e.g., $-OCF_3$).

Suitable substituents for Phenyl Rings A' and A" are as described above for Rings B-Z.

Preferred substituents for Phenyl Ring A include halogen, $-OR_{10}$, $-R_{10}$, aromatic group, substituted aromatic group, aralkyl, substituted aralkyl, aralkenyl, substituted aralkenyl, allyl and substituted allyl and R_{10} is –H, an alkyl group (e.g., a C1-C10 alkyl group) or a halogenated alkyl group (e.g., a C1-C10 halogenated alkyl group). Specific examples of suitable substituents for Phenyl Ring A include -F, -Cl,

$-OCH_3$, $-OCF_3$, $-CH_3$, ethyl, *n*-propyl, *iso*-propyl, allyl, 2-phenylethenyl, 2-phenylethyl, phenyl, *-o*-biphenyl, *-m*-biphenyl, *-p*-biphenyl, *-o*-$C_6H_4OCH_3$, *-m*-$C_6H_4OCH_3$, *-p*-$C_6H_4OCH_3$, *-o*-C_6H_4F, *-m*-C_6H_4F and *-p*-C_6H_4F.

Another embodiment of the present invention is a compound represented by Structural Formula (XLII):



(XLII).

Ar and R_1 in Structural Formula (XLI) are as defined above in Structural Formulas (I) and (VI); s is 0, 1 or 2; Ar_1 is a substituted or unsubstituted arylene group; W_6 is a covalent bond, $-W_1-$, $-CH_2W_1-$ or $-W_1CH_2-$; W_7 is a covalent bond or $-CH_2-$ and W_1 is as defined above. Preferably R_1 is represented by Structural Formula (II), s is 0 or 1, Ar_1 is phenylene (*ortho*, *meta* or *para* substituted), W_7 is a covalent bond and W_1 is -O-. More preferably, Ar is represented by any one of Structural Formulas (XXVIII)-(XXXIX) and R_1 is represented by Structural Formulas (III) or (IV). Even more preferably, Ar is represented by Structural Formulas (XL) or (XLI) and R_1 is represented by Structural Formula (V).

Also included in the present invention are methods of treatment as described above, wherein the compound represented by Structural Formula (XLI) is administered as the therapeutic agent and the use of the compound for the manufacture of a medicament for the treatment of the PPAR mediated disorders described herein.

The following are specific examples of the compounds of the present invention:

(2*S*)-3-{4-[3-(Biphenyl-4-yloxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 1);

(2*S*)-3-{4-[3-(4-Benzoyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 2);

(2*S*)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-prop-1-ynyl]-phenyl}-propionic acid (Compound 3);

(2S)-3-{4-[3-(4-Fluoro-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 4);

(2S)-2-Methoxy-3-{4-[3-(3-phenyl-benzofuran-6-yloxy)-prop-1-ynyl]-phenyl}-propionic acid (Compound 5);

(2S)-3-{4-[3-(4-Butyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 6);

(2S)-2-Methoxy-3-(4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-prop-1-ynyl}-phenyl)-propionic acid (Compound 7);

(2S)-2-Methoxy-3-{4-[3-(9-oxo-9H-fluoren-2-yloxy)-prop-1-ynyl]-phenyl}-propionic acid (Compound 8);

(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-prop-1-ynyl]-phenyl}-propionic acid (Compound 9);

(2S)-3-(4-{3-[4-(2-Fluoro-benzoyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 10);

(2S)-2-Methoxy-3-{4-[3-(3-phenylamino-phenoxy)-prop-1-ynyl]-phenyl}-propionic acid (Compound 11);

(2S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 12);

(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-prop-1-ynyl]-phenyl}-propionic acid (Compound 13);

(2S)-3-(4-{3-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 14);

(2S)-2-Methoxy-3-(4-{3-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-prop-1-ynyl}-phenyl)-propionic acid (Compound 15);

(2S)-2-Methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-prop-1-ynyl]-phenyl}-propionic acid (Compound 16);

(2S)-3-{4-[3-(4-Benzyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 17);

(2S)-3-[4-(3-{4-[(2-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid (Compound 18);

(2S)-3-(4-{3-[4-(Hydroxyimino-phenyl-methyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 19);

(2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid (Compound 20);

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 21);

(2S)-2-Methoxy-3-{4-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 22);

(2S)-3-{4-[5-(4-Benzoyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 23);

(2S)-3-{4-[5-(4-Benzyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 24);

(2S)-3-(4-{5-[4-(4-Fluoro-benzoyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 25);

(2S)-2-Methoxy-3-(4-{5-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-pent-1-ynyl}-phenyl)-propionic acid (Compound 26);

(2S)-2-Methoxy-3-{4-[5-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 27);

(2S)-2-Methoxy-3-{4-[5-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 28);

(2S)-2-Methoxy-3-(4-{5-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-pent-1-ynyl}-phenyl)-propionic acid (Compound 29);

(2S)-2-Methoxy-3-{4-[5-(9-oxo-9H-fluoren-2-yloxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 30);

(2S)-2-Methoxy-3-{4-[5-(3-phenylamino-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 31);

(2S)-3-(4-{5-[4-(2-Fluoro-benzoyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 32);

(2S)-2-Methoxy-3-{4-[5-(3-phenyl-benzofuran-6-yloxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 33);

(2S)-3-(4-{5-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 34);

(2S)-2-Methoxy-3-{4-[5-(4-phenylacetyl-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 35);

(2S)-3-{4-[5-(4-Butyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 36);

(2S)-3-[4-(5-{4-[(2-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-pent-1-ynyl)-phenyl]-2-methoxy-propionic (Compound 37);

(2S)-3-[4-(5-{4-[(4-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid (Compound 38);

(2S)-3-(4-{5-[4-(Hydroxyimino-phenyl-methyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 39);

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 40);

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-but-1-ynyl]-phenyl}-propionic acid (Compound 41);

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 42);

(2S)-3-(4-{4-[4-(Hydroxyimino-phenyl-methyl)-phenoxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 43);

(2S)-3-(4-{4-[4-(4-Fluoro-benzoyl)-phenoxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 44);

(2S)-3-(4-{4-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid (Compound 45);

(2S)-2-Methoxy-3-(4-{4-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-but-1-ynyl}-phenyl)-propionic acid (Compound 46);

(2S)-2-Methoxy-3-{4-[4-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-but-1-ynyl]-phenyl}-propionic acid (Compound 47);

(2S)-2-Methoxy-3-{4-[4-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-but-1-ynyl]-phenyl}-propionic acid (Compound 48);

(2S)-2-Methoxy-3-{4-[6-(4-phenoxy-phenoxy)-hex-1-ynyl]-phenyl}-propionic acid (Compound 49);

(2S)-3-{4-[6-(4-Benzoyl-phenoxy)-hex-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 50);

(2S)-3-{4-[6-(Biphenyl-4-yloxy)-hex-1-ynyl]-phenyl}-2-methoxy-propionic acid (Compound 51);

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pentanoyl]-phenyl}-2-methoxy-propionic acid (Compound 52);

(2S)-3-{4-[5-(4-Benzoyl-phenoxy)-pentanoyl]-phenyl}-2-methoxy-propionic acid (Compound 53);

(2S)-2-Methoxy-3-{4-[5-(4-phenoxy-phenoxy)-pentanoyl]-phenyl}-propionic acid (Compound 54);

3-{4-[4-(4-Benzoyl-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid (Compound 55);

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butyryl]-phenyl}-propionic acid (Compound 56);

(2S)-3-[4-(Biphenyl-4-yloxy)-butyryl-phenyl]-2-methoxy-propionic acid (Compound 57);

(2S)-3-{4-[6-(Biphenyl-4-yloxy)-hexanoyl]-phenyl}-2-methoxy-propionic acid (Compound 58);

(2S)-2-Methoxy-3-{4-[6-(4-phenoxy-phenoxy)-hexanoyl]-phenyl}-propionic acid (Compound 59);

(2S)-3-{4-[6-(4-Benzoyl-phenoxy)-hexanoyl]-phenyl}-2-methoxy-propionic acid (Compound 60);

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-1-hydroxyimino-pentyl]-phenyl}-2-methoxy-propionic acid (Compound 61);

(2*S*, 1'*R**, 2'*S**)-3-(4-{2'-[4-(4-Fluoro-benzoyl)-phenoxy]-cyclopentyloxy}-phenyl)-2-methoxy-propionic acid (Compound 62);

(2S)-(1'R,3'R)-2-Methoxy-3-{4-[1',3'-dimethyl-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid (Compound 63);

(2S)-(1'*R*,3'*R*)-3-{4-[3-(4-Benzoylphenoxy)-1',3'-dimethylpropoxyl]-phenyl}2-methoxy-propionic acid (Compound 64);

(2S)-(1'*S*,3'*S*)-2-Methoxy-3-{4-[1',3'-dimethyl-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid (Compound 65);

(2S)-(1'*S*,3'*S*)-3-{4-[3-(4-Benzoylphenoxy)-1',3'-dimethylpropoxyl]-phenyl}2-methoxy-propionic acid (Compound 66);

(2S)-(1'*R*,2'*R*)-2-Methoxy-3-{4-[1',2'-dimethyl-(4-phenoxy-phenoxy)-ethoxyl]-phenyl}-propionic acid (Compound 67);

(2S)-(1'*R*,2'*R*)-3-{4-[1-(4-Benzoylphenoxy)-1',2'-dimethyl-ethoxyl]-phenyl}-2-methoxypropionic acid (Compound 68);

(2S)-(1'*S*,4'*S*)-2-Methoxy-3-{4-[1'-methyl-4'-(4-phenoxy-phenoxy)-pentyloxy]-phenyl}-propionic acid (Compound 69);

(2S)-(1'S,4'S)-3-{4-[4-(4-Benzoyl-phenoxy)-1-methyl-pentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 70);

(2S)-(1'*R*,4'*R*)-2-Methoxy-3-{4-[1'-methyl-4'-(4-phenoxy-phenoxy)-pentyloxy]-phenyl}-propionic acid (Compound 71);

(2S)-(1'*R*,4'*R*)-3-{4-[4-(4-Benzoyl-phenoxy)-1-methyl-pentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 72);

(2S)-(1'*S*,2'*S*)-2-Methoxy-3-{4-[1',2'-dimethyl-(4-phenoxy-phenoxy)-ethoxyl]-phenyl}-propionic acid (Compound 73);

(2S)-2-Methoxy-{4-[2-methylen-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid (Compound 74);

(2S)-2-Methoxy-{4-[2-oxo-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid (Compound 75);

(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxymethyl)-benzyloxy]-phenyl}-propionic acid (Compound 76);

(2S)-2-Methoxy-3-{4-[2-(4-phenoxy-phenoxymethyl)-benzyloxy]-phenyl}-propionic acid (Compound 77);

(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-phenoxy]-phenyl}-propionic acid (Compound 78);

(2S)3-[3'-(3-Benzoyl-phenoxymethyl)-biphenyl-4-yl]-2-methoxy-propionic acid (Compound 79);

(2S)-3-[4'-(4-Benzoyl-phenoxymethyl)-biphenyl-4-yl]-2-methoxy-propionic acid (Compound 80);

(2S)-(1'*R**,3'*R**)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 81);

(2S)-(1'*R**,3'*S**)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 82);

(2S)-(1'*R**,3'*R**)-2-Methoxy-3-{4-[3'-(4-phenoxy-phenoxy)-1'-cyclopentyloxy]-phenyl}-propionic acid (Compound 83);

(2S)-(1'*R**,3'*R**)-3-{4-[3-(4-Benzoyl-phenoxy)-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 84);

(2S)-(1'R*,3'R*)-2-Methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-cyclopentyloxy]-phenyl}-propionic acid (Compound 85);

(2S)-(1'*R*,3'*S*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 86);

(2S)-(1'*S*,3'*R*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 87);

(2S)-(1'*S*,3'*S*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 88);

(2S)-(1'*R*,3'*R*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid (Compound 89);

(2S)-(1'*R*,3'*S*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid (Compound 90);

(2S)-(1'*S*,3'*R*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid (Compound 91);

(2S)-(1'*R*,3'*R*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid (Compound 92);

(2S)-(1'S,3'*S*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid (Compound 93);

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 94);

(2S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 95);

(2S)-3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 96);

(2S)-2-Methoxy-3-{4-[3-(3-phenylamino-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 97);

(2S)-3-{4-[3-(4-Butyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 98);

(2S)-3-(4-{3-[4-(2-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 99);

(2S)-2-Methoxy-3-{4-[3-(9-oxo-9H-fluoren-2-yloxy)-propoxy]-phenyl}-propionic acid (Compound 100);

(2S)-2-Methoxy-3-{4-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic acid (Compound 101);

(2S)-2-Methoxy-3-{4-[3-(3-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 102);

(2S)-3-{4-[3-(Biphenyl-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 103);

(2S)-3-{4-[3-(4-Cyclopentyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 104);

(2S)-3-{4-[3-(4-Cyano-3-fluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 105);

(2S)-3-{4-[3-(2,4-Difluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 106);

(2S)-2-Methoxy-3-{4-[3-(4-trifluoromethyl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 107);

(2S)-2-Methoxy-3-{4-[3-(3-trifluoromethyl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 108);

(2S)-2-Methoxy-3-{4-[3-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (Compound 109);

(2S)-3-{4-[3-(3,5-Difluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 110);

(2S)-3-{4-[3-(Isoquinolin-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 111);

(2S)-2-Methoxy-3-{4-[3-(4-trifluoromethoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 112);

(2S)-3-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 113);

(2S)-2-Methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 114);

(2S)-2-Methoxy-3-(4-{3-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 115);

(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-propoxy]-phenyl}-propionic acid (Compound 116);

4-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid benzyl ester (Compound 117);

(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-chroman-6-yloxy)-propoxy]-phenyl}-propionic acid (Compound 118);

(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-chroman-6-yloxy)-propoxy]-phenyl}-propionic acid (Compound 119);

(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-chroman-7-yloxy)-propoxy]-phenyl}-propionic acid (Compound 120);

(2S)-2-Methoxy-3-(4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 121);

(2S)-3-{4-[2-(4-benzoyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 122);

(2S)-3-{4-[2-(Biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound123);

(2S)-3-{4-[2-(Biphenyl-4-yloxy)-acetyl]-phenyl}-2-methoxy-propionic acid (Compound 124);

(2S)-2-Methoxy-3-{4-[2-(4-phenoxy-phenoxy)-acetyl]-phenyl}-propionic acid (Compound 125);

(2S)-3-{4-[2-(4-Benzoyl-phenoxy)-acetyl]-phenyl}-2-methoxy-propionic acid (Compound 126);

(2S)-3-{4-[3-(Biphenyl-4-yloxy)-propyl]-phenyl}-2-methoxy-propionic acid (Compound 127);

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-butyl]-phenyl}-2-methoxy-propionic acid (Compound 128);

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pentyl]-phenyl}-2-methoxy-propionic acid (Compound 129);

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methoxy-propionic acid (Compound 130);

3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-3-methoxy-phenyl)-2-methoxy-propionic acid (Compound 131);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid (Compound 132);

2-Methoxy-3-{3-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 133);

(2S)-3-(4-[3-(Biphenyl-4-yloxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid (Compound 134);

3-{3-Chloro-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 135);

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid (Compound 136);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3,5-dichloro-phenyl}-2-methoxy-propionic acid (Compound 137);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-2-methoxy-propionic acid (Compound 138);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-trifluoromethyl-phenyl}-2-methoxy-propionic acid (Compound 139);

(2S)-3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-4'-methoxy-biphenyl-3-yl}-2-methoxy-propionic acid (Compound 140);

3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-4'-fluoro-biphenyl-3-yl}-2-methoxy-propionic acid (Compound 141);

3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-[1,1';4',1"] terphenyl-3-yl}-2-methoxy-propionic acid (Compound 142);

3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-2'-methoxy-biphenyl-3-yl}-2-methoxy-propionic acid (Compound 143);

2-Methoxy-3-{6-[3-(4-phenoxy-phenoxy)-propoxy]-[1,1';4',1"]terphenyl-3-yl}-propionic acid (Compound 144);

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-styryl-phenyl}-2-methoxy-propionic acid (Compound 145);

3-(4-{3-[4-(Hydroxy-phenyl-methyl)-phenoxy]-propoxy}-3-phenethyl-phenyl)-2-methoxy-propionic acid (Compound 146);

3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-3-phenethyl-phenyl}-2-methoxy-propionic acid (Compound 147);

(2S)-3-{3-Allyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 148);

(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-3-propyl-phenyl}-propionic acid (Compound 149);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-acrylic acid (Compound 150);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-propionic acid (Compound 151);

3-{3-[3-(Biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 152);

'2-Methoxy-3-{3-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 153);

3-{3-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 154);

2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid (Compound 155);

2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pentyl]-phenyl}-propionic acid (Compound 156);

2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pentanoyl]-phenyl}-propionic acid (Compound 157);

3-{4-[3-(3-Allyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 158);

(2S)-2-Methoxy-3-{4-[3-(3-propyl-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid (Compound 159);

(2S)-3-{4-[3-(2-Allyl-4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 160);

(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-2-propyl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 161);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid (Compound 162);

2-Methoxy-3-{3-methyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 163);

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid (Compound 164);

(2S)-3-{4-[3-(Dibenzofuran-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 165);

(2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid (Compound 166);

(2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxy-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid (Compound 167);

(2S)-2-Methoxy-3-(4-{3-[4-(4-piperidin-1-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 168);

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-morpholin-4-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 169);

(2*S*)-3-(4-{3-[4-(4-Hydroxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 170);

2S-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid sodium salt (Compound 171);

(2S)-3-[4-(3-{4-[Hydroxyimino-(4-hydroxy-phenyl)-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid (Compound 172);

(2S)-3-{4-[3-(4-Benzoyl-3-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 173);

(2S)-3-(4-{3-[4-(2,4-Dimethoxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 174);

3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid (Compound 175);

(*S*)-3-(4-benzyloxy-phenyl)-2-isopropoxy-propionic acid (Compound 176);

2S-2-isopropoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid sodium salt (Compound 176A);

2-Methoxy-3-{3-methoxy-4-[3-(4-phenylacetyl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 177);

3-{4-[3-(4-Butoxy-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid (Compound 178);

2-Methoxy-3-{3-methoxy-4-[3-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-propoxy]-phenyl}-propionic acid (Compound 179);

2-Methoxy-3-(3-methoxy-4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 180);

3-{4-[3-(4-Benzyloxy-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid (Compound 181);

3-{4-[3-(4-Dibenzofuran-3-yl-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid (Compound 182);

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-butoxy]-phenyl}-2-methoxy-propionic acid (Compound 183);

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-butoxy]-phenyl}-2-methoxy-propionic acid (Compound 184);

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butoxy]-phenyl}-propionic acid (Compound 185);

(2S)-2-Methoxy-3-{4-[2-(2,3,6-trifluoro-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 186);

(2S)-3-[4-(3-Benzyloxy-benzyloxy)-phenyl]-2-methoxy-propionic acid (Compound 187);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methoxy-phenyl}-2-methoxy-propionic acid (Compound 188);

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-methoxy-phenyl}-2-methoxy-propionic acid (Compound 189);

2-Methoxy-3-{2-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 190);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid (Compound 191);

3-{2-Chloro-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 192);

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid (Compound 193);

(2S)-4-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (Compound 194);

(2S)-3-{4-[3-(4-Dibenzothiophen-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 195);

(2S)-3-{4-[3-(4'-Hydroxy-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 196);

(2S)-4'-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid (Compound 197);

(2S)-3-{4-[2-(4-Benzoyl-phenoxy)-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid (Compound 198);

(2S)-3-(4-{2-[4-(4-Fluoro-benzoyl)-phenoxy]-cyclohexyloxy}-phenyl)-2-methoxy-propionic acid (Compound 199);

(2S)-3-(4-{3-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 200);

(2S)-2-Methoxy-3-{4-[3-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (Compound 201);

(2S)-3-{4-[3-(4-Benzyloxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 202);

(2S)-3-{4-[3-(4-Butoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 203);

(2S)-3-{4-[3-(4-Heptyloxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 204);

(2S)-3-{4-[3-(6-Benzoyl-naphthalen-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 205);

(2S)-3-{4-[3-(Benzo[1,3]dioxol-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 206);

(2S)-3-{4-[3-(9H-Fluoren-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 207);

(2S)-2-Methoxy-3-{4-[3-(4-octyl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 208);

(2S)-2-Methoxy-3-{4-[3-(naphthalen-1-yloxy)-propoxy]-phenyl}-propionic acid (Compound 209);

(2S)-3-{4-[3-(1H-Indol-7-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 210);

(2S)-3-{4-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 211);

(2S)-3-{4-[3-(4'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 212);

(2S)-3-{4-[3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 213);

(2S)-3-{4-[3-(4-Dibenzofuran-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 214);

(2*S*)-2-Methoxy-3-{4-[3-(4'-phenoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid (Compound 215);

(2*S*)-2-Methoxy-3-{4-[3-(4-thiophen-2-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 216);

(2*S*)-3-{4-[3-(3'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 217);

(2*S*)-3-{4-[3-(2'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 218);

(2*S*)-3-{4-[3-(2'-Fluoro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 219);

(2*S*)-3-{4-[3-(4-Benzo[1,3]dioxol-5-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 220);

(2*S*)-3-{4-[3-(4'-tert-Butyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 221);

(2*S*)-2-Methoxy-3-{4-[3-(3'-trifluoromethoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid (Compound 222);

(2*S*)-2-Methoxy-3-{4-[3-(4'-trifluoromethoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid (Compound 223);

(2*S*)-3-(4-{3-[4-(2-Chloro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 224);

(2*S*)-2-Methoxy-3-(4-{3-[4-(2-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 225);

(2*S*)-3-(4-{3-[4-(2,2-Dimethyl-propionylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 226);

(2*S*)-3-(4-{3-[4-(3-Fluoro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 227);

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 228);

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methyl-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 229);

(2*S*)-3-(4-{3-[4-(4-Fluoro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 230);

(2*S*)-3-(4-{3-[4-(4-Chloro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 231);

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 232);

(2*S*)-2-Methoxy-3-{4-[3-(4-phenylacetylamino-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 233);

(2*S*)-3-(4-{3-[4-(2-Chloro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 234);

(2*S*)-2-Methoxy-3-(4-{3-[4-(naphthalene-1-carbonyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 235);

(2*S*)-3-(4-{3-[4-(3-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 236);

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methoxy-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 237);

(2*S*)-2-Methoxy-3-(4-{3-[4-(naphthalene-2-carbonyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 238);

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-methyl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 239);

(2*S*)-3-(4-{3-[4-(2,2-Dimethyl-propionyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 240);

(2*S*)-3-{4-[3-(4-Isobutyryl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 241);

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-phenyl-propionyl)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 242);

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-propionic acid (Compound 243);

2-phenoxy-3-[4-(4-phenoxy-phenoxy)propoxyphenyl]propanoic acid (Compound 244);

(2S,2'S)-3-(4-{3-[4-(2'-Carboxy-2'-methoxy-ethyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 245);

α-Methoxycinnamate intermediate, ethyl 2*S*-2-methoxy-3-(4-hydroxyphenyl) propanoate (Compound 246);

2*S*-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid (Compound 247);

(2*S*)-(2'*RS*)-2-Methoxy-{4-[2'-methyl-3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 248);

2(S)-3-[4-(3-Benzyloxy-propoxy)-phenyl]-2-methoxypropionic acid (Compound 249);

(2S)-3-[4-(5-Benzyloxy-pentyloxy)-phenyl]-2-methoxypropionic acid (Compound 250);

(2S)-2-ethoxy-{4-[3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid (Compound 251);

(2S)-2-Benzyloxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 252);

(2S)-3-{4-[3-(4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzoyl}-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 253);

(2S)- 3-[4-(3-{4-[4-(2-Hydroxy-ethoxy)-benzoyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid (Compound 254);

(2S)-3-{4-[3-(4-Phenoxy-phenoxy)-propoxy]-phenyl}-2-propoxy-propionic acid (Compound 255);

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid (Compound 256);

(2S)- 3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid (Compound 257);

(2*S*)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-ethoxy-propionic acid (Compound 258);

(2*S*)-4'-{3-[4-(2-Carboxy-2-methoxy-ethyl)-2-methoxy-phenoxy]-propoxy}-biphenyl-4-carboxylic acid (Compound 259);

(2*S*)-3-{4-[3-(4'-*tert*-Butyl-biphenyl-4-yloxy)-propoxy]-2-methoxy-propionic acid (Compound 260);

(2*S*)-3-(4-{3-[4-(4-Hydroxy-phenoxy)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 261);

(2*S*)-2-Methoxy-3-(4-{3-[4-(2,2,3,3-tetrafluoro-propoxy)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 262);

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methyl-butoxy)-phenoxy]-propoxy}-phenyl)-propionic acid (Compound 263);

(2*S*)-3-{4-[3-(4-Isobutoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 264);

(2*S*)-3-{4-[3-(4-Isopropoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 265);

(2*S*)-3-{4-[3-(4-Cyclohexylmethoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 266);

(2*S*)-2-Methoxy-3-{4-[3-(4-phenetyloxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 267);

(2*S*)-3-(4-{3-[4-(3-Dimethylamino-propoxy)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 268);

(2*S*)-3-{4-[3-(4-Carboxymethoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 269);

(2*S*)-3-(4-{3-[4-(1H-Indol-5-yl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 270);

(2*S*)-2-Methoxy-3-{4-[3-(4-pyridin-3-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 271);

(2*S*)-2-Methoxy-3-{4-[3-(4-pyridin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 272);

(2*S*)-2-Methoxy-3-{4-[3-(4-quinolin-8-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 273);

(2*S*)-3-{4-[3-(4'-Cyano-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 274);

(2*S*)-2-Methoxy-3-(4-{3-[4'-(1*H*-tetrazol-5-yl)biphenyl-4-yloxy]-propoxy}-phenyl)-propionic acid (Compound 275);

(2*S*)-3-{4-[3-(4-Imidazol-1-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 276);

(2*S*)-3-(4-{3-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 277);

(2*S*)-3-(4-{3-[4-(4-Acetyl-piperazin-1-yl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Compound 278);

(2*S*)-2-Methoxy-3-{4-[3-(4-piperazin-1-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 279);

(2*S*)-2-Methoxy-3-{4-[3-(4-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 280);

(2*S*)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-ethoxy-propionic acid (Compound 281);

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-chloro-phenyl}-2-ethoxy-propionic acid (Compound 282);

(2*S*)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 283);

(2*S*)-2-methoxy-3-{4-[3-(3-trifluoromethyl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 284);

(2*S*)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Compound 285);

(2*S*)-3-{4-[3-(biphenyl-3-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 286);

(2*S*)-2-methoxy-3-{4-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic (Compound 287);

(2S)-2-methoxy-3-{4-[3-(3-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 288);

(2S)-2-methoxy-3-{4-[3-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (Compound 289);

2-methoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 290);

3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 291);

3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Isomer 2) (Compound 292);

(2S)-3-{4-[3-(2-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 293);

(2S)-2-methoxy-3-{4-[3-(2-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 294);

(2S)-2-{3-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (Compound 295);

(2S)-3-{4-[3-(3-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 296);

(2S)-3-{4-[3-(3-dimethylamino-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 297);

(2S)-3-{3-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (Compound 298);

(2S)-3-{4-[3-(indan-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 299);

(2S)-2-methoxy-3-{4-[3-(naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (Compound 300);

(2S)-3-{4-[3-(1H-indol-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 301);

(2S)-2-methoxy-3-{4-[3-(quinolin-6-yloxy)-propoxy]-phenyl}-propionic acid (Compound 302);

(2S)-2-methoxy-3-{4-[3-(3-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (Compound 303);

(2S)-3-{4-[3-(3-fluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 304);

(2S)-3-{4-[3-(2-isopropyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Compound 305);

(2S)-2-methoxy-3-[4-(2-phenoxy-ethoxy)-phenyl]-propionic acid (Compound 306);

(2S)-3-{4-[2-(2-cyano-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 307);

(2S)-2-methoxy-3-{4-[2-(2-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 308);

(2S)-3-{4-[2-(biphenyl-2-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 309);

(2S)-2-{2-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-ethoxy}-benzoic acid (Compound 310);

(2S)-3-{4-[2-(2-isopropyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 311);

(2S)-3-{4-[2-(3-cyano-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 312);

(2S)-3-{4-[2-(3-dimethylamino-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic (Compound 313);

(2S)-3-{4-[2-(biphenyl-3-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 314);

(2S)-3-{2-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-ethoxy}-benzoic acid (Compound 315);

(2S)-3-{4-[2-(indan-5-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 316);

(2S)-2-methoxy-3-{4-[2-(naphthalen-2-yloxy)-ethoxy]-phenyl}-propionic acid (Compound 317);

(2S)-2-Methoxy-3-{4-[2-(quinolin-6-yloxy)-ethoxy]-phenyl}-propionic acid (Compound 318);

(2S)-2-Methoxy-3-{4-[2-(3-morpholin-4-yl-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 319);

(2S)-2-methoxy-3-{4-[2-(2-methyl-benzothiazol-5-yloxy)-ethoxy]-phenyl}-propionic (Compound 320);

(2S)-2-methoxy-3-{4-[2-(3-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 321);

(2S)-3-{4-[2-(3-fluoro-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 322);

2-methoxy-3-[3-(3-phenoxy-propoxy)-phenyl]-propionic acid (isomer 1) (Compound 323);

3-{3-[3-(2-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 324);

3-{3-[3-(3-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 325);

2-methoxy-3-[3-(3-phenoxy-propoxy)-phenyl]-propionic acid (isomer 2) (Compound 326);

3-{3-[3-(2-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 327);

3-{3-[3-(3-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 328);

2-methoxy-3-{3-[3-(2-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 1) (Compound 329);

2-methoxy-3-{3-[3-(2-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 2) (Compound 330);

3-{3-[3-(2-isopropyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 331);

3-{3-[3-(2-isopropyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 332);

3-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer 1) (Compound 333);

3-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer2) (Compound 334);

2-methoxy-3-{3-[3-(3-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 1) (Compound 335);

2-methoxy-3-{3-[3-(3-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 2) (Compound 336);

2-methoxy-3-{3-[3-(naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (isomer 1) (Compound 337);

2-methoxy-3-{3-[3-(naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (isomer 2) (Compound 338);

2-methoxy-3-{3-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic acid (isomer 1) (Compound 339);

2-methoxy-3-{3-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic acid (isomer 2) (Compound 340);

3-{3-[3-(2-chloro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 341);

3-{3-[3-(2-chloro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 342);

3-{3-[3-(3,4-dimethyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 343);

3-{3-[3-(3,4-dimethyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 344);

2-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer 1) (Compound 345);

2-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer 2) (Compound 346);

3-{3-[3-(biphenyl-3-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 347);

3-{3-[3-(biphenyl-3-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 348);

2-methoxy-3-{3-[3-(quinolin-6-yloxy)-propoxy]-phenyl}-propionic acid (isomer 1) (Compound 349);

2-methoxy-3-{3-[3-(quinolin-6-yloxy)-propoxy]-phenyl}-propionic acid (isomer 2) (Compound 350);

3-{3-[2-(2-isopropyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 351);

2-methoxy-3-{3-[2-(3-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (isomer 1)(Compound 352);

3-{3-[2-(3-fluoro-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (isomer 1) (Compound 353);

2-methoxy-3-{3-[2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-ethoxy]-phenyl}-propionic acid (isomer 1) (Compound 354);

2-methoxy-3-{3-[2-(3-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (isomer 2) (Compound 355);

3-{3-[2-(3-fluoro-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (isomer 2) (Compound 356);

2-methoxy-3-{3-[2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-ethoxy]-phenyl}-propionic acid (isomer 2) (Compound 357);

(2S)-2-methoxy-3-{4-[2-(4-trifluoromethyl-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 358);

(2S)-2-methoxy-3-(4-{2-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-ethoxy}-phenyl)-propionic acid (Compound 359);

(2S)-3-{4-[2-(4-benzyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 360);

(2S)-2-methoxy-3-{4-[2-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-ethoxy]-phenyl}-propionic acid (Compound 361);

(2S)-3-{4-[2-(4-cyclopentyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 362);

(2S)-3-{4-[2-(9H-fluoren-2-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 363);

(2S)-3-{4-[2-(4-butyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 364);

(2S)-3-{4-[2-(2'-fluoro-biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 365);

(2S)-3-(4-{2-[4-(2,2-dimethyl-propionyl)-phenoxy]-ethoxy}-phenyl)-2-methoxy-propionic acid (Compound 366);

3-(4-{2-[4-(2,2-dimethyl-propionylamino)-phenoxy]-ethoxy}-phenyl)-2-methoxy-propionic acid (Compound 367);

(2S)-3-(4-{2-[4-(cyclopentanecarbonyl-amino)-phenoxy]-ethoxy}-phenyl)-2-methoxy-propionic acid (Compound 368);

(2S)-3-[4-(2-{4-[(furan-2-carbonyl)-amino]-phenoxy}-ethoxy)-phenyl]-2-methoxy-propionic acid (Compound 369);

(2S)-2-methoxy-3-[4-(2-{4-[(pyridine-3-carbonyl)-amino]-phenoxy}-ethoxy)-phenyl]-propionic acid (Compound 370);

(2S)-2-methoxy-3-{4-[2-(2-pyrrolidin-1-yl-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 371);

(2S)-2-methoxy-3-{4-[2-(pyridin-2-yloxy)-ethoxy]-phenyl}-propionic acid (Compound 372);

(2S)-2-methoxy-3-{4-[2-(2-morpholin-4-yl-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 373);

(2S)-3-{4-[2-(4'-tert-butyl-biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Compound 374);

(2S)-2-ethoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 375);

(2R)-2-ethoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (Compound 376);

(2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-propoxy-propionic acid (Compound 377);

3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-ethoxy-propionic acid (isomer 1) (Compound 378);

3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-ethoxy-propionic acid (isomer 2) (Compound 379).

The present invention also includes compounds represented by Structural Formula (I), wherein Ar is the corresponding aromatic group from any one of Compounds 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formulas (I) or (VI), wherein Phenyl Ring A is the corresponding phenyl or substituted phenyl group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_3-O-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_4-O-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_5-O-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379.

Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-CH_2-C\equiv CH-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_2-C\equiv CH-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_3-C\equiv CH-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_4-C\equiv CH-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

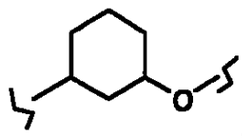
Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_5-C\equiv CH-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379.

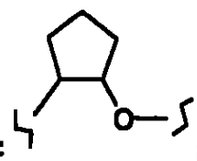
Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-CH_2CO-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_2CO-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is $-(CH_2)_3CO-$ and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is represented by the following structural formula:  ; and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein W is represented by the following structural formula:  ; and Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W, W_1 or W_2 and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein Ar-O-W- is the corresponding group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379. Preferably, R_1 is *para* to the carbon atom bonded to W and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379, W is $-CH(CH_3)W_3CH(CH_3)O-$ and W_3 is a covalent bond, methylene or ethylene. Preferably, R_1 is *para* to the carbon atom bonded to W and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Also included are compounds represented by Structural Formula (I), wherein Ar is the corresponding aromatic group from any one of Compounds 1-379 or from one of the compounds disclosed in Examples 1-379, W is $-W_4C(=O)W_5O-$ or $-W_4C(=CH_2)W_5O-$ and W_4 and W_5 are independently methylene or ethylene. Preferably, R_1 is *para* to the carbon atom bonded to W and is represented by Structural Formula (II), more preferably Structural Formula (III) or (IV) and even more preferably Structural Formula (V).

Prodrugs are compounds of the present invention, which have chemically or metabolically cleavable groups and become by solvolysis or under physiological

conditions the compounds of the invention that are pharmaceutically active *in vivo*. Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

Methyl ester prodrugs may be prepared by reaction of the acid form of a compound of the present invention in a medium such as methanol with an acid or base esterification catalyst (e.g., NaOH, H_2SO_4). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol.

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of the present invention (in a medium such as dimethylformamide) with 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients and salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof. Pharmaceutical formulations of the present invention are prepared by procedures known in the art using well-known and readily available ingredients.

Also included in the present invention are pharmaceutically acceptable salts, hydrates, stereoisomers and solvates of the compounds of the present invention and mixtures of such compounds, salts, hydrates, stereoisomers and/or solvates.

By virtue of its acidic moiety, certain compounds of the present invention form salts with pharmaceutically acceptable bases. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and

potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, and basic amino acid such as lysine and arginine. These salts may be prepared by methods known to those skilled in the art.

Compounds of the present invention that are substituted with a basic group, may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as glutamic acid.

Certain compounds of the present invention may contain one or more chiral centers, and exist in different optically active forms. When compounds of the present invention contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired

enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of the present invention has one or more chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of such compounds and mixtures thereof.

Certain compounds of the present invention may exist in zwitterionic form and the present invention includes each zwitterionic form and mixtures thereof.

Certain compounds of the present invention and their salts may exist in more than one crystal form. Polymorphs of compounds of the present invention form part of this invention and may be prepared by crystallization of a given compound under different conditions. For example, using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting a compound of the present invention followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

"Treatment" or "treating", as it is used herein, refers to both therapeutic treatment and prophylactic treatment. "Therapeutic treatment" refers to preventing the further progression or ameliorate the symptoms associated with a disease or condition. "Prophylactic treatment" refers to inhibiting, preventing or delaying the

onset of the symptoms of a disease or condition in a subject who is at risk for the disease or condition. "Prophylactic treatment" also includes reducing the severity of the symptoms of a disease or condition by treating a subject at risk for developing the disease or condition before symptoms appear.

The language an "effective amount" or "pharmaceutically effective amount" is intended to include an amount that is sufficient to mediate a disease or condition and prevent its further progression or ameliorate the symptoms associated with the disease or condition. An "effective amount" or "pharmaceutically effective amount" can also include an amount sufficient to prevent or delay the onset of a disease or condition in a patient at risk for developing the disease or condition, i.e., prophylactic treatment. Such amount when administered prophylactically to a patient can also be effective to lessen the severity of the mediated condition. Such an amount is intended to include an amount that is sufficient to modulate a PPAR receptor, such as a PPARγ or PPARα receptor, which mediate a disease or condition. Conditions mediated by PPARα or PPARγ receptors include diabetes mellitus, cardiovascular disease, Syndrome X, obesity and gastrointestinal disease. Other such diseases are described below.

The compounds of the present invention and the pharmaceutically acceptable salts, solvates, stereoisomers and hydrates thereof have valuable pharmacological properties and can be used in pharmaceutical preparations containing the compound or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or diluent. They are useful as therapeutic substances in r treating (therapeutically or prophylactically) hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease (especially atherosclerosis)or other diseases where insulin resistance is a component or other diosorders mediated by a PPAR receptor. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound

will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein. Techniques for formulation and administration of the compounds of the instant invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995).

For oral administration, the compound or salts thereof can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, pills, powders, syrups, solutions, suspensions and the like.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacias, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, a lubricant such as magnesium stearate; and a sweetening agent such as sucrose lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained.

The active compounds can also be administered intranasally as, for example, liquid drops or spray. For oral or nasal inhalation, the compounds for use according to the present invention are conveniently delivered in the form of a dry powder inhaler, or an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable

gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

For parental administration the compounds of the present invention, or salts thereof can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically acceptable salts of the compounds. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that each syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against any contamination. The carrier can be solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition, to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation, for example, subcutaneously or intramuscularly or by intramuscular injection. Thus, for example, as an emulsion in an acceptable oil, or

ion exchange resins, or as sparingly soluble derivatives, for example, as sparingly soluble salts.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated.

When used herein Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the therapeutic treatment and/or prophylaxis of any one of or any combination of the following: hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease (especially atherosclerosis)or other diseases where insulin resistance is a component or other diosorders mediated by a PPAR receptor.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of the present invention and one or more additional active agents, as well as administration of a compound of the present invention and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of an insulin secretogogue such as biguanides, thiazolidinediones, sulfonylureas, insulin, or α-glucosidose inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, a compound of the present invention and one or more additional active agents can be

administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially. Combination therapy is understood to include all these regimens.

An example of combination therapeutic or prophylactic treatment of atherosclerosis may be wherein a compound of the present invention or a salt thereof is administered in combination with one or more of the following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As noted above, the compounds of the present invention can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating (therapeutically or prophylactically) diabetes and related disorders wherein the compounds of the present invention and salts thereof can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating atherosclerosis.

Other examples of therapeutic agents which can be used in combination with the compounds of the present invention include insulin sensitizers, PPARγ agonists, glitazones, troglitazone, pioglitazone, englitazone, MCC-555, BRL 49653, biguanides, metformin, phenformin, insulin, insulin minetics, sufonylureas, tolbutamide, glipizide, alpha-glucosidase inhibitors, acarbose, cholesterol lowering agent, HMG-CoA reductase inhibitors, lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, rivastatin, other statins, sequestrants, cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran, nicotinyl alcohol, nicotinic acid, a nicotinic acid salt, PPARα agonists, fenofibric acid derivatives, gemfibrozil, clofibrate, fenofibrate, benzafibrate, inhibitors of cholesterol absorption, beta-sitosterol, acyl CoA:cholesterol acyltransferase inhibitors, melinamide, probucol, PPARδ agonists, antiobesity compounds, fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, and ileal bile acid transporter inhibitors.

An effective amount of a compound of the present invention can be used for the preparation of a medicament useful for treating (therapeutic and prophylactic) hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease (especially atherosclerosis), lowering tryglyceride levels, raising the plasma level of high density lipoprotein or other diseases where insulin resistance is a component or other diosorders mediated by a PPAR receptor. Included is treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, an effective amount of a compound of the present invention (1) reduces serum glucose levels of a patient, or more specifically HbA1c, typically by about 0.7%; (2) reduces the serum triglyceride levels of a patient, typically by about 20 %; and/or (3) increases the serum HDL levels in a patient, preferably about 30 %.

Additionally, an effective amount of a compound of the present invention and an effective amount of one or more of the active agents listed above can be used together for the preparation of a medicament useful for the above-described treatments.

Preferably compounds of the invention or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be any unit dosage form known in the art including, for example, a capsule, an IV bag, a tablet, or a vial. The quantity of active ingredient (viz., a compound of the present invention or salts thereof) in a unit dose of composition is a therapeutically effective amount and may be varied according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration

that may be by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) an effective amount of a compound of the invention together with a pharmaceutically acceptable carrier or diluent. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients.

In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier that may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilized solid or paste, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of about 0.05 to about 5.0 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution.

Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substance that may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Advantageously, compositions containing the compound of the present invention or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of the compound or compounds of the present invention actually to be administered will be determined by a physician, in the light of all the relevant circumstances.

Powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient that is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active Ingredient", refers to a compound according to the present invention or salts thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Active Ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The Active Ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The Active Ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of Active Ingredient, are made as follows:

Active Ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The Active Ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of Active Ingredient, are made as follows:

Active Ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The Active Ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of Active Ingredient per 5 ml dose, are made as follows:

Active Ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active Ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

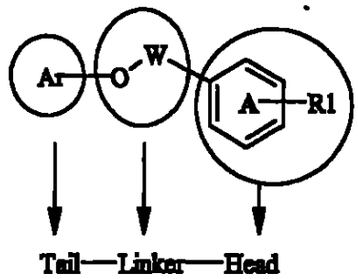
An intravenous formulation may be prepared as follows:

Active Ingredient	100 mg
Isotonic saline	1,000 ml

The solution of the above materials generally is administered intravenously to a subject at a rate of 1 ml per minute.

The compounds of the present invention, in general, may be prepared according to the Reaction Schemes described below. When describing various aspects of the present compounds, the terms "Tail", "Linker" and "Head" are used as their concept is illustrated below in General Reaction Scheme.

General Reaction Scheme



A) Tail—OH + Y_1—Linker'—Head ⟶ Tail—Linker—Head

B) Y_1—Linker'—Y_2 + Y_3—Head ⟶ Y_1—Linker'—Head

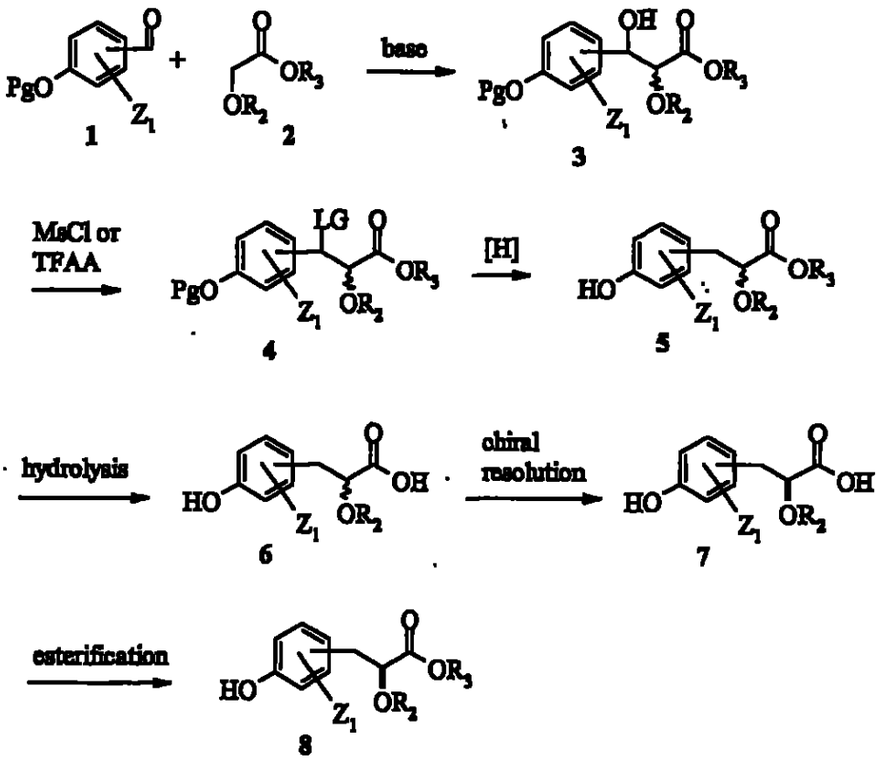
C) Tail—Linker'—Y_2 + Y_3—Head ⟶ Tail—Linker—Head

D) Tail—OH + Y_1—Linker'—Y_2 ⟶ Tail—Linker'—Y_2

Y_1 = OH or LG (leaving grp)
Y_2 = Y_1 or H
Y_3 = OH, OTf, or I
Linker' = Linker modified to accomodate Y substitution

As shown in General Reaction Scheme, the compounds of the present invention can be divided into three regions designated as Tail, Linker and Head. By a retrosynthetic analysis, key bond disconnections occur between each of these 3 regions. According to route A, a nucleophilic tailpiece is coupled to an electrophilic compound linker-headpiece, which in turn is derived by coupling the linker region with the headpiece by route B. Alternately according to route C, the headpiece can be coupled to the compound tailpiece-linker, derived by coupling the nucleophilic tailpiece with the electophilic linker by route D. The following reaction schemes illustrate more detailed synthetic routes to prepare the compounds of the present invention.

Reaction Scheme A: Synthesis of Head Piece

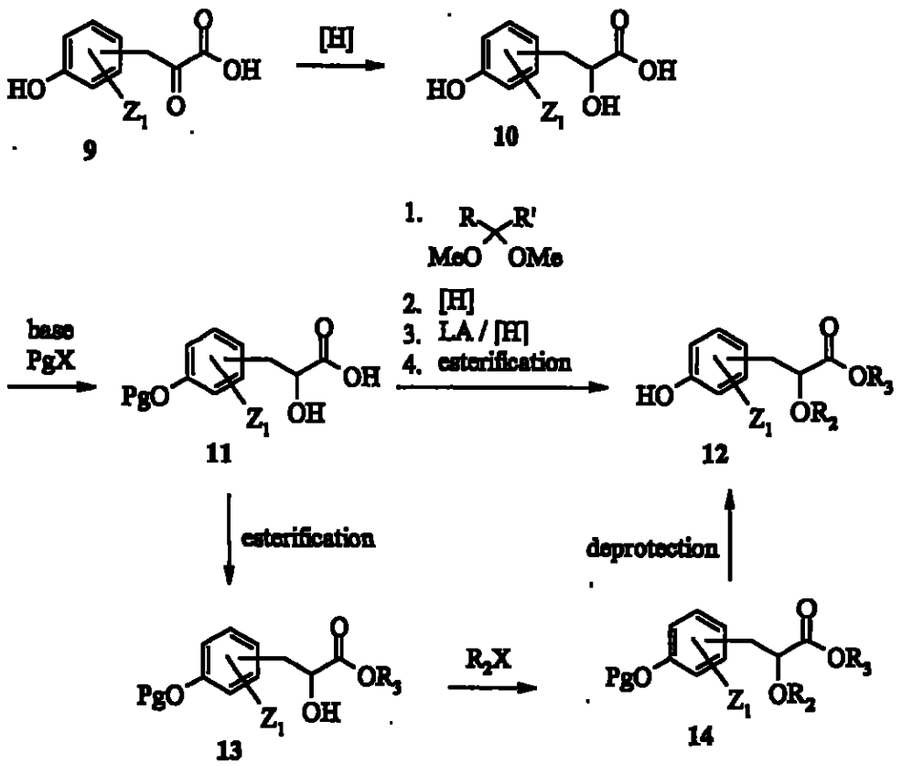


Z_1 = H, aliphatic, aralkyl, heteroalkylene, alkoxy, halo, haloalkyl
Pg = protecting group, such as CH_3 or $PhCH_2$

Reaction Scheme A shows the preparation of a general headpiece of the present compounds. Condensation of an aromatic aldehyde (1) with an alpha-alkoxyacetic acid ester (2) in the presence of a suitable base, such as lithium bis(trimethylsilyl)amide yields hydroxyester (3). The free hydroxyl group is converted into a leaving group by treatment with either methanesulfonyl chloride or trifluoroacetic anhydride. When the aromatic alcohol is protected as a benzyl ether (Pg is $PhCH_2$), exhaustive hydrogenolysis using hydrogen over Pd/C yields compound (5). Ester hydrolysis of (5) using aqueous hydroxide solution affords acid compound (6), which can be resolved into the corresponding enantiomers by using an appropriate chiral amine, such as (-)-cinchonidine. The acid (7) can be esterified

using the appropriate alcohol under acidic conditions, such as ethanol and sulfuric acid, or an alkyl halide under basic conditions, such as cesium carbonate in DMF to give compound (8).

Reaction Scheme B: Synthesis of Head Piece

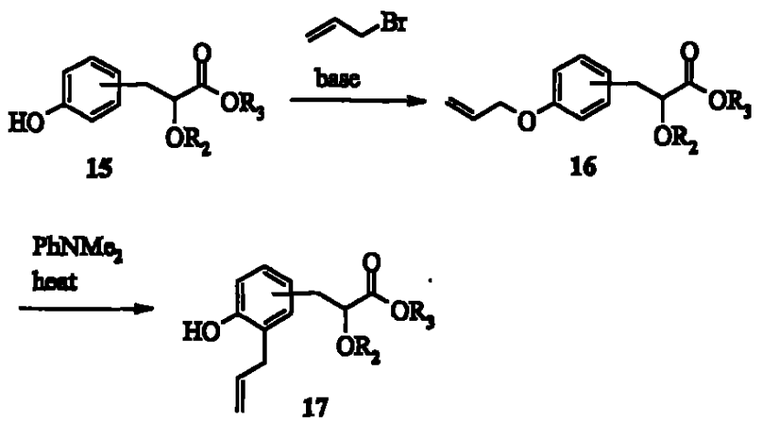


R, R' = H or alkyl

An alternate route to the headpiece is shown in Reaction Scheme B. The ketone function of ketoacid (9) is subjected to a reducing agent, such as *B*-chloro-diisopinocampheylborane, to give hydroxyacid (10). The phenolic hydroxyl group is then protected with the protecting group to give compound (11). The compound (11) reacted with a dimethyl ketal followed by phenol ether cleavage gives an dioxolanone intermediate, which affords a 2-alkoxyacid upon treatment with a suitable Lewis acid, such as $TiCl_4$ and a reducing reagent, such as a trialkylsilane.

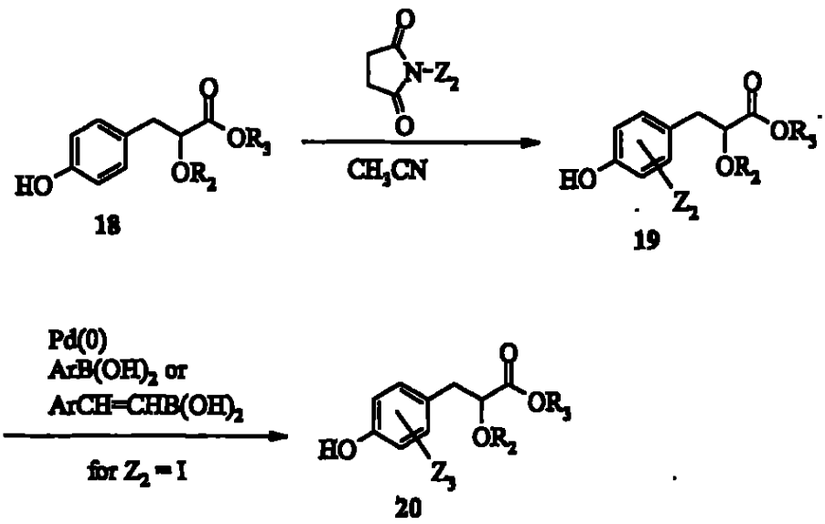
Esterification yields 2-alkoxyester (12). Alternatively, acid (11) can be esterified to yield ester (13), which can be treated with an electrophile such as an alkyl halide, and an additive such as NaH or silver (I) oxide to afford ether compound (14).

Reaction Scheme C: Synthesis of Head Piece



As shown in Reaction Scheme C, a Claisen rearrangement can be used to alkylate the headpiece. Aryl alcohol (15) is treated with an allyl bromide in the presence of a suitable base, such as NaH to give allyl ether (16). Heating the ether compound (16) in dimethylaniline affords the allylated headpiece compound (17).

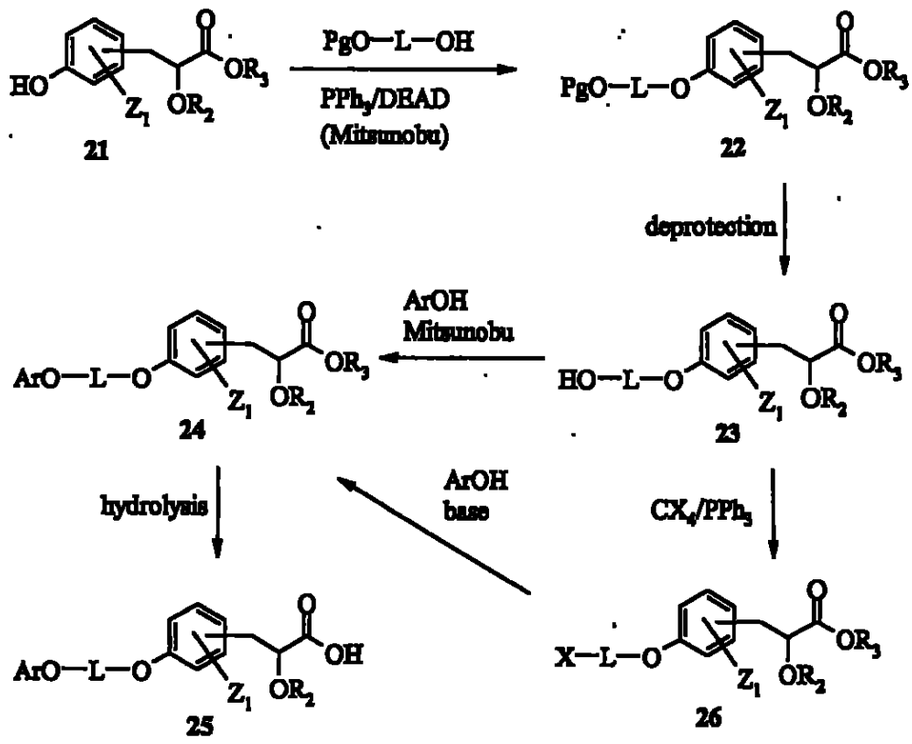
Reaction Scheme D: Synthesis of Head Piece



Z_2 = Cl, Br, I
Z_3 = Ar, -CH=CHAr

As shown in Reaction Scheme D, halogen substitution can be introduced into the headpiece by treating aryl alcohol (18) with an *N*-halosuccinimide in organic solvent to yield the compound (19). The compound (19) then undergoes a coupling reaction in the presence of palladium catalyst to yield the corresponding aryl and styrenyl compounds (20).

Reaction Scheme E: Synthesis of Head-Linker

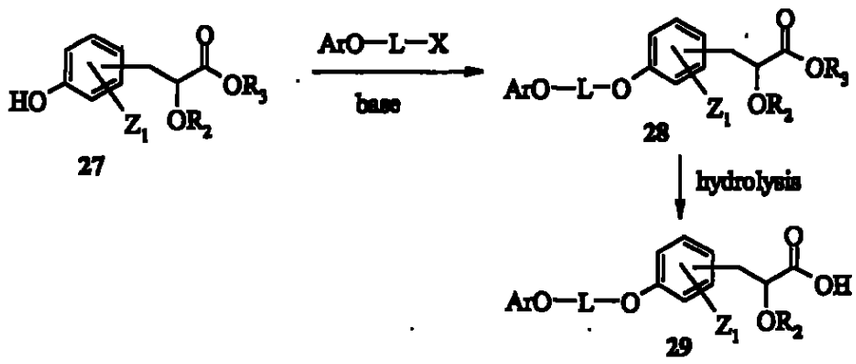


L = Linker: aliphatic, aralkyl, heteroalkylene
X = Cl, Br, I

Reaction Scheme E illustrates a synthesis of the present compounds by the general linker-headpiece route (General Scheme, routes A and B). The headpiece compoud (21) is coupled with a suitably monoprotected diol using a trialkylphosphine or triarylphosphine and an azodicarboxylate derivative (Mitsunobu conditions) to yield aryl ether (22). Deprotection of the alcohol function in the linker affords the compound (23), which then undergoes Mitsunobu coupling reaction with a tailpiece aryl alcohol (ArOH) to give compound (24). Further ester hydrolysis affords acid compound (25). Alternatively, the alcohol compound (23) can be converted to the corresponding halide (26) using a carbon tetrahalide and triphenylphosphine. Treatment of compound (26) with a tailpiece aryl alcohol

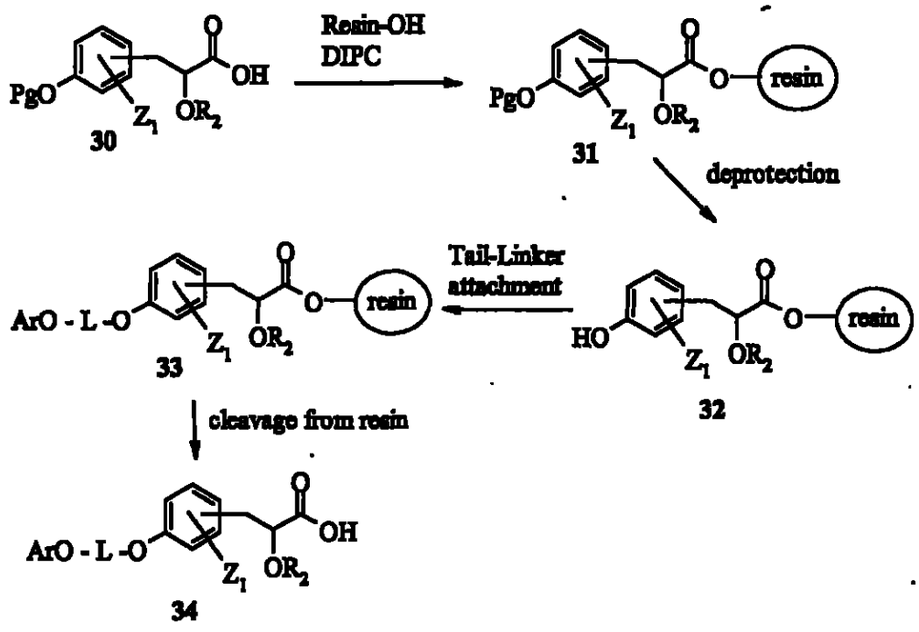
(ArOH) in the presence of a suitable base, such as cesium carbonate affords compound (24), which then undergoes hydrolysis to give acid compound (25).

Reaction Scheme F: Synthesis of Head-Linker



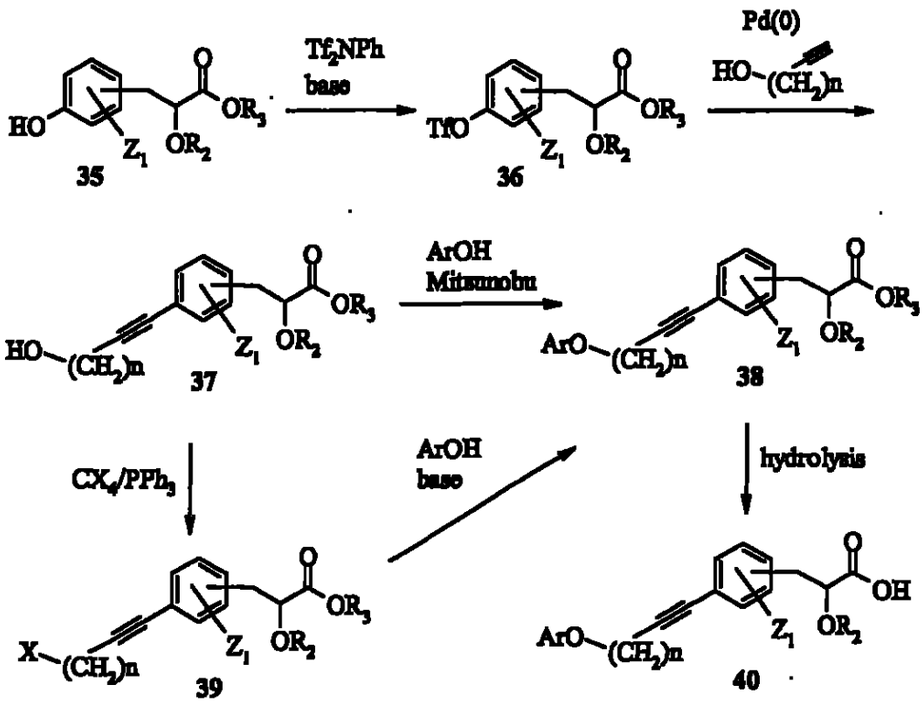
As shown in Reaction Scheme F, the compounds of the present invention can be prepared by the general tailpiece-linker to headpiece route (General Scheme, route C). The headpiece compound of alcohol (27) is treated with a tailpiece-linker halide (ArO-L-X) in the presence of a suitable base, such as potassium or cesium carbonate to afford the compound (28), which then undergoes ester hydrolysis to yield acid compound (29).

Reaction Scheme G: Solid Phase Synthesis



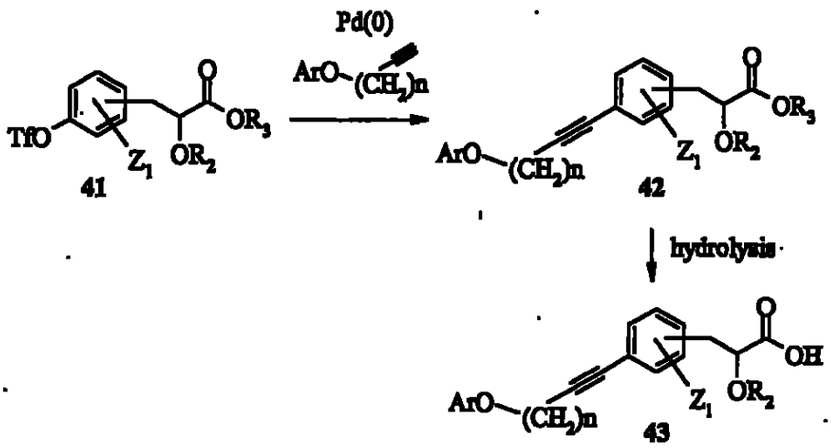
As shown in Reaction Scheme G, the headpiece can be attached to a resin allowing for a solid phase synthesis of the target compounds. Carboxylic acid (30) is attached to a suitable resin, such as the Wang resin, using an appropriate coupling reagent, such as diisopropyl carbodiimide (DIPC). Cleavage of the aryl alcohol protecting group, such as a tert-butyldimethylsilyl ether (t-$BuMe_2Si$) with the appropriate reagent, such as tetra-*n*-butylammonium fluoride gives aryl alcohol (32). The tail and linker regions are introduced as described in Reaction Schemes E and F to produce the compound (33). The carboxylic acid (34) can be released from the resin under suitable conditions, such as trifluoroacetic acid.

Reaction Scheme H: Synthesis of Head-Linker



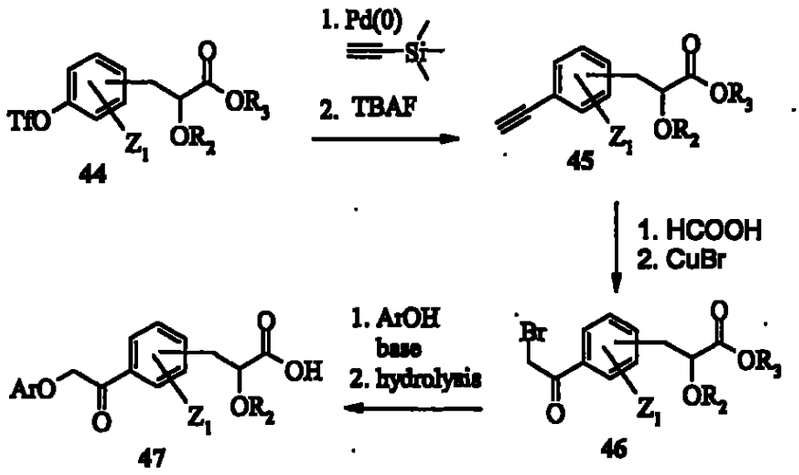
Reaction Scheme H illustrates a synthetic route to prepare the compounds of the present invention having alkynyl linkers. The headpiece compound (35) can be converted to the corresponding aryl triflate (36) (or aryl iodide) using phenyl triflamide and an appropriate base, such as NaH. The palladium catalyzed coupling reaction of compound (36) with an alkynyl alcohol gives the linker-headpiece intermediate (37). Coupling of compound (37) with various tailpiece alcohols can be achieved as described in Reaction Scheme E to afford the compound (38), which then undergoes a hydrolysis to yield the acid compound (40).

Reaction Scheme I: Synthesis of Head-Linker



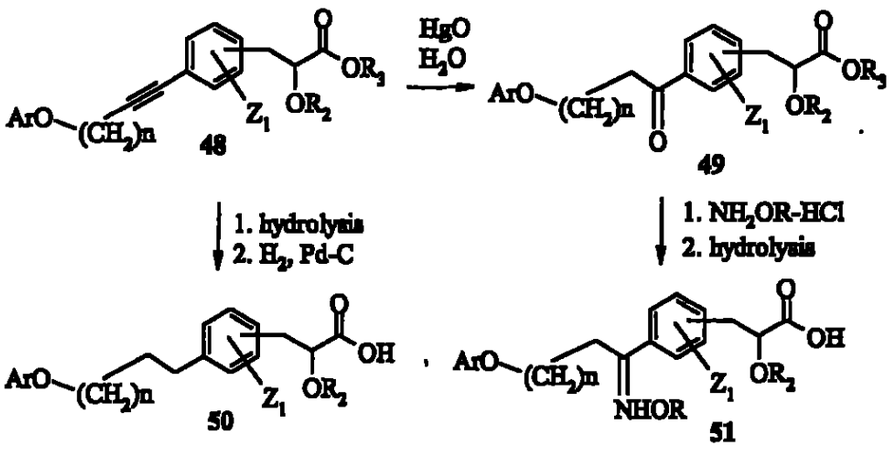
Alternative to Reaction Scheme H, the headpiece compound of triflate (41) can be combined with a tailpiece-linker to give the coupled compound (42) in one step as shown in Reaction Scheme I. The compound (42) then undergoes a hydrolysis to give the acid compound (43).

Reaction Scheme J: Synthesis of Head-Linker



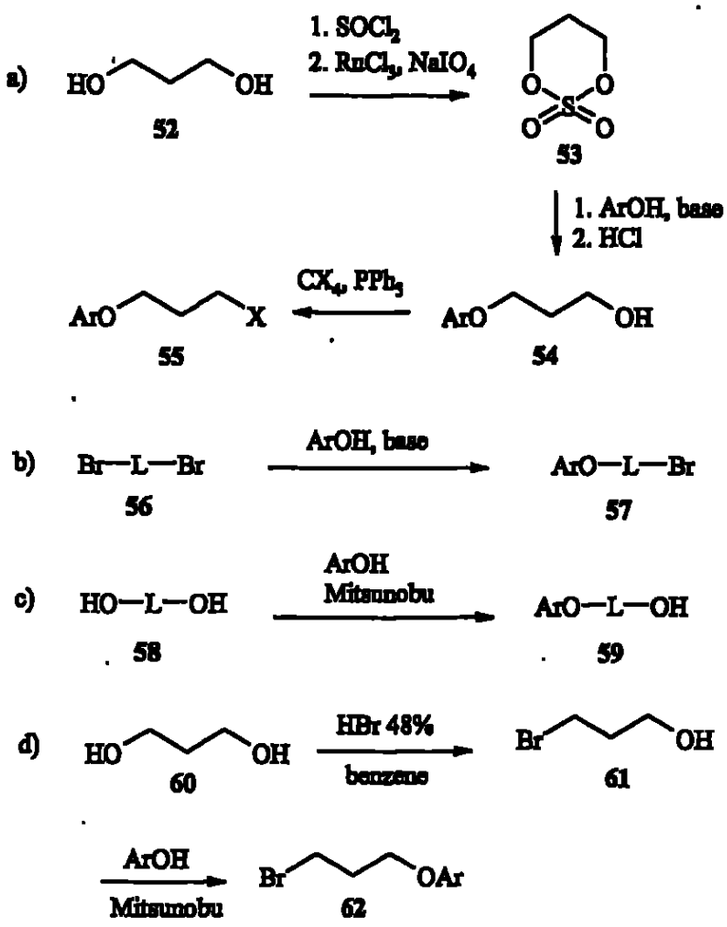
As shown in Reaction Scheme J, the headpiece compound of triflate (44) can be coupled with trimethylsilylacetylene using palladium catalysis to give the acetylenic headpiece (45) after fluoride mediated cleavage of the silyl group. The alkyne (45) is hydrolyzed under aqueous acidic conditions to the methyl ketone, which is then brominated with a suitable agent, such as copper (I) bromide to give bromoketone (46). Treatment of the compound (46) with a tailpiece aryl alcohol in the presence of a suitable base, such as potassium carbonate and aqueous base hydrolysis affords the acid compound (47).

Reaction Scheme K: Alkyne-Linker Modification



As shown in Reaction Scheme K, an alkyne function in the linker region of the present compounds can be modified. The alkyne can be oxidized to ketone to give compound (49) by using an appropriate oxidizing agent, such as mercuric oxide. The ketone can be further modified to the corresponding oximes (51) by treatment with an alkoxyamine followed by hydrolysis. Alternatively, the alkynyl function can be reduced to the alkylene as in compound (50) by using an appropriate reducing agent, such as hydrogen over palladium-on-carbon.

Reaction Scheme L: Synthesis of Linker



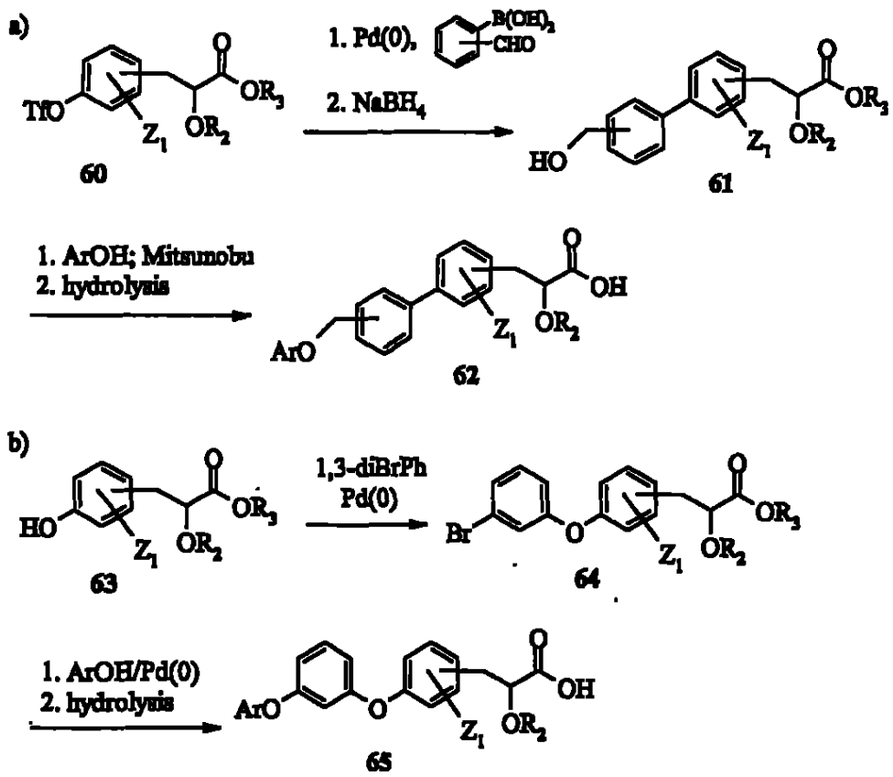
Reaction Scheme L illustrates various synthetic routes to the linker region. In route (a), 1,3-propane diol (52) is converted to the cyclic sulfonate ester (53) upon treatment with thionyl chloride followed by appropriate oxidation reagents, such as ruthenium trichloride and sodium periodate. Ring opening of the intermediate (53) is effected upon treatment with a tailpiece alcohol and a suitable base such as potassium tert-butoxide, followed by an acidic workup procedure to give the linker alcohol compound (54). The alcohol is then converted to the halide by using an appropriate reagent, such as a carbontetrahalide and a triarylphosphine to afford the

compound (55). In route (b), the compound of dibromo-linker (56) is reacted with approximately one mole equivalent of the tailpiece aryl alcohol in the presence of a suitable base, such as potassium carbonate to give the bromo-ether compound (57).

In route (c), the compound of diol-linker (58) is coupled with approximately one mole equivalent of the tailpiece alcohol under Mitsunobu reaction conditions to give the hydroxy-ether compound (59).

In route (d), 1,3-propane diol (60) is converted to the halide (61), which is then reacted with the headpiece aryl alcohol under the Mitsunobu reaction condition to give the bromo-ether compound (62).

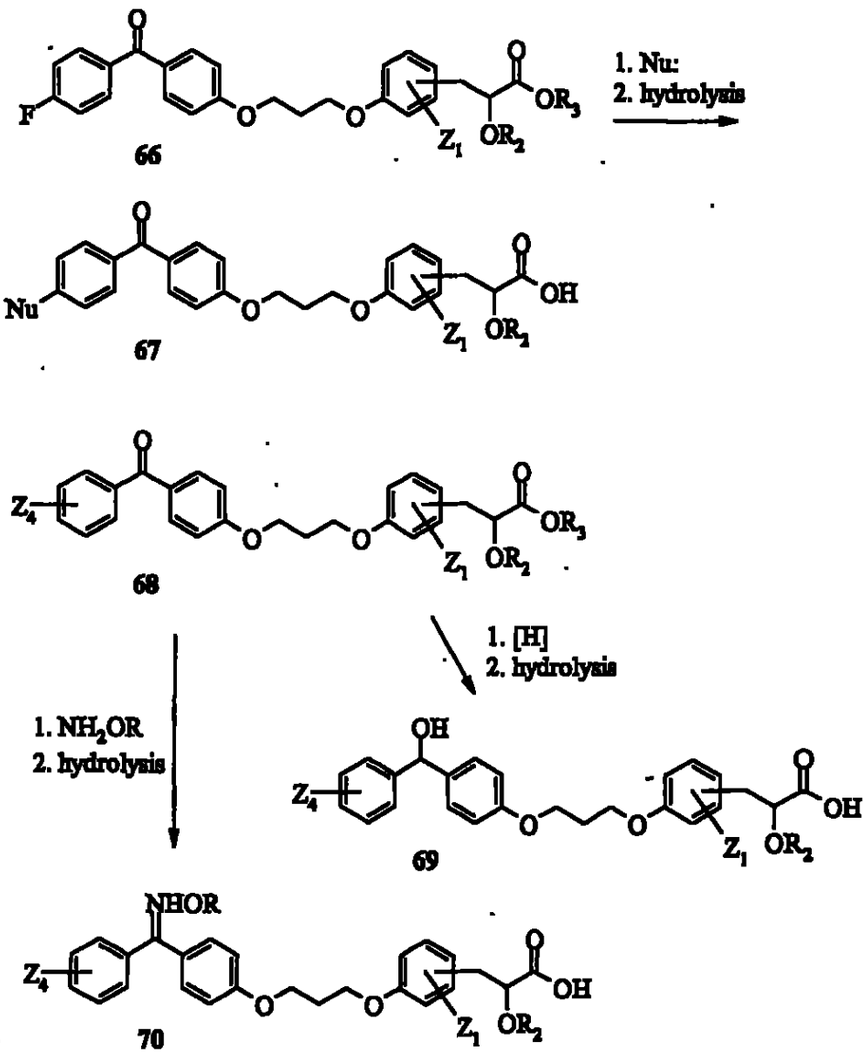
Reaction Scheme M: Synthesis of Modified Linker



Reaction Scheme M illustrates the synthetic routes to compounds with aryl-containing linkers. In route (a), The compound of headpiece triflate (60) is coupled with an arylboronic acid in the presence of palladium catalyst. Reduction of the intermediate aldehyde using a suitable reagent such as sodium borohydride, affords the arylic alcohol compound (61). The compound (61) can be coupled with the tailpiece aryl alcohol (ArOH) under Mitsunobu conditions followed by ester hydrolysis to give the acid compound (62).

In route (b), the headpiece alcohol (63) is coupled with approximately one mole equivalent of aryl dibromide in the presence of palladium catalyst to give aryl bromide (64). The compound (64) is then coupled similarly to the tailpiece aryl alcohol (ArOH) followed by ester hydrolysis to afford the acid compound (65).

Reaction Scheme N: Tailpiece Modification



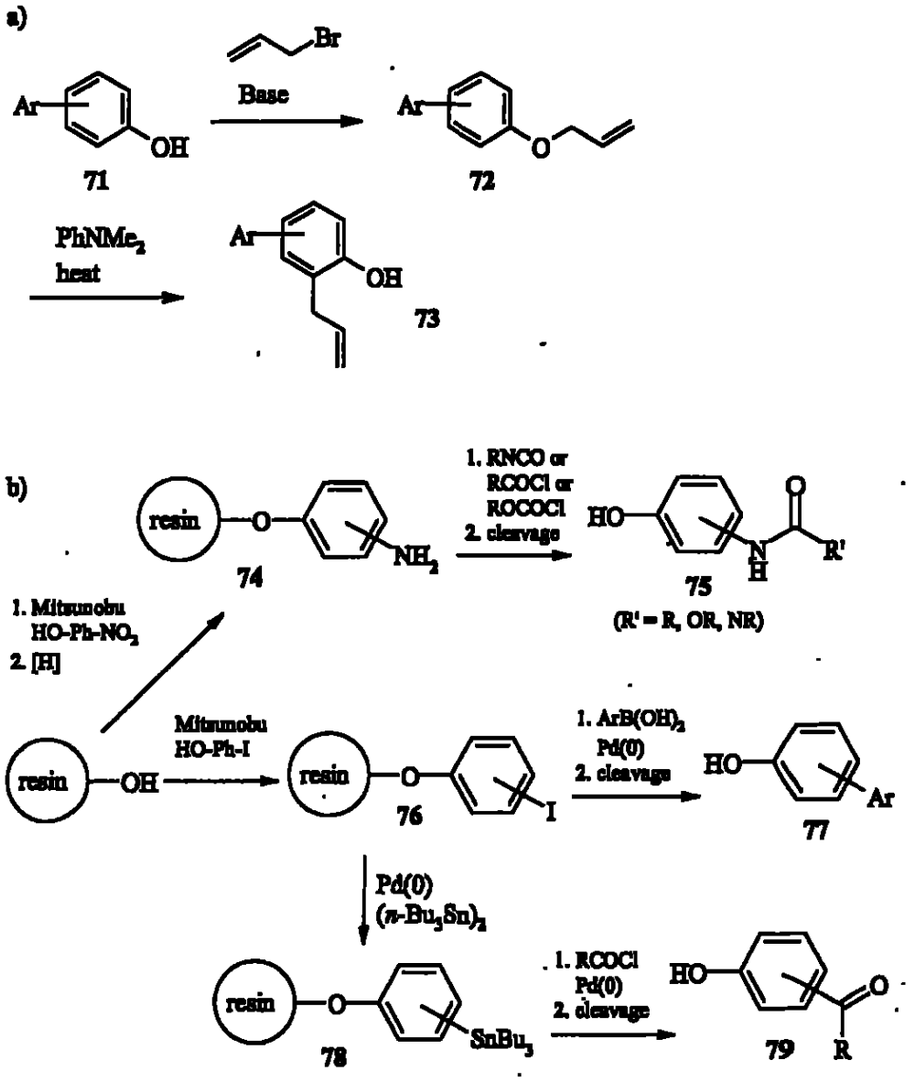
66 67 68 69 70

Nu: = nucleophile
Z_4 = suitable Ar substituent

Reaction Scheme N shows a synthetic route to modify the tailpiece region of the present compounds. The compound of *para*-fluorobenzophenone (66) is treated with a suitable nucleophile such as secondary amines and alkoxides, and then subjected to ester hydrolysis to give the acid compound (67).

The carbonyl function of benzophenone (68) can be reduced by using an appropriate reagent, such as hydrogen over palladium-on-carbon to yield the corresponding alcohol (69) after ester hydrolysis. The ketone moiety of compound (68) can be also modified to the corresponding oximes (70) by treatment with an alkoxyamine followed by hydrolysis.

Reaction Scheme O: Synthesis of Modified Tailpiece



Reaction Scheme O shows the synthetic routes to prepare the tailpiece region of the compounds. A Claisen rearrangement is used to alkylate the tailpiece aryl ring as shown in route (a). Aryl alcohol (71) is treated with an allyl bromide in the presence of a suitable base, such as NaH to give allyl ether (72). Heating this ether in dimethylaniline gives the allylated headpiece (73).

Solid phase methods to synthesize the tailpiece are described in route (b). Aryl alcohol is coupled to a suitable resin, such as the Wang resin under Mitsunobu conditions. Coupling the resin with a nitro aryl alcohol gives an intermediate that is reduced under appropriate conditions, such as tin (II) chloride in DMF to give aniline (74). The nitrogen function is reacted further with suitable reagents, such as isocyanates, acid chlorides or chloroformates to give the corresponding ureas, carbamates and amides, respectively. Cleavage from the resin under acidic conditions, such as trifluoroacetic acid in dichloromethane affords the amino substituted tailpiece of aryl alcohol compound (75).

Alternatively, coupling the resin with an iodo aryl alcohol gives iodide intermediate (76). The aryl iodide (76) then can be coupled directly with aryl boronic acids under palladium catalysis to give biaryl tailpiece aryl alcohols (77) upon cleavage from the resin under acidic condition. Iodide intermediate (76) can also be converted to the trialkylstannane (78) in the presence of palladium catalyst. Subsequent palladium catalyzed coupling with suitable reagents, such as acid chloride and upon cleavage from the resin under acidic condition afford the carbonyl substituted tailpiece aryl alcohol compound (79).

EXEMPLIFICATION

Instrumental Analysis

^{1}H NMR spectra were recorded on Varian 400 MHz, Bruker 200, 300 or 500 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Bruker 200, 300 or 500 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.5 ppm). High resolution mass spectra were obtained on VG ZAB 3F or VG 70 SE spectrometers. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light.

Standard Synthesis Procedures

Certain standard synthesis procedures were used in preparing many of the exemplified compounds of the present invention. These Standard Procedures were:

Standard Procedure for Mitsounobu coupling-hydrolysis procedure (A): A solution of triphenylphosphine (1.42 mmol) in 10 mL of dry THF was treated at 0°C with diethylazodicarboxylate (1.42 mmol) and stirred for 20 min. A solution of (2S)-3-[4-(3-Hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (1.19 mmol) and 4-phenylphenol (1.42 mmol) in 5 mL of dry THF was added to the solution, and the mixture stirred at room temperature overnight. The mixture was concentrated to dryness under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 10:1 to 3:1). Fractions with Rfs 0.5 and 0.42 (hexanes/ethyl acetate 2:1) corresponding to the couple compound and starting phenol, respectively, were combined and concentrated to dryness. The mixture was dissolved in 4 mL of 1N NaOH and 12 mL of methanol and stirred at room temperature until TLC indicated the disappearance of starting material. The

methanol was removed under vacuum, and the aqueous solution was diluted with 20 mL of brine and washed with diethyl ether (3 x 15 mL). The aqueous phase was acidified with 1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL). The organic layer dried ($MgSO_4$) and concentrated under vacuum.

Standard Procedure for the Mitsunobu coupling procedure (B): A solution of triphenylphosphine (1.42 mmol) in 10 mL toluene or THF was treated at 0°C with DEAD or DIAD (1.42 mmol) and stirred for 20 min. A solution of (2S)-3-(4-Hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (1.19 mmol) and the corresponding alcohol (1.42 mmol) in 5 mL of toluene or THF was added to the solution, and the mixture stirred at room temperature overnight. The mixture was concentrated to dryness under vacuum and purified by silica gel chromatography

Standard hydrolysis Procedure (C): (2S)-3-{4-[4-(Biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid ethyl ester (0.5 g, 1.17 mmol) was dissolved in 20 mL of 1N NaOH (or LiOH) and 60 mL of methanol and was stirred at room temperature until TLC indicated the disappearance of starting material (ca. 3 h). The methanol was removed under vacuum, and the aqueous solution diluted with 20 mL of brine and washed with diethyl ether (3 x 60 mL). The aqueous phase was acidified with 1N HCl (until pH 1-2) and extracted with ethyl acetate (3 x 60 mL). The organic layer dried ($MgSO_4$) and concentrated under vacuum.

Standard Procedure for Monoprotection of diols (D): A solution of the corresponding diol (1 eq) in dry THF was cooled to 0 °C. Sodium hydride (1 eq) was added, and the mixture reaction was stirred 30 min at that temperature. *Tert*-butyldimethylsilyl chloride (0.95 eq) was added, and the mixture was stirred at room temperature overnight. Then a 10 % Na_2CO_3 solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silicagel chromatography.

Standard Procedure for the cleveage of the protected alcohols (E): A mixture solution of the corresponding protected alcohol in THF was treated with tetrabutylamonium fluoride (1M in THF) (2 eq) . The solution was stirred at room temperature until reaction is completed by TLC, then quenched with water and extracted with Ethyl Acetate to give a crude product which was purified by silica gel chromatography.

Standard Procedure (F): The reaction was carried out in a polypropylene syringe equipped with a polypropylene frit. A suspension of the resin-linked phenol (1 eq) was suspended in THF (0.02 M). A solution of 1,3-propanediol (5 eq) in THF was added followed by a mixture of triphenylphosphine (5 eq) and diisopropylazo-dicarboxylate (5 eq) in THF. The mixture was shaken at room temperature overnight. The reaction solvent was removed, and the resin was washed sequentially with THF (2x), CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), methanol and CH_2Cl_2 (3x). The resultant polymer was dried under vacuum overnight to produce the targeted immobilized alcohol.

Standard Procedure (G): The reaction was carried out in a polypropylene syringe equipped with a polypropylene frit. A suspension of the resin-linked alcohol (1 eq) was suspended in a mixture 1:1 THF/CH_2Cl_2 (0.015 M). A solution of phenol (10 eq) dissolved in a mixture of 1:1 THF/CH_2Cl_2 was added followed by a mixture of triphenylphosphine (5 eq) and diisopropylazo-dicarboxylate (5 eq) in THF/CH_2Cl_2 1:1. The mixture was shaken at room temperature overnight, and the reaction solvent was removed. The resin was washed sequentially with 1:1 THF/CH_2Cl_2 (2x), THF (2x), CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), methanol, and CH_2Cl_2 (2x). The resin was dried under vacuum for 5 h and treated with 50% TFA in CH_2Cl_2. The solution was filtered and concentrated, and the residue was purified by HPLC-MS chromatography to produce the desired product.

Standard Procedure (H): Lithium hydroxide 1N solution in water (0.245 mL) was added to a solution of the ester (0.073 mmol) in tetrahydrofuran (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 hours,

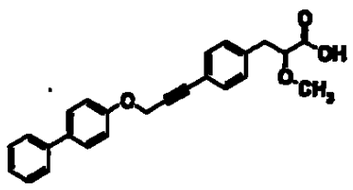
diluted with water (10 mL) and extracted with diethyl ether (3 X 10 mL). The aqueous layer was acidified with 1N HCl to pH 1 and extracted with Diethyl ether (5 X 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to produce the corresponding acid.

Standard Procedure (I): A mixture of the corresponding phenol (1 eq) and the bromoalkyl derivative (1 eq) with K_2CO_3 (3 eq) were refluxed in acetonitrile overnight. Cooled the mixture reaction and concentrated to dryness to give a crude which was purified by chromatography in silicagel to give the product.

Standard Procedure (J): A mixture of the corresponding phenol (1.5 eq), and the bromoalkyl derivative (1 eq) in DMF were treated with Cs_2CO_3 (3 eq). The mixture reaction was stirred at room temperature overnight and then filtered. Removed the DMF under vacuo and added methanol to the residue treating the mixture with NaOH 1M (10 eq) and stirred for 3h. The solvent was evaporated and the salts were dissolved in water. The aqueous phase was acidified to pH 2 and extracted with dichloromethane, filtered through a hydrophobic syringe and the organic layer purified by HPLC-MS.

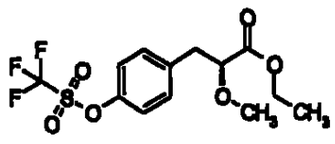
Example 1

(2S)-3-{4-[3-(Biphenyl-4-yloxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid



Step A

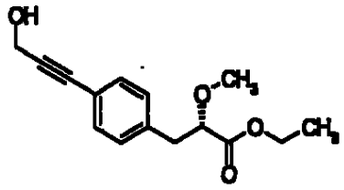
(2S)-2-Methoxy-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid ethyl ester



To a solution of (*S*)-2-methoxy-3-hydroxyphenyl-propionic acid ethyl ester (0.388 g, 1.73 mmol) in 40 mL of dry THF cooled to –20° C was added sodium hydride (0.073 g, 1.82 mmol, 60% oil dispersion). The mixture was stirred at –20°C for 30 min. Phenyl triflimide (0.68 g, 1.90 mmol) was added in one portion, and the solution was stirred at room temperature overnight and concentrated to dryness under vacuum. The residue was partitioned between water (20 mL) and diethyl ether (20 mL). The layers were separated, and the aqueous solution was extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with 10% Na_2CO_3 (6 x 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to a yellow oil (574 mg, 97 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.34-7.16 (m, 4H), 4.18 (q, 2H, *J*=7.0), 3.93 (dd, 1H, *J*=7.3, 5.6), 3.36 (s, 3H), 3.05 (s, 1H), 3.02 (d, 1H, *J*=2.4 Hz), 1.22 (t, 3H, *J*=7.25).

Step B

(2S)-3-[4-(3-Hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester



A solution of (2S)-2-methoxy-3-(4-trifluoromethane-sulfonyloxy-phenyl)-propionic acid ethyl ester (0.861 g, 2.53 mmol), propargyl alcohol (0.88 mL, 15.18 mmol), triethylamine (1.41 mL, 10.12 mmol) and dichlorobis(triphenylphosphine)palladium (II) in 10 mL of dry DMF was heated to 90°C for 2 hours. The reaction mixture was cooled to room temperature, diluted with 50 mL of water, and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with 0.5 N HCl (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The residue purified by column chromatography (silica gel, hexanes/ethyl acetate 2:1, R_f 0.17) to give a yellow-brown oil (0.211 g, 32%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.35 (d, 2H, *J*=8.1), 7.18 (d, 2H, *J*=8.1), 4.48 (s, 2H), 4.17 (q, 2H, *J*=7.3), 3.93 (dd, 1H, *J*=7.3, 5.7), 3.34 (s, 3H), 3.02 (s, 1H), 2.99 (d, 1H, *J*=2.2), 1.8 (s, 1H), 1.22 (t, 3H, *J*=7.3).

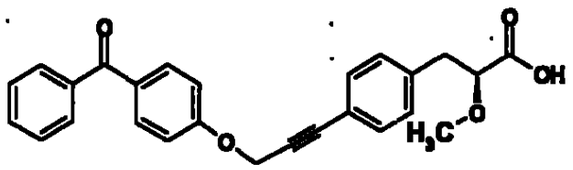
Step C

(2S)-3-{4-[3-(Biphenyl-4-yloxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-[4-(3-hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester using the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce a white solid. Mp 111-112°C. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.58-7.52 (m, 4H), 7.45-7.30 (m, 5H), 7.19 (d, 1H, *J*=8.3), 7.10 (dd, 3H, *J*=6.7, 1.9), 4.94 (s, 2H), 3.98 (dd, 1H, *J*=7.5, 4.3); 3.37 (s, 3H), 3.13 (dd, 1 H, J=14.5, 4.6), 2.99 (dd, 1H, *J*=14.2, 7.8).MS (ES) for $C_{25}H_{22}O_4$ $[M+NH_4]^+$: 404, $[M+Na]^+$:409.

Example 2

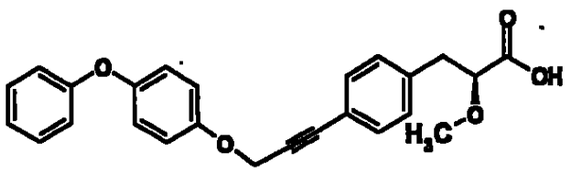
(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid:



The title compound was prepared from (2S)-3-[4-(3-hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (from Example 1, Step B) via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce a white oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.84-7.71 (m, 4H), 7.55-7.33 (m, 5H), 7.17 (d, 2H, *J*=8.0), 7.07 (d, 2 H, *J*=8.8), 4.96 (s, 2H), 3.96 (dd, 1H, *J*=7.7, 4.4), 3.35 (s, 3H), 3.11 (dd, 1H, *J*=14.3, 4.4), 2.97 (dd, 1H, *J*=14.3, 7.3).

Example 3

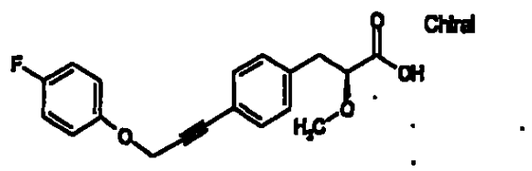
(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-prop-1-ynyl]-phenyl}-propionic acid:



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester via (from Example 1, Step B) the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce a white oily solid (41 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.38-7.15 (m, 5H), 7.02-6.76 (m, 8H), 4.86 (s, 2H), 3.98 (dd, 1H, *J*=7.3, 4.4), 3.36 (s, 3H), 3.12 (dd, 1H, *J*=14.3, 4.4), 2.98 (dd, 1H, *J*=14.3, 7.3). MS (ES) for $C_{25}H_{22}O_5$ $[M+NH_4]^+$: 420.2, $[M+Na]^+$: 425.2.

Example 4

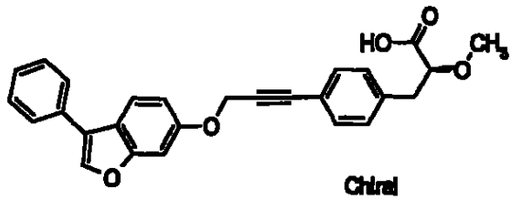
(2S)-3-{4-[3-(4-Fluoro-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (from Example 1, Step B) via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce a white solid of the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.34 (d, J = 8.1 Hz, 2 H); 7.16 (d, J = 8.0 Hz, 2 H); 6.98-6.86 (m, 4 H); 4.84 (s, 2 H); 3.97 (dd, J = 7.7, 4.4 Hz, 1 H); 3.36 (s, 3 H); 3.12 (dd, J = 14.3, 4.4 Hz, 1 H); 2.98 (dd, J = 14.3, 7.3 Hz, 1 H). MS (ES) for $C_{19}H_{17}FO_4$ $[M+NH_4]^+$: 346, $[M+Na]^+$: 351.

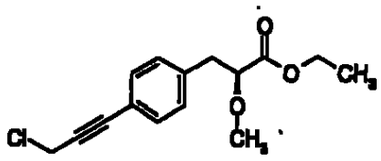
Example 5

(2S)-2-Methoxy-3-{4-[3-(3-phenyl-benzofuran-6-yloxy)-prop-1-ynyl]-phenyl}-propionic acid



Step A

(2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-[4-(3-hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (0.060 g, 0.23 mmol) (from Example 1, Step B) in dry DMF (5 ml) and treated with triethyl amine (0.69 mmol) and mesylchloride (0.46 mmol). The mixture reaction was stirred overnight, and the crude product was extracted with H_2O/Ether. The organic layer was dried and concentrated to give a product that was purified in silica using Hexane /Ethyl Acetate (5/1) to give the title compound as an oil (0.020g, 30% yield). MS (ES) for $C_{15}H_{17}ClO_3$ $[M+H]^+$: 281.2

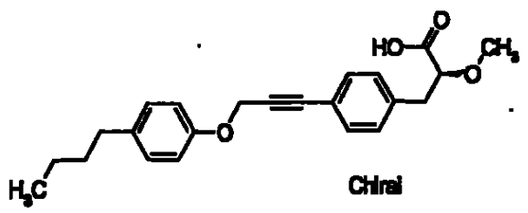
Step B

(2S)-2-Methoxy-3-{4-[3-(3-phenyl-benzofuran-6-yloxy)-prop-1-ynyl]-phenyl}-propionic acid

A solution of (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Step A (0.071 mmol, 1 eq) in 0.7 ml of DMF in a 16 x 100 mm tube treated with 3-phenyl-6-hydroxybenzofurane (0.078 mmol, 1.1 eq) Cesium Carbonate (0.213 mmol, 3 eq) and NaI (0.071 mmol, 1 eq) and stirred at room temperature overnight. The reactants were filtered and washed with DMF several times. The solvent was evaporated under vacuo and the residue reconstituted in a mixture of Ethanol (2 ml) and NaOH (1M) (1 ml) and stirred at room temperature until reaction is completed by HPLC-MS. Then HCl (1M) was added (until pH=3) and the solvent were eliminated under vacuo. The residue was reconstituted in CH_2Cl_2/H_2O and filtered through a hidrofobic syringer. The organic layer was separated, concentrated and purified by HPLC-MS to get the title compound. MS(ES) for $C_{27}H_{22}O_3$ $[M+H]^+$: 427.2.

Example 6

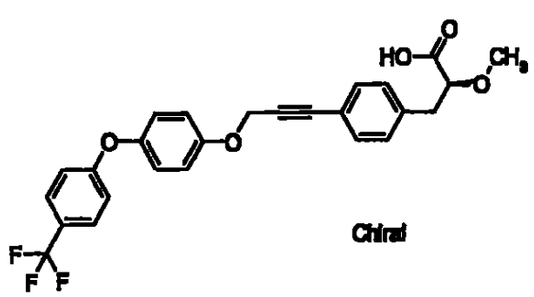
(2S)-3-{4-[3-(4-Butyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 4-*n*-butylphenol in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{23}H_{26}O_4$ [M-H]⁻: 365.2

Example 7

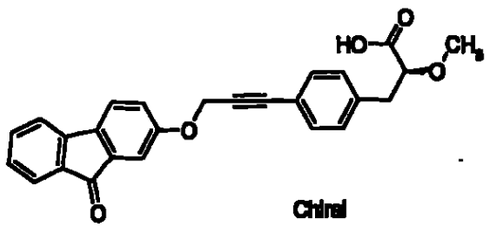
(2S)-2-Methoxy-3-{4-[3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-prop-1-ynyl}-phenyl)-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5 Step A and 4-(4-trifluoromethylPhenoxy)phenol in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{26}H_{21}F_3O_5$ [M-H]⁻: 469.2

Example 8

(2S)-2-Methoxy-3-{4-[3-(9-oxo-9H-fluoren-2-yloxy)-prop-1-ynyl]-phenyl}-propionic acid

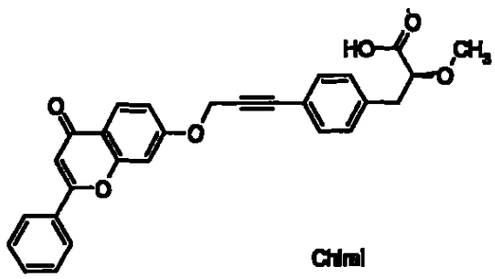


Chiral

The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5 Step A and 2-hydroxy-9-fluorenone in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{28}H_{20}O_5$ [M-H]$^-$: 411.2

Example 9

(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-prop-1-ynyl]-phenyl}-propionic acid

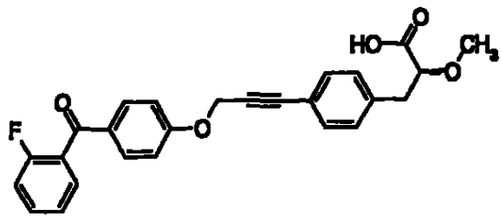


Chiral

The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 7-hydroxyflavone in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{28}H_{22}O_6$[M+H]$^+$: 455.2.

Example 10

(2S)-3-(4-{3-[4-(2-Fluoro-benzoyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid

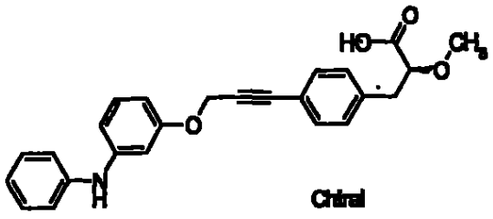


Chiral

The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 2-fluoro-4-hydroxybenzophenone in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{26}H_{21}FO[M+H]^+$: 433.2.

Example 11

(2S)-2-Methoxy-3-{4-[3-(3-phenylamino-phenoxy)-prop-1-ynyl]-phenyl}-propionic acid

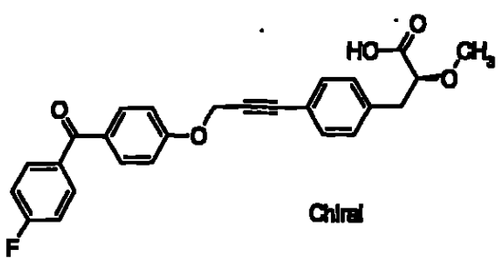


Chiral

The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 3-hydroxydiphenylamine in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{25}H_{23}NO$ $[M+H]^+$: 402.2.

Example 12

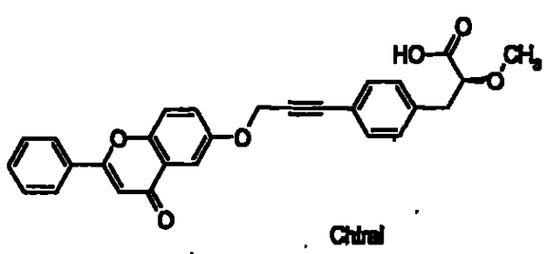
(2S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 4-fluoro-4'-hydroxybenzophenone in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{28}H_{21}FO[M+H]^+$: 433.2.

Example 13

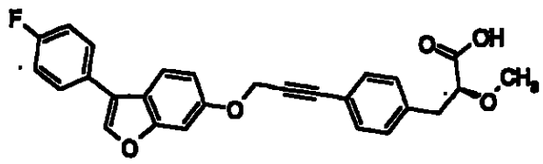
(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-prop-1-ynyl]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 6-hydroxyflavone in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{28}H_{22}O_6[M+H]^+$: 455.2.

Example 14

(2S)-3-(4-{3-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid

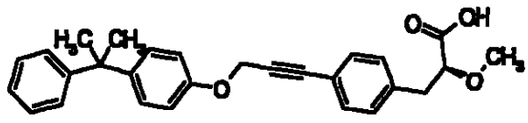


Chiral

The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 6-hydroxy-3-(4-fluorophenyl)benzofurane in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{27}H_{21}FO_5$ [M-H]$^-$: 443.2.

Example 15

(2S)-2-Methoxy-3-(4-{3-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-prop-1-ynyl}-phenyl)-propionic acid

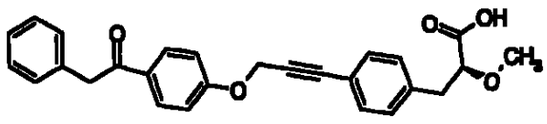


Chiral

The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 4-cumylphenol in a manner analogous to that described for Example 5, Step B. MS(ES) for$C_{28}H_{28}O_4$[M+NH_4]$^+$:446.2.

Example 16

(2S)-2-Methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-prop-1-ynyl]-phenyl}-propionic acid

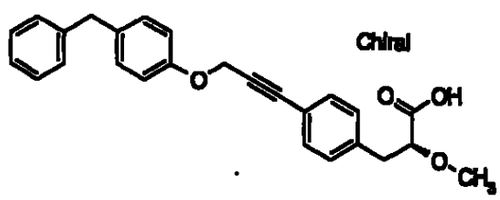


Chiral

The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and benzyl-4-hydroxyphenylketone in a manner analogous to that described for Exapmle 5, Step B. MS(ES) for $C_{27}H_{24}O_5$ [M-H]$^-$: 427.2.

Example 17

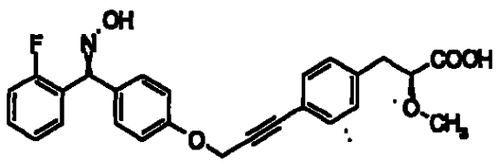
(2S)-3-{4-[3-(4-Benzyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Chloro-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 5, Step A and 4-hydroxydiphenylmethane in a manner analogous to that described for Example 5, Step B. MS(ES) for $C_{26}H_{24}O_4$[M-H]$^-$:399.

Example 18

(2S)-3-[4-(3-{4-[(2-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid



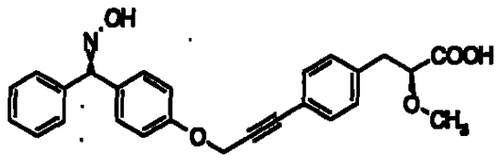
Chiral

(2S)-3-(4-{3-[4-(2-Fluoro-benzoyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid from Example 10, (0.01 mmol, 1 eq) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5% was added to the residue to pH = 3. Extracted with ethyl acetate and concentrated to give

the title product as a mixture of two oximes. MS(ES) for $C_{26}H_{22}FNO_5$ $[M+H]^+$: 448.2, $[M-H]^-$: 446.2.

Example 19

(2S)-3-(4-{3-[4-(Hydroxyimino-phenyl-methyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid

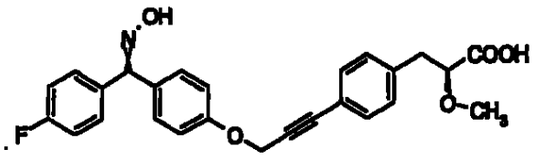


Chiral

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid (0.01 mmol, 1 eq) (Example 2) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5 % was added to the residue to pH = 3. Extracted with Ethyl Acetate and concentrated to give the title product as a mixture of two oximes. MS(ES) for $C_{26}H_{23}NO_5$ $[M+H]^+$: 430.2, $[M-H]^-$: 428.2.

Example 20

(2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid



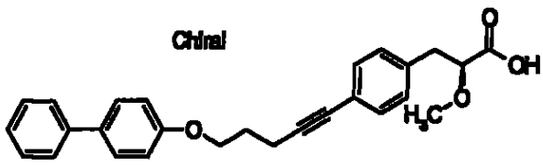
Chiral

(2S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-prop-1-ynyl}-phenyl)-2-methoxy-propionic acid from Example 12 (0.01 mmol, 1 eq) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5% was added to the residue to pH = 3. Extracted with Ethyl Acetate and concentrated to

give the title product as a mixture of two oximes. MS(ES) for $C_{26}H_{22}FNO_5$ $[M+H]^+$: 448.2, $[M-H]^-$: 446.2.

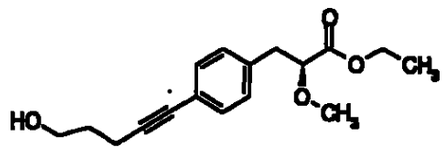
Example 21

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid:



Step A

(2S)-3-[4-(5-Hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester



This compound was prepared form 4-pentyn-1-ol following the procedure described in Example 1, Step B. Yellow-brown oil. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.33 (d, 2H, *J*=8.1), 7.16 (d, 2H, *J*=8.1), 4.17 (q, 2H, *J*=7.3), 3.92 (dd, 1H, *J*=7.3, 5.7), 3.80 (t, 2H, *J*=6.5), 3.34 (s, 3H), 3.01 (s, 1H), 2.98 (d, 1H, *J*=2.4), 2.68 (t, 2H, *J*=6.2), 1.86 (br, 1H), 1.23 (t, 3H, *J*=7.3).

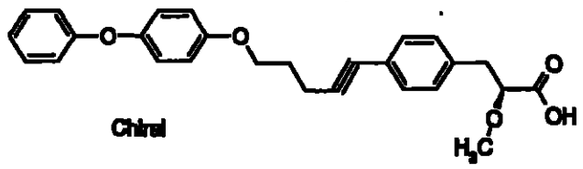
Step B

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-[4-(5-hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester and 4-phenylphenol via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce a white oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.56-7.28 (m, 9H); 7.15 (d, 2H, *J*=8.4), 6.98 (d, 2H, *J*=8.8), 4.15 (t, 2H, *J*=6.2), 3.97 (dd, 1H, *J*=7.7, 4.4), 3.36 (s, 3H), 3.11 (dd, 1H, *J*=14.3, 4.4), 2.97 (dd, 1H, *J*=14.3, 7.7), 2.62 (t, 2H, *J*=7.0), 2.08 (qn, 2H, *J*=6.6).

Example 22

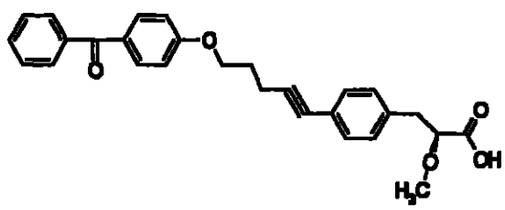
(2S)-2-Methoxy-3-{4-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid:



The title compound was prepared from (2S)-3-[4-(5-hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid (Example 21, Step A) and 4-phenoxyphenol via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce a white oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.26-7.19 (m, 4H), 7.07 (d, 2H, *J*=8.3), 6.98-6.78 (m, 7H), 4.01 (t, 2H, *J*=5.9), 3.91 (dd, 1H, *J*=7.3, 4.3), 3.30 (s, 3H), 3.05 (dd, 1H, *J*=14.2, 4.3), 2.90 (dd, 1H, *J*=14.2, 7.5), 2.54 (t, 2H, *J*=6.7), 1.98 (qn, 2H, *J*=6.4). MS (ES for $C_{27}H_{26}O_5$ $[M+NH_4]^+$: 448, $[M+Na]^+$: 453.

Example 23

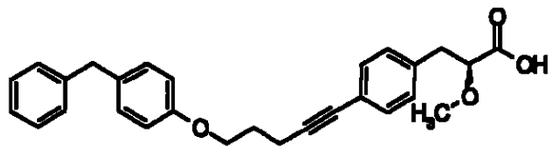
(2S)-3-{4-[5-(4-Benzoyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(5-hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid (Example 21, Step A) and 4-hydroxybenzophenone via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce a white oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.82-7.70 (m, 3H), 7.54-7.43 (m, 4H), 7.31-7.23 (m, 2H), 7.14 (d, 2H, *J*=8.1), 6.95 (d, 2H, *J*=8.8), 4.19 (d, 2H, *J*=5.9), 3.96 (dd, 1H, *J*=7.7, 4.4), 3.34 (s, 3H), 3.09 (dd, 1H, *J*=14.3, 4.4), 2.95 (dd, 1H, *J*=14.3, 7.7), 2.61 (t, 2H, *J*=7.0), 2.08 (qn, 2H, *J*=6.6).

Example 24

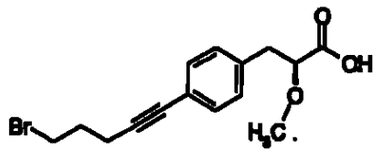
(2S)-3-{4-[5-(4-Benzyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid



Chiral

Step A

3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester



Chiral

To a solution of (2S)-3-[4-(5-Hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 21, Step A (0.17 mmol, 1 eq) in dichloromethane (5 ml) and CBr_4 (0.34 mmol, 2 eq) at 0°C, Ph_3P was added (0.34 mmol, 2 eq) portionwise and the mixture reaction was stirred 1 hour the solvent was removed under vacuo and the residue purified by flash chromatography using Hexane/ Ethyl acetate as eluent (6:1) to give the title product in 85% yield.

Step B

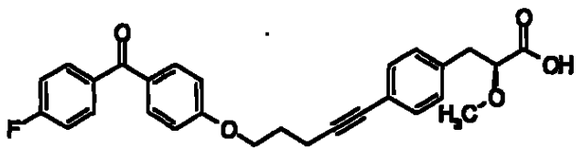
(2S)-3-{4-[5-(4-Benzyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid

A solution of 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Step A (0.1 mmol, 1 eq) in 0.7 ml of DMF in a 16 x 100 mm tube treated with 4-hydroxydiphenylmethane (0.11 mmol, 1.1 eq) and Cesium Carbonate (0.3 mmol, 3 eq) and stirred at room temperature overnight. The reactants were filtered and washed with DMF several times. The solvent was evaporated under vacuo and the residue reconstituted in a mixture of Ethanol (2 ml) and NaOH (1M) (1 ml) and stirred at room temperature until reaction is completed by HPLC-MS. Then HCl (1M) was added (until pH=3) and the solvent were eliminated under vacuo. The

residue was reconstituted in CH_2Cl_2/H_2O and filtered through a hidrofobic syringer. The organic layer was separated, concentrated and purified by HPLC-MS to get the title compound. MS(ES) for $C_{28}H_{28}O_4[M+NH_4]^+$: 446.2.

Example 25

(2S)-3-(4-{5-[4-(4-Fluoro-benzoyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid

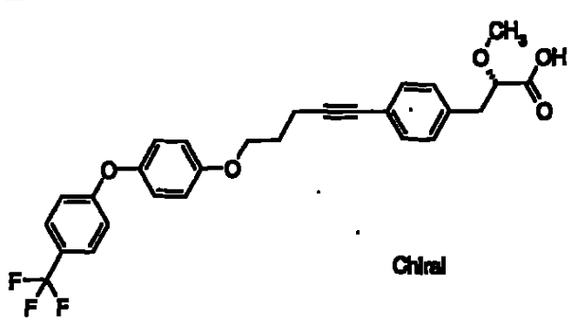


Chiral

The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 4-fluoro-4-hydroxybenzophenone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{28}H_{25}F_3O_5[M+H]^+$: 461.2.

Example 26

(2S)-2-Methoxy-3-(4-{5-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-pent-1-ynyl}-phenyl)-propionic acid



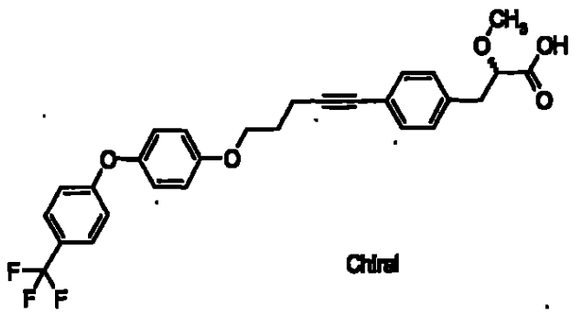
Chiral

The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester

From Example 24, Step A and 4-(4-trifluoromethylphenoxy)phenol in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{28}H_{25}F_3O_5[M+NH_4]^+$: 516.2.

Example 27

(2S)-2-Methoxy-3-{4-[5-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-pent-1-ynyl]-phenyl}-propionic acid

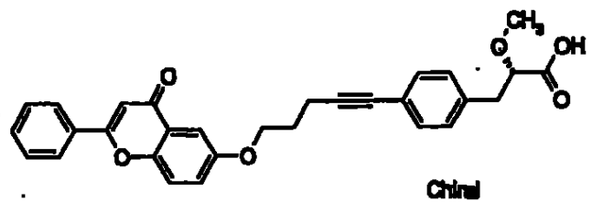


Chiral

The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 7-hydroxyflavone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{30}H_{26}O_6[M+H]^+$:483.2.

Example 28

(2S)-2-Methoxy-3-{4-[5-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-pent-1-ynyl]-phenyl}-propionic acid

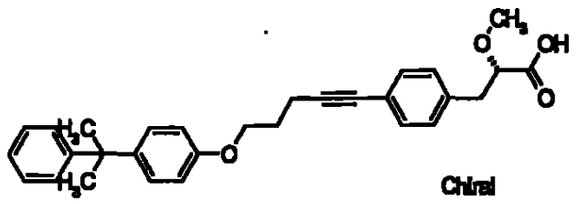


Chiral

The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 6-hydroxyflavone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{30}H_{26}O_6[M+H]^+$:483.2

Example 29

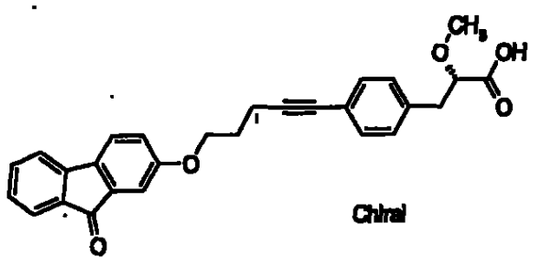
(2S)-2-Methoxy-3-{4-[5-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-pent-1-ynyl]-phenyl}-propionic acid



The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 4-cumylphenol in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{30}H_{32}O_4$ $[M+NH_4]^+$:474.3

Example 30

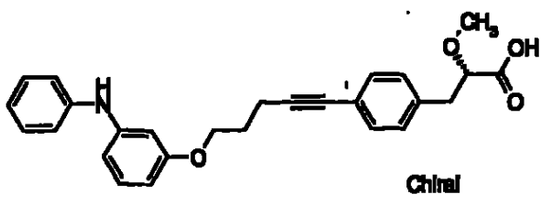
(2S)-2-Methoxy-3-{4-[5-(9-oxo-9H-fluoren-2-yloxy)-pent-1-ynyl]-phenyl}-propionic acid



The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 2-hydroxy-9-fluorenone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{29}H_{24}O_5[M+H]^+$:441.2.

Example 31

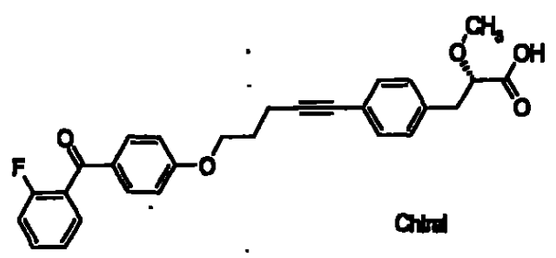
(2S)-2-Methoxy-3-{4-[5-(3-phenylamino-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid



The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24 Step A and 3-hydroxydiphenylamine in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{27}H_{27}NO_4[M+H]^+$:430.2.

Example 32

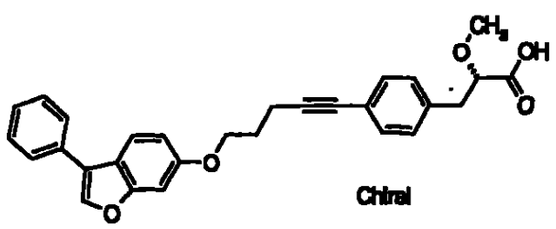
(2S)-3-(4-{5-[4-(2-Fluoro-benzoyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 2-fluoro-4'-hydroxybenzophenone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{28}H_{25}FO_5[M+H]^+$:461.2.

Example 33

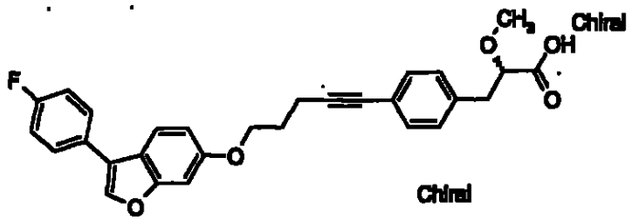
(2S)-2-Methoxy-3-{4-[5-(3-phenyl-benzofuran-6-yloxy)-pent-1-ynyl]-phenyl}-propionic acid



The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 6-hydroxy-4-phenylbenzophenone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{29}H_{26}O_5[M+H]^+$:455.2.

Example 34

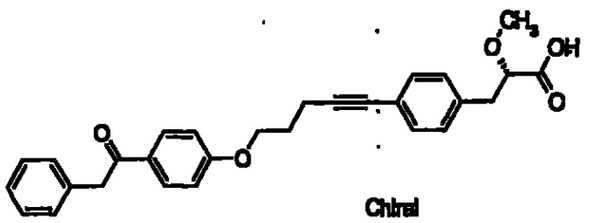
(2S)-3-(4-{5-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 3-(4'-fluorophenyl)-6-hydroxybenzophenone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{29}H_{25}FO_5[M+H]^+$:473.2.

Example 35

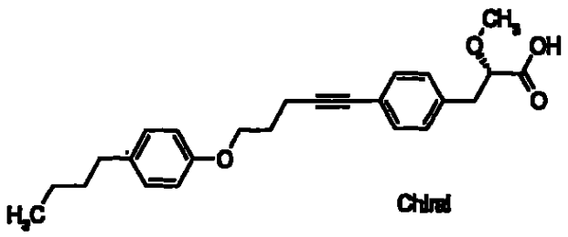
(2S)-2-Methoxy-3-{4-[5-(4-phenylacetyl-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid



The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and benzyl-4-hydroxyphenylketone in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{29}H_{28}O_5[M-H]^-$:455.2.

Example 36

(2S)-3-{4-[5-(4-Butyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid

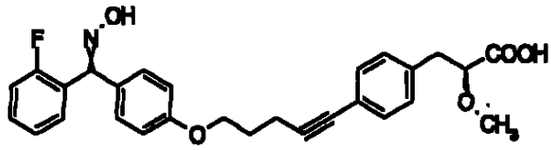


Chiral

The title compound was prepared from 3-[4-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 24, Step A and 4-N-butylphenol in a manner analogous to that described for Example 24, Step B. MS(ES) for $C_{25}H_{30}O_4$[M-H]$^-$:393.2.

Example 37

(2S)-3-[4-(5-{4-[(2-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-pent-1-ynyl)-phenyl]-2-methoxy-propionic

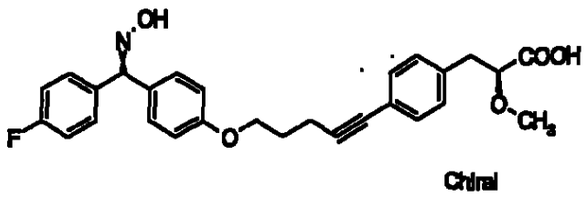


Chiral

(2S)-3-(4-{5-[4-(2-Fluoro-benzoyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid from Example 32, (1 eq) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5% was added to the residue to pH = 3. Extracted with Ethyl Acetate and concentrated to give the title product as a mixture of two oximes. MS(ES) for $C_{28}H_{26}FNO_5$ [M+H]$^+$: 476.2, [M-H]$^-$: 474.2.

Example 38

(2S)-3-[4-(5-{4-[(4-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid

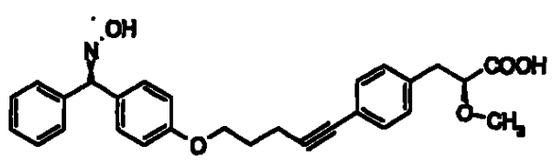


Chiral

(2S)-3-(4-{5-[4-(4-Fluoro-benzoyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid from Example 25 (1 eq) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5% was added to the residue to pH = 3. Extracted with Ethyl Acetate and concentrated to give the title product as a mixture of two oximes. MS(ES) for $C_{28}H_{26}FNO_5$ $[M+H]^+$: 476.2, $[M-H]^-$: 474.2.

Example 39

(2S)-3-(4-{5-[4-(Hydroxyimino-phenyl-methyl)-phenoxy]-pent-1-ynyl}-phenyl)-2-methoxy-propionic acid

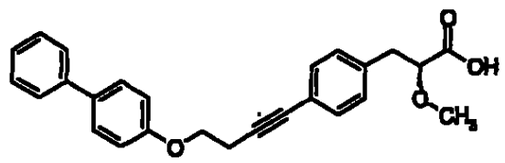


Chiral

(2S)-3-{4-[5-(4-Benzoyl-phenoxy)-pent-1-ynyl]-phenyl)-2-methoxy-propionic acid from Example 23, (1 eq) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5 % was added to the residue to pH = 3. Extracted with Ethyl Acetate and concentrated to give the title product as a mixture of two oximes. MS(ES) for $C_{28}H_{27}NO_5$ $[M+H]^+$: 458.2.

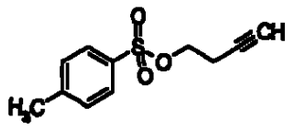
Example 40

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid:



Step A

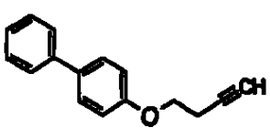
Toluene-4-sulfonic acid but-3-ynyl ester



A solution of 3-butyn-1-ol (1 mL, 13.31 mmol), p-toluenesulphonyl chloride (2.519 g, 13.21 mmol), triethylamine (2.03 mL, 14.53 mmol) and 4-dimethylaminopyridine (0.081 g, 0.66 mmol) in 20 mL of dichloromethane were stirred at room temperature overnight. The solution was diluted with dichloromethane (20 mL), washed with 0.5N HCl (40 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated to produce an oil (2.82 g, 95 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.80 (d, 2H, *J*=8.3), 7.35 (d, 2H, *J*=8.1), 4.10 (t, 2H, *J*=7.0), 2.55 (dt, 2H, *J*=2.7, 7.0), 2.45 (s, 3H), 1.97 (t, 1H, *J*=2.7).

Step B

4-But-3-ynyloxy-biphenyl

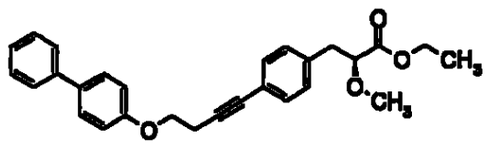


A solution of 4-phenylphenol (0.774 g, 4.55 mmol) and potassium *tert*-butoxide (0.51 g, 4.55 mmol) in toluene (20 mL) was stirred for 1 h at room temperature. Sodium iodide (0.068 g, 0.45 mmol) and toluene-4-sulfonic acid but-3-ynyl ester (1.02 g, 4.55 mmol) were added, and the mixture heated to reflux for 24 hours. The mixture was cooled to room temperature, diluted with diethyl ether (20 mL), washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by silica gel chromatography (silica gel,

hexanes/ethyl acetate 3:1, R_f 0.57) to give an oil (140 mg, 14 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.50 (m, 4H), 7.46-7.38 (m, 2H), 7.32 (d, 1H, *J*=7.3), 7.02-6.95 (m, 2H), 4.15 (t, 2H, *J*=7.0), 2.71 (dt, 2H, *J*=2.7, 7.3), 2.06 (t, 1H, *J*=2.7).

Step C

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid ethyl ester



To a solution of (2S)-2-methoxy-3-(4-trifluoro-methanesulfonyloxy-phenyl)-propionic acid ethyl ester (1.157 g, 3.4 mmol) (Example 1, Step A) in 30 mL of degassed piperidine was added 4-but-3-ynyloxy-biphenyl (0.9 g, 4.85 mmol), tetrakis(triphenylphosphine)palladium (0) (0.196 g, 0.17 mmol), triphenylphosphine (0.09 g, 0.34 mmol), and cooper (I) iodide (0.065 g, 0.34 mmol). The solution was stirred for 3 h at 80 °C and cooled to room temperature. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (silica gel, hexanes/diethyl ether 9:1, R_f 0.27) to a brown oil (0.7 g, 48%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.58-7.30 (m, 9H), 7.17 (d, 2H, *J*=8.0), 7.02 (d, 2H, *J*=8.9), 4.22 (t, 2H, *J*=7.3), 4.18 (q, 2H, *J*=7.0), 3.93 (dd, 1H, *J*=7.3, 5.6), 3.35 (s, 3H), 3.02 (s, 1H), 2.99 (d, 1H, *J*=2.4), 2.92 (t, 2H, *J*=7.3), 1.24 (t, 3H, *J*=7.3).

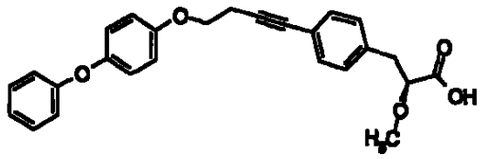
Step D

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-{4-[4-(biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid ethyl ester via the standard hydrolysis procedure C. The residue was purified by chromatography (silica gel, hexanes/ethyl acetate/acetic acid 50:50:1, R_f 0.25) to produce a white solid (86 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.51 (m, 4H), 7.45-7.30 (m, 5H), 7.19 (d, 2H, *J*=8.0), 7.01 (d, 2H, *J*=8.8), 4.20 (t, 2H, *J*=6.9), 3.98 (dd, 1H, *J*=7.7, 4.4), 3.37 (s, 3 H), 3.11 (dd, 1H, *J*=14.3, 4.4), 3.00 (dd, 1H, *J*=14.3, 7.7), 2.91 (t, 2H, *J*=7.0).

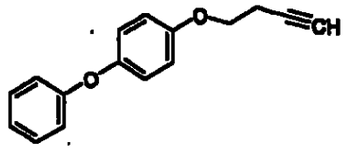
Example 41

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-but-1-ynyl]-phenyl}-propionic acid



Step A

1-But-3-ynyloxy-4-phenyloxybenzene



This compound was prepared from 4-phenoxyphenol and toluene-4-sulfonic acid but-3-ynyl ester (Example 40, Step A) following the procedure described in Example 40, Step B. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 77.35-7.26 (m, 2H), 7.05-6.87 (m, 5H), 4.09 (t, 2H, *J*=7.0), 2.69 (dt, 2H, *J*=2.4, 7.0), 2.05 (t, 1H, *J*=2.1).

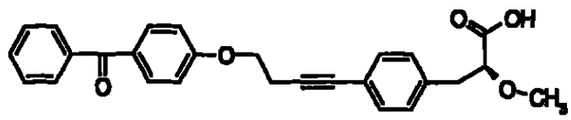
Step B

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-but-1-ynyl]-phenyl}-propionic acid

The title compound was prepared from 1-but-3-ynyloxy-4-phenyloxybenzene and (2S)-2-methoxy-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid ethyl ester (Example 1, Step A) following the procedure described in Example 40, Step C. The ethyl ester derivative was contaminated with starting triflate. The mixture was hydrolyzed using the Standard Procedure C. The residue was purified by chromatography (silica gel, hexanes/ethyl acetate-Acetic acid 50:50:1, R_f 0.25) to produce a white solid (7%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.35-7.28 (m, 4H), 7.16 (d, 2H, *J*=8.0), 7.02-6.87 (m, 7H), 4.13 (t, 2H, *J*=7.0), 3.97 (dd, 1H, *J*=7.7, 4.4), 3.36 (s, 3H), 3.11 (dd, 1H, *J*=14.3, 4.4), 2.97 (dd, 1H, *J*=14.3, 7.7), 2.87 (t, 2H, *J*=7.0).MS (ES) fro $C_{26}H_{24}O_5$ $[M+NH_4]^+$: 434.2, $[M+Na]^+$: 439.2.

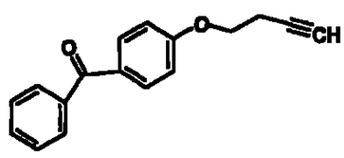
Example 42

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid



Step A

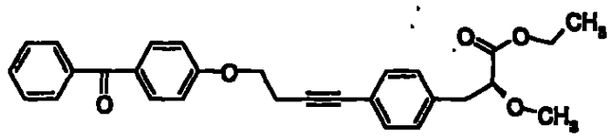
(4-But-3-ynyloxy-phenyl)-phenyl-methanone



This compound was prepared from 4-hydroxybenzophenone and toluene-4-sulfonic acid but-3-ynyl ester (Example 40, Step A) following the procedure described in Example 40, Step B (8 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.84-7.73 (m, 4 H), 7.57-7.43 (m, 3H), 6.97 (d, 2H, *J*=8.6), 4.18 (t, 2H, *J*=7.0), 2.73 (dt, 2H, *J*=2.7, 7.0), 2.06 (t, 1H, *J*=2.7).

Step B

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid ethyl ester



This compound was prepared from (4-but-3-ynyloxy-phenyl)-phenylmethanone and (2S)-2-Methoxy-3-(4-trifluoromethane-sulfonyloxy-phenyl)-propionic acid ethyl ester (Example 1, Step A) following the procedure described in Example 38, Step C (66 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.85-7.73 (m, 4H), 7.57-7.43 (m, 3H), 7.34 (d, 2H, *J*=8.1), 7.16 (d, 2H, *J*=8.3), 7.00 (d, 2H, *J*=8.6), 4.25 (t, 2H, *J*=7.0), 4.18 (q, 2H, *J*=7.0), 3.92 (dd, 1H, *J*=7.3, 5.6), 3.34 (s, 3H), 3.01 (s, 1H), 2.98 (d, 1H, *J*=3.5), 2.93 (t, 2H, *J*=7.0), 1.23 (t, 3H, *J*=7.3).

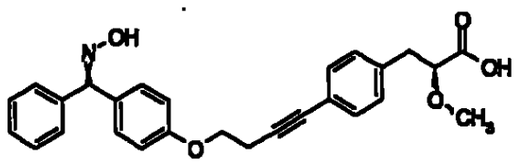
Step C

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-{4-[4-(4-benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid ethyl ester via the standard hydrolysis procedure C to produce a white solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.83-7.71 (m, 4H), 7.55-7.44 (m, 3H), 7.32 (d, 2H, *J*=8.0), 7.16 (d, 2H, *J*=8.4), 6.97 (d, 2H, *J*=9.1), 4.22 (t, 2H, *J*=7.0), 3.96 (dd, 1H, *J*=7.7, 4.4), 3.35 (s, 3H), 3.10 (dd, 1H, *J*=13.9, 4.4), 2.98 (dd, 1H, *J*=13.9, 7.7), 2.91 (t, 2H, *J*=7.0).

Example 43

(2S)-3-{4-[4-[4-(Hydroxyimino-phenyl-methyl)-phenoxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid

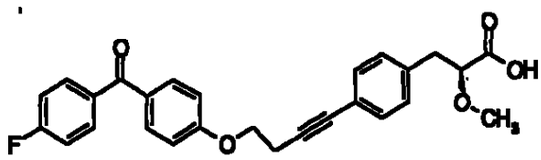


Chiral

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid from Example 42, (1 eq) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5% was added to the residue to pH = 3. Extracted with Ethyl Acetate and concentrated to give the title product as a mixture of two oximes. MS (ES) for $C_{27}H_{25}NO_5$ [M+H]+: 444.2

Example 44

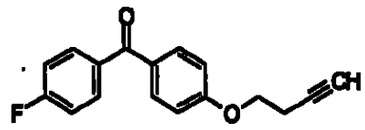
(2S)-3-(4-{4-[4-(4-Fluoro-benzoyl)-phenoxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid



Chiral

Step A

(4-But-3-ynyloxy-phenyl)-(4-fluoro-phenyl)-methanone



This compound was prepared from 4-fluoro-hydroxybenzophenone and toluene-4-sulfonic acid but-3-ynyl ester (Example 40, Step A) following the procedure described in Example 40, Step B.

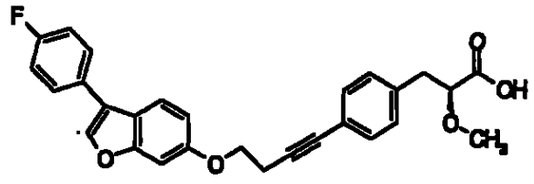
Step B

(2S)-3-(4-{4-[4-(4-Fluoro-benzoyl)-phenoxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid

The title compound was prepared from (4-But-3-ynyloxy-phenyl)-(4-fluoro-phenyl)-methanone and (2S)-2-methoxy-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid ethyl ester (Example 1, Step A) following the procedure described in Example 40, Step C. The ethyl ester derivative was contaminated with starting triflate. The mixture was hydrolyzed using the standard hydrolysis procedure C. The residue was purified by chromatography. MS(ES) for $C_{27}H_{23}FO$ $[M+H]^+$: 447.2.

Example 45

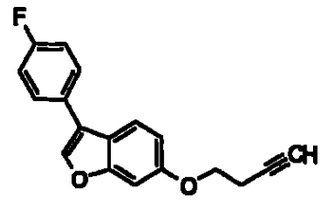
(2S)-3-(4-{4-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid



Chiral

Step A

6-But-3-ynyloxy-3-(4-fluoro-phenyl)-benzofuran



This compound was prepared from 6-hydroxy-3-(4-fluorophenyl)benzofurane and toluene-4-sulfonic acid but-3-ynyl ester (Example 40, Step A) following the procedure described in Example 40, Step B.

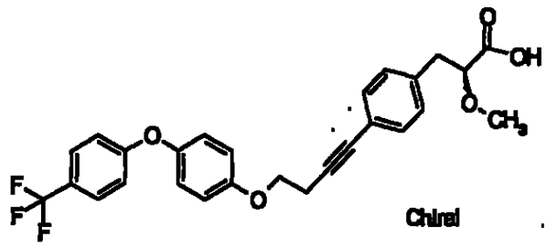
Step B

(2S)-3-{4-{4-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid

The title compound was prepared from 6-But-3-ynyloxy-3-(4-fluoro-phenyl)-benzofuran and (2S)-2-methoxy-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid ethyl ester (Example 1, Step A) following the procedure described in Example 40, Step C. The ethyl ester derivative was contaminated with starting triflate. The mixture was hydrolyzed using the Standard Procedure C. The residue was purified by chromatography. MS(ES) for $C_{28}H_{23}FO_5$ [M-H]$^-$: 457.2

Example 46

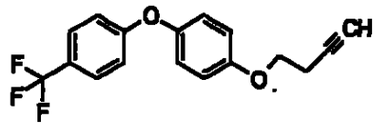
(2S)-2-Methoxy-3-(4-{4-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-but-1-ynyl}-phenyl)-propionic acid



Chiral

Step A

4-(3-butynyloxy)-4'-trifluoromethylphenyloxy phenyl



This compound was prepared from trifluoromethylphenoxyphenol and toluene-4-sulfonic acid but-3-ynyl ester (Example 40, Step A) following the procedure described in Example 40, Step B.

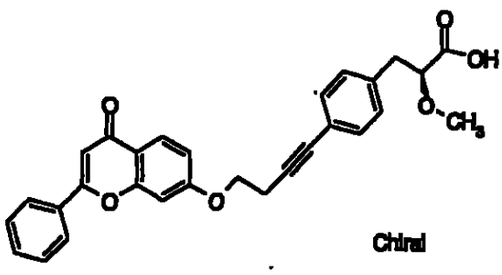
Step B

(2S)-2-Methoxy-3-{4-[4-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-but-1-ynyl}-phenyl)-propionic acid

The title compound was prepared from 4-(3-butynyloxy)-4'-trifluoromethylphenyloxy phenyl and (2S)-2-methoxy-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid ethyl ester (Example 1, Step A) following the procedure described in Example 40, Step C. The ethyl ester derivative was contaminated with starting triflate. The mixture was hydrolyzed using the Standard Procedure C. The residue was purified by chromatography. MS(ES) for $C_{27}H_{23}F_3O_5$ [M-H]-: 483.2

Example 47

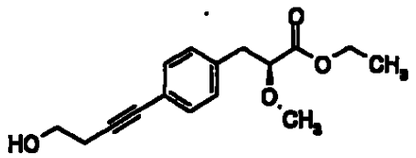
(2S)-2-Methoxy-3-{4-[4-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-but-1-ynyl]-phenyl}-propionic acid



Chiral

Step A

3-[4-(4-Hydroxy-but-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester



This compound was prepared form 4-butyn-1-ol following the procedure described in Example 1, Step B.

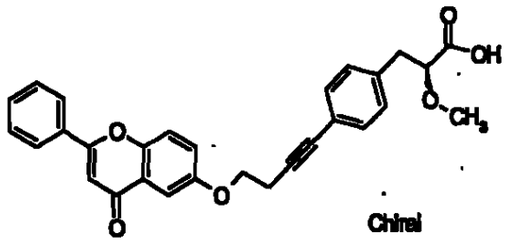
Step B

(2S)-2-Methoxy-3-{4-[4-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-but-1-ynyl]-phenyl}-propionic acid

The title compound was prepared from 7-hydroxyflavone by the Standard coupling-hydrolisis Procedure A but using for the Mitsounobu reaction toluene as solvent and DIAD instead DEAD. MS(ES) for $C_{28}H_{24}O_6$ $[M+H]^+$: 429.2.

Example 48

(2S)-2-Methoxy-3-{4-[4-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-but-1-ynyl]-phenyl}-propionic acid

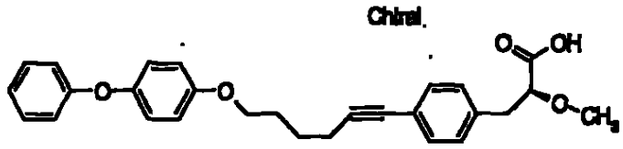


Chiral

The title compound was prepared from 3-[4-(4-Hydroxy-but-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 47, Step A and 6-hydroxyflavone following the standard coupling-hydrolysis procedure A using toluene as solvent and DIAD instead DEAD. MS(ES) for $C_{28}H_{24}O_6$ $[M+H]^+$: 469.2.

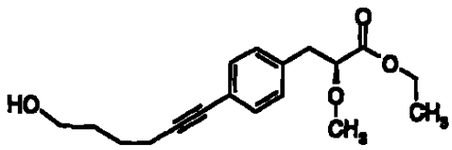
Example 49

(2S)-2-Methoxy-3-{4-[6-(4-phenoxy-phenoxy)-hex-1-ynyl]-phenyl}-propionic acid



Step A

(2S)-3-[4-(6-Hydroxy-hex-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester



To a solution of (2S)-(3-(4-iodophenyl)-2-methoxy-propionic acid ethyl ester (1.6 g, 4.81 mmol) in 100 mL of degassed piperidine was added 5-hexin-1-ol (0.709 g, 7.24 mmol), tetrakis(triphenylphosphine)palladium (0) (0.278 g, 0.24 mmol), triphenylphosphine (0.125 g, 0.48 mmol), and cooper (I) iodide (0.091 g, 0.48 mmol). The solution was stirred for 3 hours at 80°C and cooled to room temperature. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 3:1 to give title compound as a yellow oil (1.18g, 74% yield). MS(ES) for $C_{18}H_{24}O_4[M+NH_4]^+$: 322.2.

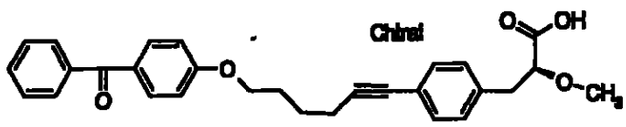
Step B

(2S)-2-Methoxy-3-{4-[6-(4-phenoxy-phenoxy)-hex-1-ynyl]-phenyl}-propionic acid

The title compound was prepared from 3-[4-(6-Hydroxy-hex-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester and 4-phenoxyphenol via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce the title compound. MS(ES) for $C_{28}H_{28}O_5[M+H]^+$: 445.2

Example 50

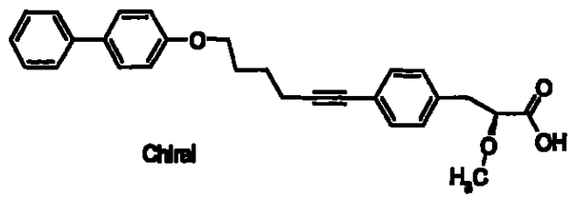
(2S)-3-{4-[6-(4-Benzoyl-phenoxy)-hex-1-ynyl]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(6-Hydroxy-hex-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 49, Step A) and 4-hydroxybenzophenone via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce the title compound. MS(ES) for $C_{28}H_{28}O_5[M+H]^+$: 457.2

Example 51

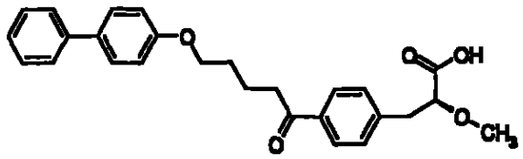
(2S)-3-{4-[6-(Biphenyl-4-yloxy)-hex-1-ynyl]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(6-Hydroxy-hex-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 49, Step A) and 4-phenylphenol via the standard Mitsunobu coupling-hydrolysis procedure (Standard Procedure A) to produce the title compound. MS(ES) for $C_{28}H_{28}O_4[M+NH_4]^+$: 446.2.

Example 52

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pentanoyl]-phenyl}-2-methoxy-propionic acid

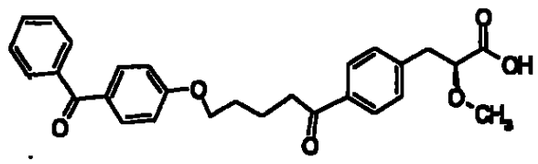


A solution of triphenylphosphine (0.24 g, 0.915 mmol) in 5 mL of dry THF was treated at 0 °C with diethylazodicarboxylate (0.159 g, 0.915 mmol) and stirred for 20 min. A solution of (2S)-3-[4-(5-hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 21, Step A) (0.18 g, 0.61 mmol) and 4-phenylphenol (0.156 g, 0.915 mmol) in 2 mL of dry THF was added, and the mixture was stirred

at room temperature overnight. The mixture was concentrated under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 10:1 to 3:1). Fractions with R_fs 0.48 and 0.45 (hexanes/ethyl acetate 2:1) corresponding to the coupled compound and starting phenol, respectively, were combined and concentrated. The mixture was dissolved in 5 mL of methanol and was treated with a mixture of 75 mg of mercury (II) oxide and 4% sulfuric acid in water. The solution was stirred at 55 °C for 3 h, cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (20 mL), and extracted with dichloromethane (4 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in 6 mL of methanol and 2 mL of 1N NaOH and stirred for 2 hours. The methanol was evaporated under vacuum, and the aqueous solution was diluted with brine (6 mL) and washed with diethyl ether (3 x 15 mL). The aqueous layer was acidified with 1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated to a white solid (19 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.89 (d, 2H, J=8.4), 7.55-7.23 (m, 9H), 6.93 (d, 2H, J=8.8), 4.06-3.99 (m, 3H), 3.38 (s, 3H), 3.18 (dd, 1H, J=4.3, 4.4), 3.03 (t+m, 3 H, J=6.9), 1.96-1.86 (m, 4H).

Example 53

(2S)-3-{4-[5-(4-Benzoyl-phenoxy)-pentanoyl]-phenyl}-2-methoxy-propionic acid



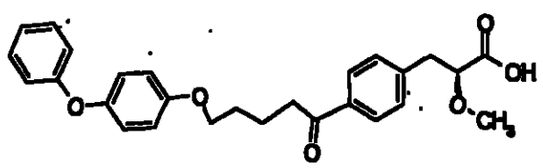
Chiral

A solution of triphenylphosphine (0.915 mmol) in 5 mL of dry THF was treated at 0°C with diethylazodicarboxylate (0.915 mmol) and stirred for 20 min. A solution of (2S)-3-[4-(5-hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 21, Step A) (0.61 mmol) and 4-benzoylphenol (0.915 mmol) in 2 mL of dry THF was added, and the mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 10:1 to 3:1). Fractions with R_fs

0.48 and 0.45 (hexanes/ethyl acetate 2:1) corresponding to the coupled compound and starting phenol, respectively, were combined and concentrated. The mixture was dissolved in 5 mL of methanol and was treated with a mixture of 75 mg of mercury (II) oxide and 4% sulfuric acid in water. The solution was stirred at 55°C for 3 hours, cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (20 mL), and extracted with dichloromethane (4 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in 6 mL of methanol and 2 mL of 1N NaOH and stirred for 2 hours. The methanol was evaporated under vacuum, and the aqueous solution was diluted with brine (6 mL) and washed with diethyl ether (3 x 15 mL). The aqueous layer was acidified with 1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL) then concentrated to give the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.91-7.72 (m, 5H), 7.56-7.32 (m, 6H), 6.92 (d, 2H, J=8.9), 4.12-4.03 (m, 3H), 3.42 (s, 3H), 3.19-3.05 (m, 4H), 1.95-1.92 (m, 4H).

Example 54

(2S)-2-Methoxy-3-{4-[5-(4-phenoxy-phenoxy)-pentanoyl]-phenyl}-propionic acid



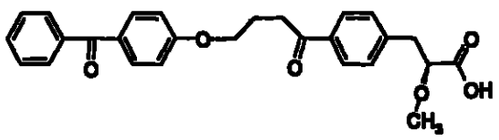
Chiral

A solution of triphenylphosphine (0.915 mmol) in 5 mL of dry THF was treated at 0°C with diethylazodicarboxylate (0.915 mmol) and stirred for 20 min. A solution of (2S)-3-[4-(5-hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 21, Step A) (0.61 mmol) and 4-phenoxyphenol (0.915 mmol) in 2 mL of dry THF was added, and the mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 10:1 to 3:1). Fractions with R_fs 0.48 and 0.45 (hexanes/ethyl acetate 2:1) corresponding to the coupled compound and starting phenol, respectively, were combined and concentrated. The mixture was dissolved in 5 mL of methanol and was treated with a mixture of 75 mg of

mercury (II) oxide and 4% sulfuric acid in water. The solution was stirred at 55°C for 3 hours, cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (20 mL), and extracted with dichloromethane (4 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in 6 mL of methanol and 2 mL of 1N NaOH and stirred for 2 hours. The methanol was evaporated under vacuum, and the aqueous solution was diluted with brine (6 mL) and washed with diethyl ether (3 x 15 mL). The aqueous layer was acidified with 1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL) then concentrated to give the title compound. ^{1}H-NMR (CDCl3, 200.15 MHz): 7.91 (d, 2H, J=8.3), 7.36-7.27 (m, 4H), 7.07-6.83 (m, 7H), 4.08-3.96 (m, 3H), 3.41 (s, 3H), 3.22 (dd, 1H, J=14.0, 4.3), 3.14-3.01 (m, 4H), 1.26 (s, 1H).

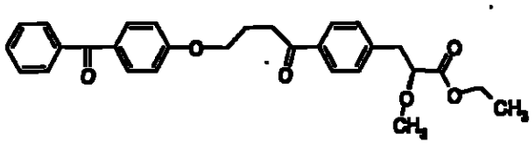
Example 55

3-{4-[4-(4-Benzoyl-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid



Step A

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid ethyl ester



(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-but-1-ynyl]phenyl}-2-methoxy-propionic acid ethyl ester (Example 42, Step B) (0.08 g, 0.17 mmol) was dissolved in 4 mL of methanol. To this solution was added 3 mL of a solution of 0.075 g of mercury (II) oxide in 12 mL of 4% sulfuric acid. The mixture was stirred at 55°C for 3 hours, cooled to room temperature, and diluted with 20 mL saturated $NaHCO_3$ solution.

The mixture was extracted with of dichloromethane (4 x 20 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 3:1) to give a yellow oil (72 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.92 (d, 2H, *J*=8.6), 7.83-7.72 (m, 4H), 7.60-7.42 (m, 3H), 7.34 (d, 2H, *J*=8.6), 6.95 (d, 2 H, *J*=8.9), 4.19 (q, 2H, *J*=7.3), 4.15 (t, 2H, *J*=6.2), 3.97 (dd, 1H, *J*=7.3, 5.4), 3.35 (s, 3H), 3.19 (t, 2H, *J*=7.0), 3.08 (d, 1H, *J*=5.1), 3.07 (d, 1H, *J*=7.5), 2.27 (qn, 2H, *J*=6.2), 1.24 (t, 3H, *J*=7.3).

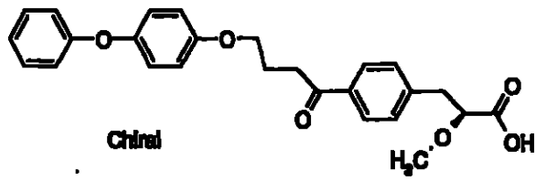
Step B

3-{4-[4-(4-Benzoyl-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2*S*)-3-{4-[4-(4-benzoyl-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid ethyl ester via the standard hydrolysis procedure C. White solid (71%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.90 (d, 2H, *J*=8.0), 7.80-7.70 (m, 4H), 7.58-7.39 (m, 3H), 7.32 (d, 2H, *J*=8.4), 6.92 (d, 3H, *J*=9.1), 4.13 (t, 2H, *J*=6.2), 4.02 (dd, 1H, *J*=7.3, 4.4), 3.38 (s, 3H), 3.20-3.00 (m, 4H), 2.25 (qn, 2H, *J*=6.2).

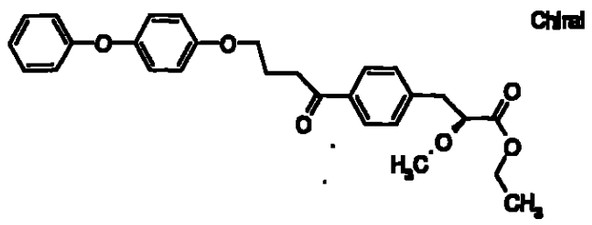
Example 56

(2*S*)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butyryl]-phenyl}-propionic acid



Step A

2*S*)-3-{4-[4-(4-phenoxy-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid ethyl ester



(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-but-1-ynyl]-phenyl}-propionic acid ethyl ester (0.17 mmol) from Example 41, was dissolved in 4 ml of methanol. To this solution was added 3 ml of a solution of 0.075 g of mercury (II) oxide in 12 mL of 4% sulfuric acid. The mixture was stirred at 55°C for 3 hour, cooled to room temperature, and diluted with 20 mL saturated $NaHCO_3$ solution. The mixture was extracted with of dichloromethane (4 x 20 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 3:1) to give a yellow oil.

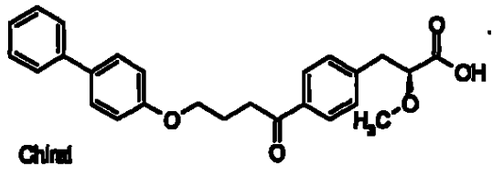
Step B

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butyryl]-phenyl}-propionic acid

The title compound was prepared from (2S)-3-{4-[4-(4-phenoxy-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid ethyl ester via the standard hydrolysis procedure C. MS (ES) for $C_{26}H_{26}O_6$ $[M+H]^+$: 435.2.

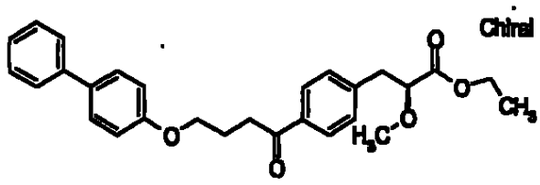
Example 57

(2S)-3-[4-(Biphenyl-4-yloxy)-butyryl-phenyl]-2-methoxy-propionic acid



Step A

(2S)-3-{4-[4-(4-phenylphenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid ethyl ester



(2S)-3-{4-[4-(Biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid ethyl ester (0.17 mmol) from Example 40, Step C, was dissolved in 4 ml of methanol. To this solution was added 3 ml of a solution of 0.075 g of mercury (II)

oxide in 12 mL of 4% sulfuric acid. The mixture was stirred at 55°C for 3 hours, cooled to room temperature, and diluted with 20 mL saturated $NaHCO_3$ solution. The mixture was extracted with of dichloromethane (4 x 20 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 3:1) to give a yellow oil

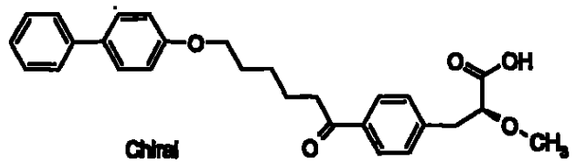
Step B

(2S)-3-[4-(Biphenyl-4-yloxy)-butyryl-phenyl]-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-{4-[4-(4-phenylphenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid ethyl ester via the standard hydrolysis procedure C. MS (ES) for $C_{26}H_{26}O_5$ $[M+H]^+$: 419.2.

Example 58

(2S)-3-{4-[6-(Biphenyl-4-yloxy)-hexanoyl]-phenyl}-2-methoxy-propionic acid

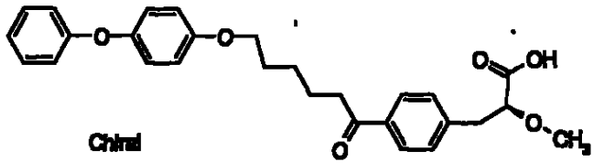


A solution of triphenylphosphine (0.474 g, 1.8 mmol) in 50 mL of dry THF was treated at 0°C with diethylazodicarboxylate (1.8 mmol) and stirred for 20 min. A solution of 3-[4-(6-Hydroxy-hex-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 49, Step A) (0.365 g, 1.2 mmol) and 4-phenylphenol (0.307g, 1.8 mmol) in 10 mL of dry THF was added, and the mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 10:1 to 3:1). Fractions with R_fs 0.48 and 0.45 (hexanes/ethyl acetate 2:1) corresponding to the coupled compound and starting phenol, respectively, were combined and concentrated. The mixture was dissolved in 5 mL of methanol and was treated with a mixture of 0-712 mg of mercury (II) oxide and 12 ml of4% sulfuric acid in water. The solution was stirred at 55°C for 3 hours, cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (20 mL), and extracted with dichloromethane (4 x 20 mL). The

combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in 6 mL of methanol and 2 mL of 1N NaOH and stirred for 2 hours. The methanol was evaporated under vacuum, and the aqueous solution was diluted with brine (6 mL) and washed with diethyl ether (3 x 15 mL). The aqueous layer was acidified with 1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give the title compound. MS(ES) for $C_{28}H_{30}O_5[M+H]^+$: 447.2.

Example 59

(2S)-2-Methoxy-3-{4-[6-(4-phenoxy-phenoxy)-hexanoyl]-phenyl}-propionic acid

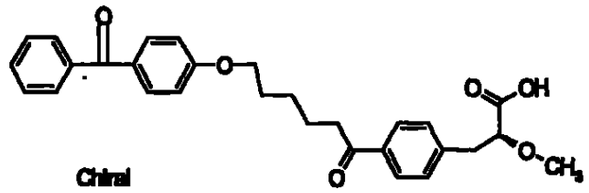


A solution of triphenylphosphine (1.8 mmol) in 50 mL of dry THF was treated at 0°C with diethylazodicarboxylate (1.8 mmol) and stirred for 20 min. A solution of 3-[4-(6-Hydroxy-hex-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 49, Step A) (1.2 mmol) and 4-phenoxyphenol (1.8 mmol) in 10 mL of dry THF was added, and the mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 10:1 to 3:1). Fractions with R_fs 0.48 and 0.45 (hexanes/ethyl acetate 2:1) corresponding to the coupled compound and starting phenol, respectively, were combined and concentrated. The mixture was dissolved in 5 mL of methanol and was treated with a mixture of 0.712 mg of mercury (II) oxide and 12 ml of 4% sulfuric acid in water. The solution was stirred at 55°C for 3 hours, cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (20 mL), and extracted with dichloromethane (4 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in 6 mL of methanol and 2 mL of 1N NaOH and stirred for 2 hours. The methanol was evaporated under vacuum, and the aqueous solution was diluted with brine (6 mL) and washed with diethyl ether (3 x 15 mL). The aqueous layer

was acidified with 1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give the title compound. MS(ES) for $C_{28}H_{30}O_6[M+H]^+$: 463.2.

Example 60

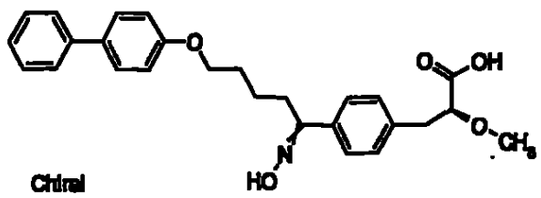
(2S)-3-{4-[6-(4-Benzoyl-phenoxy)-hexanoyl]-phenyl}-2-methoxy-propionic acid



A solution of triphenylphosphine (1.8 mmol) in 50 mL of dry THF was treated at 0 °C with diethylazodicarboxylate (1.8 mmol) and stirred for 20 min. A solution of 3-[4-(6-Hydroxy-hex-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 49, Step A) (1.2 mmol) and 4-phydroxybenzophenone (1.8 mmol) in 10 mL of dry THF was added, and the mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 10:1 to 3:1). Fractions with R_fs 0.48 and 0.45 (hexanes/ethyl acetate 2:1) corresponding to the coupled compound and starting phenol, respectively, were combined and concentrated. The mixture was dissolved in 5 mL of methanol and was treated with a mixture of 0.712 mg of mercury (II) oxide and 12 ml of 4% sulfuric acid in water. The solution was stirred at 55°C for 3 hours, cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (20 mL), and extracted with dichloromethane (4 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in 6 mL of methanol and 2 mL of 1N NaOH and stirred for 2 hours. The methanol was evaporated under vacuum, and the aqueous solution was diluted with brine (6 mL) and washed with diethyl ether (3 x 15 mL). The aqueous layer was acidified with 1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give the title compound. MS(ES) for $C_{28}H_{30}O_6[M+H]^+$: 475.2.

Example 61

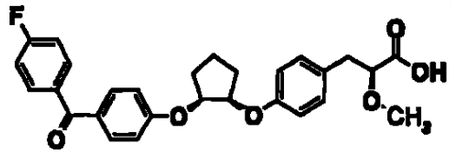
(2S)-3-{4-[5-(Biphenyl-4-yloxy)-1-hydroxyimino-pentyl]-phenyl}-2-methoxy-propionic acid



(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pentanoyl]-phenyl}-2-methoxy-propionic acid from Example 52, (1 eq) was mixed with Hydroxylamine chlorydrate (4 eq), pyrydine (10 eq) and Ethanol (2 ml) and the mixture reaction was stirred overnight. The ethanol was evaporated under vacuo and HCl 0.5% was added to the residue to pH = 3. Extracted with Ethyl Acetate and concentrated to give the title product as a mixture of two oximes. MS(ES) for $C_{27}H_{29}NO_5$ $[M+H]^+$: 448.2.2, $[M-H]^-$: 446.2.

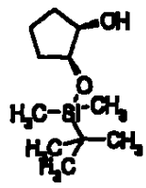
Example 62

(2*S*, 1'*R**, 2'*S**)-3-(4-{2'-[4-(4-Fluoro-benzoyl)-phenoxy]-cyclopentyloxy}-phenyl)-2-methoxy-propionic acid



Step A

cis-2-(tert-Butyl-dimethyl-silanyloxy)-cyclopentanol

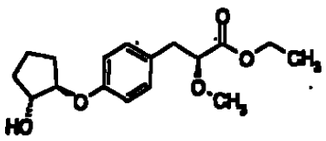


The title compound was prepared from meso-1,2-cyclopentanediol via the Standard Procedure D for the monoprotection of diols. The residue was purified by silica gel

chromatography (hexanes/ethyl 3:1, R_f 0.55) (50 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 4.04 (dt, 1H, *J*=4.6, 6.2), 3.95-3.89 (m, 1H), 2.59 (d, 1H, *J*=3.8), 1.88-1.49 (m, 6H), 0.91 (s, 9H), 0.09 (s, 6H).

Step B

(2*S*, 1'*R*, 2'*R*) 3-[4-(2'-Hydroxy-cyclopentyloxy)-phenyl]-2-methoxy-propionic acid ethyl ester



A solution of triphenylphosphine (0.634 g, 2.23 mmol) in 15 mL of dry THF was treated at 0°C with diethylazodicarboxylate (0.368 mL, 0.2.45 mmol) and stirred for 20 min. A solution of (2*S*)-2-methoxy-3-hydroxyphenylpropionic acid ethyl (0.5 g, 2.23 mmol) and *cis*-2-(tert-butyl-dimethyl-silanyloxy)cyclopentanol (0.531 g, 0.245 mmol) in 5 mL of dry THF was added to the solution, and the mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 6:1). Fraction with R_fs 0.55 (hexanes/ethyl acetate 3:1) corresponding to the coupled compound and starting phenol, respectively, were collected and concentrated. The residue was dissolved in 4 mL of THF, and tetrabutylammonium fluoride (2.23 mL, 1 M in THF) was added. The solution was stirred for 2 hours at room temperature, diluted with 30 mL of diethyl ether, and washed with 1N HCl (2 x 20 mL). The organic solution was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 3:1, R_f 0.9) to the product (60 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.11 (d, 2H, *J*=8.6), 6.80 (d, 2H, *J*=8.9), 4.43-4.40 (m, 1H), 4.23-4.12 (m, 4H); 3.90 (dd, 1H, *J*=7.0, 5.9); 3.35 (s, 3H); 2.95 (d, 2H, *J*=6.7), 2.16-1.60 (m, 6H), 1.22 (t, 3H, *J*=7.0), 0.88 (s, 9H), 0.05 (d, 3H, *J*=2.2).

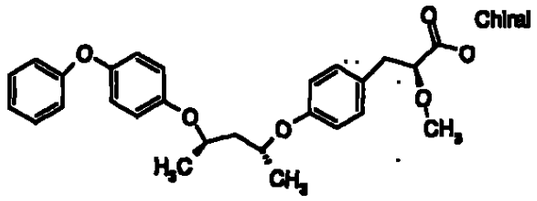
Step C

(2S, 1'R*, 2'S*) 3-(4-{2'-[4-(4-Fluoro-benzoyl)-phenoxy]-cyclopentyloxy}-phenyl)-2-methoxy-propionic acid

The title compound was prepared from (2S, 1'R, 2'R)-3-[4-(2'-hydroxy-cyclopentyloxy)-phenyl]-2-methoxy-propionic acid ethyl ester and 4-fluoro-4-hydroxybenzophenone via the Standard Procedure A. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.82-7.67 (m, 4H), 7.18-7.06 (m, 4H), 6.93 (d, 2H, *J*=8.9), 6.76 (d, 2H, *J*=8.6), 4.88-4.74 (m, 2H), 3.97-3.94 (m, 1H), 3.39 (s, 3H); 3.09-2.89 (m, 2H); 2.23-1.98 (m, 6H). MS (ES) for $C_{28}H_{27}FO_6$ $[M+H]^+$: 479.2, $[M+Na]^+$: 501.2.

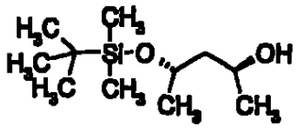
Example 63

(2S)-(1'R,3'R)-2-Methoxy-3-{4-[1',3'-dimethyl-3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid



Step A

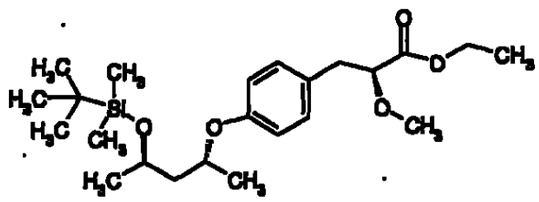
(2S,4S)-4-(tert-Butyl-dimethyl-silanyloxy)-pentan-2-ol



The title compound was prepared starting from (2S,4S)-pentanediol using the Standard Procedure D. MS (ES) for $C_{11}H_{26}O_2Si$ $[M+H]_+$: 219.2.

Step B

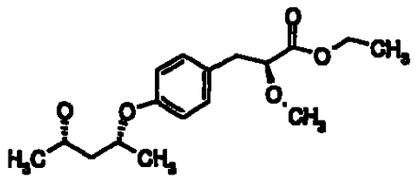
(2S)-(1'R,3'S)-3-{4-[3'-(*tert*-Butyl-dimethyl-silanyloxy)-1'-methyl-butoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



The title compound was prepared using the Standard Procedure for the Mitsounobu coupling B to give the product.

Step C

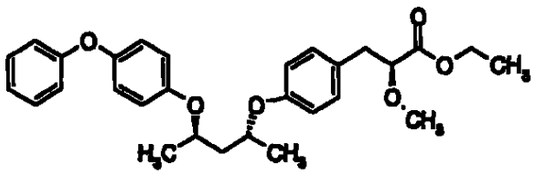
(2S)-(1'*R*,3'*S*)-3-[4-(3'-Hydroxy-1'-methyl-butoxy)-phenyl]-2-methoxy-propionic acid methyl ester



The title compound was prepared folowing the Standard Procedure E to give the product. MS (ES) for $C_{17}H_{26}O_5$ $[M+H]^+$: 328.2.

Step D

(2S)-(1'*R*,2'*R*)-2-Methoxy-3-{4-[1'-methyl-3'-(4-phenoxy-phenoxy)-butoxy]-phenyl}-propionic acid ethyl ester



The title compound was prepared following the Standard Mitsounobu coupling procedure B to give the corresponding product. MS (ES) for $C_{28}H_{34}O_6$ $[M+NH_4]^+$: 496.2.

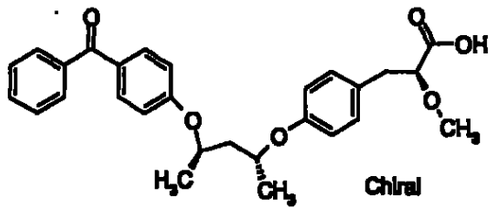
Step E

(2S)-(1'R,3'R)-2-Methoxy-3-{4-[1',3'-dimethyl-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid

The title compound was prepared by the Standard hydrolysis procedure C of the compound from Step D to give the final compound as a gummy solid. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.32-7.24 (m, 2H), 7.10-6.75 (m, 11H), 4.70-4.50 (m, 2H), 3.95 (dd, 1H, J=7.3, 4.3), 3.36 (s, 3H), 3.06 (dd, 1H, J=14.5, 4.6), 2.92 (dd, 1H, J=14.2, 7.5), 1.96 (dd, 2H, J=6.7, 5.4), 1.31 (d, 6H, J=6.2).ppm. MS(ES) for $C_{27}H_{30}O_6$ $[M+NH_4]^+$: 468.2, $[M-H]^-$: 449.2.

Example 64

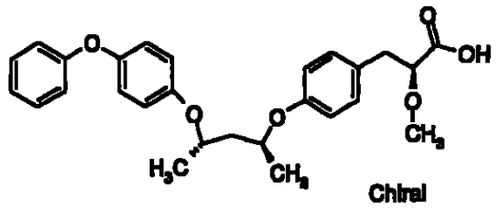
(2S)-(1'R,3'R)-3-{4-[3-(4-Benzoylphenoxy)-1',3'-dimethylpropoxyl]-phenyl}2-methoxy-propionic acid



The title compound was prepared in a manner analogous that Example 63, starting from the (2S,4S)-pentanediol to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 9.24 (s, 1H), 7.75 (t, 1H, J=1.6), 7.70 (t, 1H, J=1.9), 7.69 (dd, 2H, J=12.6, 2.2), 7.59-7.40 (m, 3H), 7.04 (d, 2H, J=8.6), 6.85 (d, 2H, J=9.1), 6.69 (d, 2H, J=8.9), 4.87-4.72 (m, 1H), 4.62-4.47 (m, 1H), 3.94 (dd, 1H, J=7.0, 5.6), 3.37 (s, 3H), 3.05-2.86 (m, 2H), 1.99 (dd, 2H, J=6.7, 5.4), 1.36 (d, 3H, J=6.2), 1.30 (d, 3H, J=6.2).

Example 65

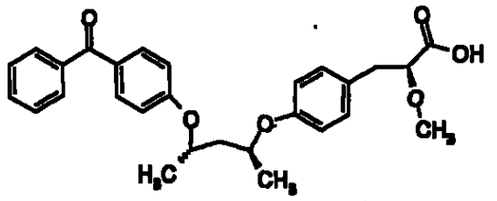
(2S)-(1'S,3'S)-2-Methoxy-3-{4-[1',3'-dimethyl-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid



The title compound was prepared in a manner analogous that Example 63, starting from the (2*R*,4*R*)-pentanediol to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.33-7.25 (m, 2H), 7.12-6.76 (m, 11H), 4.71-4.49 (m, 2H), 3.95 (dd, 1H, J=7.5, 4.6), 3.36 (s, 3H), 3.05 (dd, 1H, J=14.5, 4.6), 2.93 (dd, 1H, J=14.2, 7.5), 1.96 (dd, 2H, J=7.0, 5.7), 1.31 (d, 6H, J=6.2). MS(ES) for $C_{27}H_{30}O_5$ $[M+NH_4]^+$: 468.2, $[M-H]^-$: 449.2.

Example 66

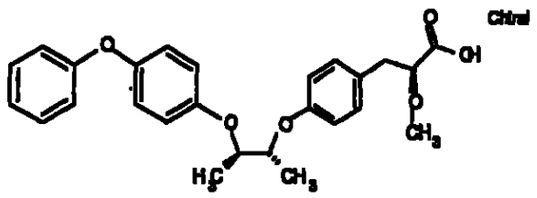
(2S)-(1'*S*,3'*S*)-3-{4-[3-(4-Benzoylphenoxy)-1',3'-dimethylpropoxyl]-phenyl}2-methoxy-propionic acid



The title compound was prepared in a manner analogous that Example 63, starting from the (2*R*,4*R*)-pentanediol to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.76-7.41 (m, 7H), 7.02 (d, 2H, J=8.6), 6.83 (d, 2H, J=8.9), 6.67 (d, 2H, J=8.6), 4.78 (dd, 1H, J=12.1, 6.2), 4.63-4.47 (m, 1H), 3.99 (dd, 1H, J=6.2, 4.8), 3.41 (s, 3H), 3.08-2.87 (m, 2H), 2.00 (dd, 2H, J=5.6, 12.4), 1.33 (dd, 6H, J=11.6, 6.2). MS(ES) for $C_{28}H_{30}O_6$ $[M+H]^+$: 463.2, $[M-H]^-$: 461.3.

Example 67

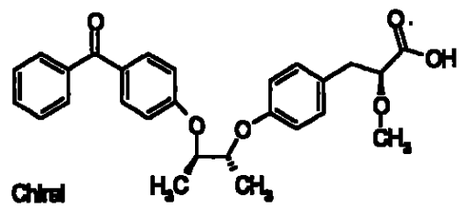
(2S)-(1'*R*,2'*R*)-2-Methoxy-3-{4-[1',2'-dimethyl-(4-phenoxy-phenoxy)-ethoxyl]-phenyl}-propionic acid



The title compound was prepared in a manner analogous that 63, starting from the (2*S*,3*S*)-butane-2,3-diol to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.94 (m, 1H), 7.34-7.26 (m, 3H), 7.17-6.83 (m, 10H), 4.59-4.38 (m, 2H), 3.98 (dd, 1H, J=7.5, 4.6), 3.39 (s, 3H), 3.08 (dd, 1H, J=14.2, 4.3), 2.95 (dd, 1H, J=14.2, 7.5), 1.36 (d, 6H, J=6.2). MS(ES) for $C_{26}H_{28}O_6$ $[M+NH_4]^+$: 454.2, $[M-H]^-$: 435.2.

Example 68

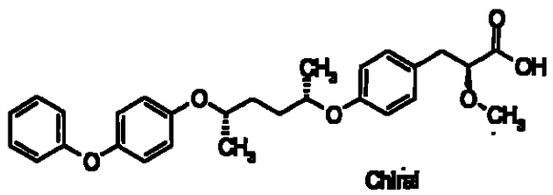
(2*S*)-(1'*R*,2'*R*)-3-{4-[1-(4-Benzoylphenoxy)-1',2'-dimethyl-ethoxyl]-phenyl}-2-methoxypropionic acid



The title compound was prepared in a manner analogous that Example 63, starting from the (2*S*,3*S*)-butane-2,3-diol to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.77 (t, 3H, J=8.9), 7.74 (s, 1H), 7.60-7.42 (m, 3H), 7.14 (d, 2H, J=8.6), 6.96 (d, 2H, J=8.9), 6.84 (d, 2H, J=8.9), 4.72-4.60 (m, 1H), 4.59-4.47 (m, 1H), 3.98 (dd, 1H, J=7.5, 4.6), 3.39 (s, 3H), 3.08 (dd, 1H, J=14.5, 4.6), 2.95 (dd, 1H, J=14.2, 7.3), 1.42 (d, 3H, J=6.2), 1.37 (d, 3H, J=6.2). MS(ES) for $C_{27}H_{28}O_6$ $[M+H]^+$: 449.2, $[M-H]^-$: 447.2.

Example 69

(2*S*)-(1'*S*,4'*S*)-2-Methoxy-3-{4-[1'-methyl-4'-(4-phenoxy-phenoxy)-pentyloxyl]-phenyl}-propionic acid

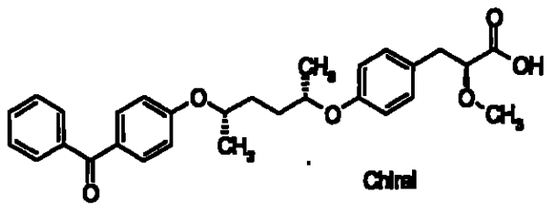


Chiral

The title compound was prepared in a manner analogous that Example 63, starting from the (2*R*,5*R*)-hexane-2,5-diol to give the final compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.3-7.2 (m, 2H), 7.14 (d, 2H, J= 8.6), 7.1-6.8 (m, 9H), 4.4-4.3 (m, 2H), 3.97 (dd, 1H, J=7.6, 4.4), 3.39 (s, 3H), 3.08 (dd, 1H, J=14.2, 4.4), 2.95 (dd, 1H, J=14.4, 7.6), 2.0-1.7 (m, 4H), 1.31 (d, 6H, J=6.2) ppm.

Example 70

(2S)-(1'S,4'S)-3-{4-[4-(4-Benzoyl-phenoxy)-1-methyl-pentyloxy]-phenyl}-2-methoxy-propionic acid

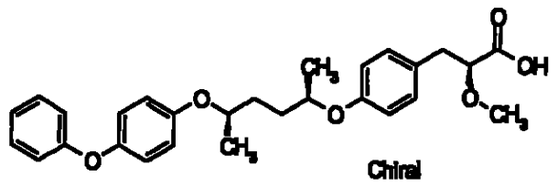


Chiral

The title compound was prepared in a manner analogous that Example 63, starting from the (2*R*,5*R*)-hexane-2,5-diol to give the final compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.8-7.7 (m, 4H), 7.6-7.5 (m, 3H), 7.13 (d, 2H, J= 8.6), 6.90 (dd, 2H, J=7.0, 2.0), 6.79 (d, 2H, J=8.6), 4.51 (c, 1H, J=6.0), 4.35 (c, 1H, J= 6.0), 3.98 (dd, 1H, J=7.2, 4.8), 3.39 (s, 3H), 3.08 (dd, 1H, J=14.4, 4.8), 2.95 (dd, 1H, J=14.4, 7.2), 2.0-1.7 (m, 4H), 1.35 (d, 3H, J=6.0), 1.30 (d, 3H, J=6.0) ppm.

Example 71

(2S)-(1'*R*,4'*R*)-2-Methoxy-3-{4-[1'-methyl-4'-(4-phenoxy-phenoxy)-pentyloxy]-phenyl}-propionic acid

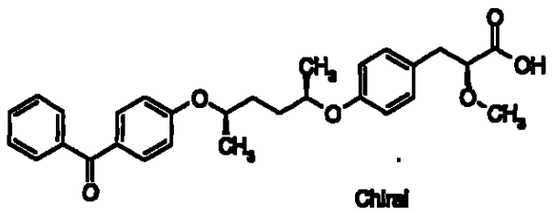


Chiral

The title compound was prepared in a manner analogous that Example 63, starting from the (2*S*,5*S*)-hexane-2,5-diol to give the final compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.3-7.2 (m, 2H), 7.14 (d, 2H, J= 8.4), 7.1-6.7 (m, 9H), 4.4-4.2 (m, 2H), 3.96 (dd, 1H, J=7.4, 4.4), 3.37 (s, 3H), 3.07 (dd, 1H, J=14.4, 4.4), 2.93 (dd, 1H, J=14.4, 7.4), 2.0-1.6 (m, 4H), 1.30 (d, 6H, J=6.0) ppm.

Example 72

(2*S*)-(1'*R*,4'*R*)-3-{4-[4-(4-Benzoyl-phenoxy)-1-methyl-pentyloxy]-phenyl}-2-methoxy-propionic acid

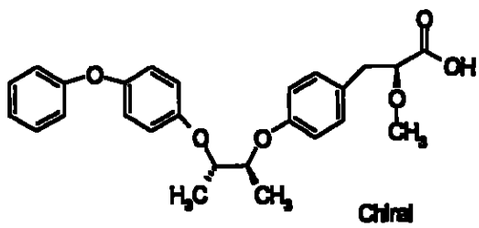


Chiral

The title compound was prepared in a manner analogous that Example 63, starting from the (2*S*,5*S*)-hexane-2,5-diol to give the final compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.8-7.5 (m, 3H), 7.5-7.4 (m, 3H), 7.06 (d, 2H, J= 5.6), 6.82 (d, 2H, J=6.0), 6.71 (d, 2H, J=5.8), 4.44 (c, 1H, J=3.6), 4.28 (c, 1H, J=3.6), 3.88 (dd, 1H, J=9.6, 2.8), 3.29 (s, 3H), 2.98 (dd, 1H, J=9.6, 2.8), 2.86 (dd, 1H, J=9.6, 5.0), 1.9-1.6 (m, 4H), 1.27 (d, 3H, J=4.0), 1.21 (d, 3H, J=4.0) ppm.

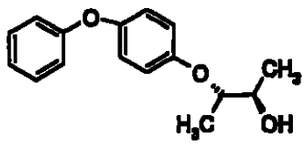
Example 73

(2*S*)-(1'*S*,2'*S*)-2-Methoxy-3-{4-[1',2'-dimethyl-(4-phenoxy-phenoxy)-ethoxyl]-phenyl}-propionic acid



Step A

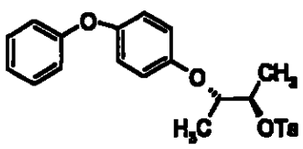
(2R,3S)-3-(4-Phenoxy-phenoxy)-butan-2-ol



A solution of (2R,3R)-butane-2,3-diol was monoprotected with tert-butyldimethylsilyl chloride using the Standard Procedure D, after purification by chromatography, the compound was coupling with 4-phenoxyphenol using Standard Procedure B (in THF) and deprotected with tetrabutylamonium fluoride as Standard Procedure E to give the title compound as an oil. MS (ES) for $C_{16}H_{18}O_3$ $[M+NH_4]^+$: 276.2.

Step B

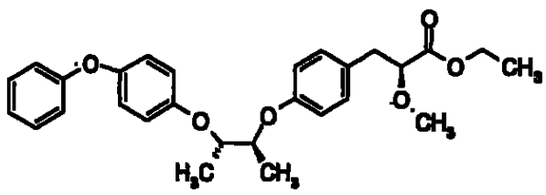
(1*R*,2*S*)-Toluene-4-sulfonic acid 1-methyl-2-(4-phenoxy-phenoxy)-propyl ester



To a solution of compound from Step A (1 eq) in neat pyridine, p-Toluenesulfonic chloride (1.5 eq) was added and the mixture reaction was stirred at room temperature over two days. The reaction was quenched with HCl 1N and extracted with ethyl acetate and washing the organic layers with brine (3 times). The organic layers were dry and concentrated in vacuo to give a residue which was purified by silicagel chromatography to give the title product. MS (ES) for $C_{23}H_{24}O_5S$ $[M+NH_4]^+$: 430.1.

Step C

(2S)-(1'S,2'S)-2-Methoxy-3-{4-[1',2'-dimethyl-(4-phenoxy-phenoxy)-ethoxyl]-phenyl}-propionic acid ethyl ester



A solution of (1R,2S)-Toluene-4-sulfonic acid 1-methyl-2-(4-phenoxy-phenoxy)-propyl ester from above Step (1 eq), potassium carbonate (3 eq) and 2S) 3-(4-Hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (1 eq) in acetonitrile was refluxed overnight. The solution was evaporated to dryness and chromatographied to get the title compound. MS (ES) for $C_{27}H_{30}O_7$ $[M+NH_4]^+$: 482.4.

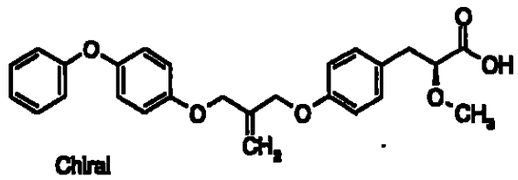
Step D

(2S)-(1'S,2'S)-2-Methoxy-3-{4-[1',2'-dimethyl-(4-phenoxy-phenoxy)-ethoxyl]-phenyl}-propionic acid

The title compound was prepared using the Standard hydrolysis Procedure C to give the final product as an oil. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.34-7.26 (m, 3H), 7.16-6.83 (m, 10H), 4.58-4.41 (m, 2H), 3.98 (dd, 1H, J=7.3, 4.3), 3.39 (s, 3H), 3.14-2.89 (m, 2H), 1.35 (d, 6H, J=6.2). MS(ES) for $C_{26}H_{28}O_6$ $[M+NH_4]_+$: 454.3, $[M-H]_-$: 435.1.

Example 74

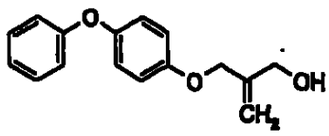
(2S)-2-Methoxy-{4-[2-methylen-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid



Chiral

Step A

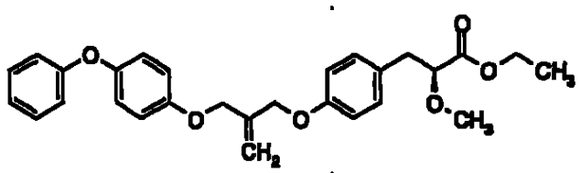
2-(4-Phenoxy-phenoxymethyl)-prop-2-en-1-ol



A solution of triphenylphosphine (1 eq) in toluene at 0° C was treated with diethylazodicarboxylate (1 eq) and stirred for 20 min. Then a solution of 4-phenoxyphenol and 2-Methylene-propane-1,3-diol in toluene was added to the solution and the mixture reaction was stirred overnight. Concentrated to dryness and chromatographied to give the title compound.

Step B

(2S)-2-Methoxy-{4-[2-methylen-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid ethyl ester



The title compound was prepared using Standard Mitsunobu coupling conditions B.

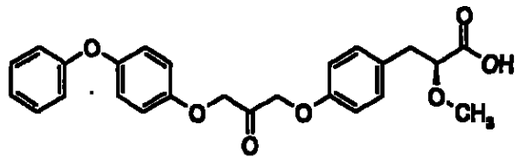
Step C

(2S)-2-Methoxy-{4-[2-methylen-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid

The title compound was prepared by using the Standard Procedure for hydrolysis C to give the final product as an oil. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 8.09 (s, 1H), 7.34-6.86 (m, 13H), 5.41 (s, 2H), 4.62 (s, 4H), 3.98 (dd, 1H, J=7.5, 4.6), 3.40 (s, 3H), 3.09 (dd, 1H, J=14.5, 4.6), 2.97 (dd, 1H, J=14.5, 7.5).

Example 75

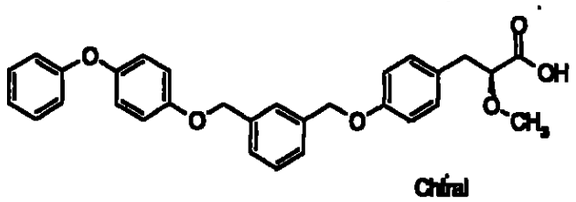
(2S)-2-Methoxy-{4-[2-oxo-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid



A solution of (2S)-2-Methoxy-{4-[2-methylen-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid from Example 74, in dichloromethane at –78°C was treated with ozone untill the solution turned blue. Washed with brine, dry and concentrated to dryness to give the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.35-6.83 (m, 13H), 4.86 (d, 4H, J=3.0), 3.98 (dd, 1H, J=7.3, 4.3), 3.40 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.0), 2.97 (dd, 1H, J=14.5, 7.3). MS(ES) for $C_{25}H_{24}O_7$ $[M+NH_4]^+$: 454.2, $[M-H]^-$: 435.2.

Example 76

(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxymethyl)-benzyloxyl-phenyl}-propionic aci

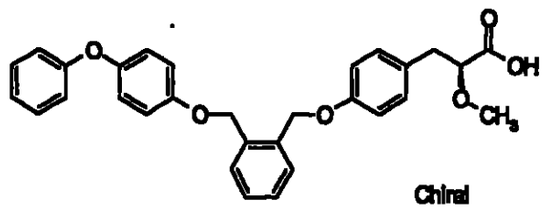


Chiral

The title compound was prepared in a manner analogous that Example 74, starting from (3-Hydroxymethyl-phenyl)-methanol to give the final compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.50 (s, 1H), 7.40 (s, 2H), 7.28 (d, 2H, J=8.6), 7.17 (d, 2H, J=8.6), 7.1-6.9 (m, 10H), 5.06 (s, 4H), 3.99 (dd, 1H, J=7.2, 4.4), 3.40 (s, 3H), 3.10 (dd, 1H, J=14.4, 4.6), 2.97 (dd, 1H, J=14.2, 7.4) ppm.

Example 77

(2S)-2-Methoxy-3-{4-[2-(4-phenoxy-phenoxymethyl)-benzyloxyl-phenyl}-propionic acid

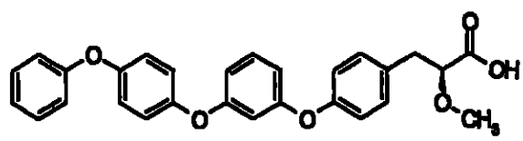


Chiral

The title compound was prepared in a manner analogous that Example 63, starting from (2-Hydroxymethyl-phenyl)-methanol to give the final compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.5-7.4 (m, 2H), 7.4-7.3 (m, 2H), 7.28 (d, 2H, J=8.0), 7.16 (d, 2H, J=8.6), 7.1-6.9 (m, 9H), 5.14 (s, 4H), 3.95 (dd, 1H, J=7.4, 4.6), 3.37 (s, 3H), 3.07 (dd, 1H, J=14.2, 4.4), 2.94 (dd, 1H, J=14.2, 7.6) ppm.

Example 78

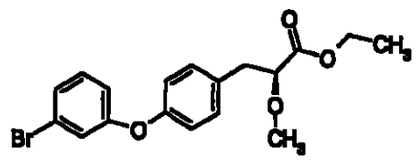
(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-phenoxy]-phenyl}-propionic acid



Chiral

Step A

(2S)-3-[4-(3-Bromo-phenoxy)-phenyl]-2-methoxy-propionic acid ethyl ester

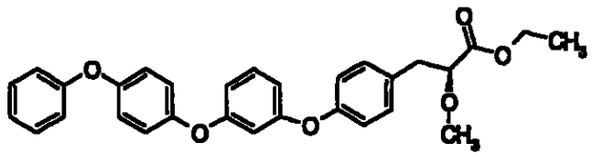


An ovendried resealable Schlenk tube was fitted with a rubber septum and was cooled to room temperature under N_2 purge. The tube was charge with $Pd(OAc)_2$(2.0 mol%), 2-(ditert-butylphosphino)biphenyl (0.03 eq), potassiumm phosphate (2 eq), 1,3-dibromobenzene (1 eq) and (2S) 3-(4-Hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (1,2 eq). The tube was capped with the septum and purged with N2, and then toluene was added through the septum. The tube was sealed with a teflon screwcap, and the reaction mixture was stirred at 100°C for 16

hours. The solvent was removed and the residue was purified by chromatography to afford the title compound.

Step B

(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester



The title compound was porcepared using the same coupling procedure described above for Step A with 4-phenoxyphenol and (2S)-3-[4-(3-Bromo-phenoxy)-phenyl]-2-methoxy-propionic acid ethyl ester.

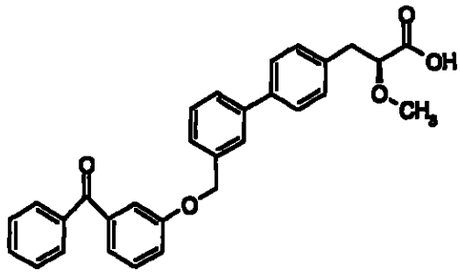
Step C

(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-phenoxy]-phenyl}-propionic acid

The title compound was prepared from Step B by using Standar Procedure for the hydrolysis C. MS (ES) for $C_{28}H_{24}O_6$ $[M+Na]^+$: 479.

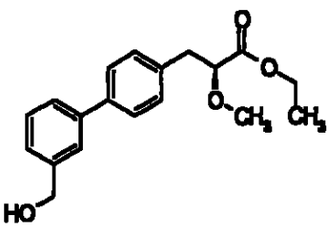
Example 79

(2S)3-[3'-(3-Benzoyl-phenoxymethyl)-biphenyl-4-yl]-2-methoxy-propionic acid



Step A

(2S)-3-(3'-Hydroxymethyl-biphenyl-4-yl)-2-methoxy-propionic acid ethyl ester



A solution of (2S) 2-Methoxy-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid ethyl ester (Example 1, Step A)(150 mg, 0.42 mmol), 3-formylphenyl boronic acid (126 mg, 0.842 mmol) and tetrakis(triphenylphosphine)-palladium (0) (15 mg, .0.013 mmol) in 11 ml of a mixture 20:1 toluene/ethanol together with 2 ml of a 2N Na_2CO_3 was heated to 120°C for 6 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and dilute with EtOAc (20 ml). It was washed with H_2O (3x5ml) and sodium tartrate (3x5 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuum. The resultant crude was purified by column chromatography (silica gel, hexanes/ethyl acetate 3:1). Fractions corresponding to the desired compound (R_f 0.27) were collected and concentrate to dryness. The product was dissolved in MeOH cooled at 0°C and sodium borohydride (3 eq) was added. The solution was stirred for 1 h. and then diluted with Ethyl-acetate (20 ml). It was washed with H_2O (3x5ml) and $NaHCO_3$(3x5 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuum. The resultant crude was purified by column (silica gel, hexanes/ethyl acetate 2:1). Obtained a colorless oil (60 mg, 45%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.55-7.23 (m, 8H), 4.71 (s, 2H), 4.18 (q, 2H, *J*= 7.0), 3.93 (dd, 1H, *J*=7.3, 5.6), 3.35 (s, 3H) 3.05 (s, 1H), 3,02 (s, 1H), 1,25 (t, 3H, *J*=7.25)

Step B

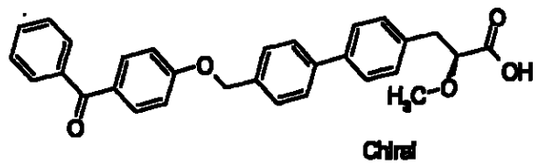
(2S)-3-[3'-(3-Benzoyl-phenoxymethyl)-biphenyl-4-yl]-2-methoxy-propionic acid

The title compound was prepared from (2S) 3-(3'-Hydroxymethyl-biphenyl-4-yl)-2-methoxy-propionic acid ethyl ester (Step A) and 4-Hidroxybenzophenone via the standard Mitsunobu coupling-hydrolisis procedure (Standard Procedure A) to produce a white oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.83-7.33 (m, 15H),

7.03 (d, 2H, *J*=8.1), 5.17 (s, 2H), 4.07 (dd, 1H, *J*=6.9, 3.7), 3.40 (s, 3H), 3.16 (dd, 1H, *J*=14.1, 3.6), 3.06 (dd, 1H, *J*=14.1, 7.0).

Example 80

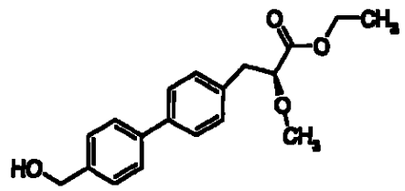
(2S)-3-[4'-(4-Benzoyl-phenoxymethyl)-biphenyl-4-yl]-2-methoxy-propionic acid



Chiral

Step A

(2S)-3-(4'-Hydroxymethyl-biphenyl-4-yl)-2-methoxy-propionic acid ethyl ester



A mixture of (2S)-2-Methoxy-3-(4-trifluoromethanesul fonyloxy-phenyl)-propionic acid ethyl ester from Example 1, Step A (1 eq), tetrakis(triphenylphosphine) palladium(0) (0.03 eq), sodium carbonate (1.5 eq) and 4-hydroxymethylphenylboronic acid (2 eq) in Toluene/Ethanol (20:1) was refluxed till the reaction is completed by TLC. The mixture was diluted with ethyl acetate, extracted and washed with water, $NaHCO_3$, sodium tartrate and brine. The organic layer was concentrated to dryness and chromatographied to afford the title compound.

Step B

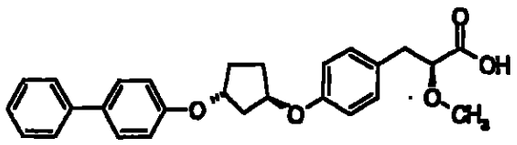
(2S)-3-[4'-(4-Benzoyl-phenoxymethyl)-biphenyl-4-yl]-2-methoxy-propionic acid

(2S)-3-(4'-Hydroxymethyl-biphenyl-4-yl)-2-methoxy-propionic acid ethyl ester from Step A, was treated with 4-hydroxybenzophenone under the standard Mitsounobu coupling procedure B (THF). The product obtained after chromatography was hydrolyzed using the Standard Procedure C to get the title compound. ^{1}H-NMR

($CDCl_3$, 200.15 MHz): 7.86-7.73 (m, 4H), 7.63-7.43 (m, 9H), 7.34-7.29 (m, 2H), 7.05 (d, 2H, J=9.1), 5.18 (s, 2H), 4.06 (dd, 1H, J=7.3, 4.0), 3.42 (s, 3H), 3.20 (dd, 1H, J=14.5, 4.0), 3.06 (dd, 1H, J=14.5, 7.3). MS (ES) for $C_{30}H_{26}O_5$ $[M+H]^+$: 467.2, $[M+Na]^+$: 489.2.

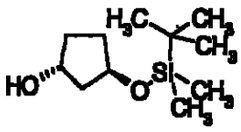
Example 81

(2S)-(1'*R**,3'*R**)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid



Step A

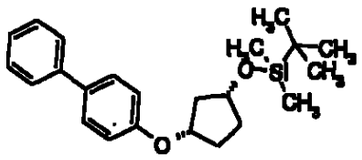
(1*RS*,3*RS*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopentanol



To a solution of rac-1,3-pentanediol (0.46 g, 4.5 mmol) in 23 mL of THF at 0°C was added sodium hydride (0.18 g, 4.5 mmol, 60% oil dispersion). The mixture was stirred at 0 °C for 1 h. *Tert*-butyldimethylsilyl chloride (0.678 g, 4.5 mmol) was added, and the mixture was stirred overnight at room temperature. The mixture compounds were concentrated and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 3:1) to give 0.682 g, of the title compound trans and 0.157 g (6%) of the other cis isomer (1*R**,3*S**)-3-(tert-Butyl-dimethyl-silanyloxy)-cyclopentanol. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 4.48-4.36 (m, 2H), 2.19-1.89 (m, 2H), 1.85-1.79 (m, 2H), 1-58-1.46 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

Step B

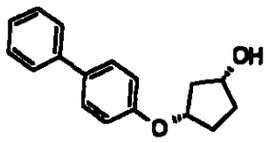
(1*R**,3*S**)-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-tert-butyl-dimethyl-silane



A solution of triphenylphosphine (0.195 g, 0.742 mmol) in 5 mL of dry THF was treated at 0° C with diethylazodicarboxylate (0.117 mL, 0.742 mmol) and stirred for 20 min. A solution of (1*R**, 3*R**)-3-(tert-butyldimethylsilanyloxy)cyclopentanol (0.146 g, 0.675 mmol) and 4-phenyl phenol (0.126 g, 0.0.724 mmol) in 5 mL of dry THF was added to the solution, and the mixture was stirred at room temperature overnight. The solution was concentrated under vacuum and purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 6:1, R_f 0.66). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.58-7.29 (m, 7H); 6.93 (d, 2H, *J*=8.92), 4.76-4.65 (m, 1H), 4.32-4.21 (m, 1H), 2.38 (qn, 1H, *J*=7.0), 2.04-1.94 (m, 2H), 1.87-1.78 (m, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

Step C

(1*R**,3*S**)-3-(Biphenyl-4-yloxy)-cyclopentanol



(1*R**,3*S**)-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-tert-butyldimethylsilane (0.25 g, 0.67 mmol) was dissolved in 2 mL of THF and tetrabutylammonium fluoride (0.67 mL, 1M in THF) and stirred at room temperature for 2 hours. The solution was diluted with 15 mL of diethyl ether and washed with 1N HCl (2 x 15 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 3:1, R_f 0.09) to give the product (100 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.58-7.26 (m, 7H), 6.95 (d, 2H, *J*=8.9), 4.92-4.84 (m, 1H), 4.40-4.38 (m, 1H), 2.18-1.92 (m, 7H).

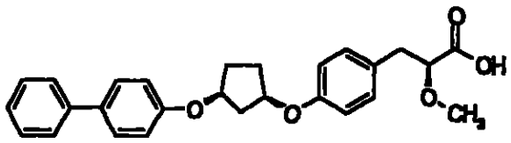
Step D

(2S)-(1'*R**,2'*R**)3-{4-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (1*R**,3*S**) 3-(Biphenyl-4-yloxy)-cyclopentanol and (2*S*)-2-methoxy-3-hydroxyphenylpropionic acid ethyl ester via the Standard Procedure A. Oily solid. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.57-7.29 (m, 7H), 7.15 (d, 2H, *J*=8.6), 6.94 (d, 2H, *J*=8.9), 6.81 (d, 2H, *J*=8.6), 4.99-4.91 (m, 2H), 3.99 (dd, 1H, *J*=7.3, 4.6), 3.41 (s, 3H), 3.10 (dd, 1H, *J*=14.2, 4.6), 2.96 (dd, 1H, *J*=14.5, 7.3), 2.31 (t, 2H, *J*=4.8), 2.26-1.97 (m, 4H).

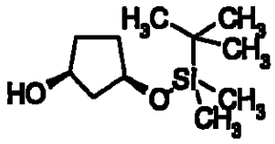
Example 82

(2S)-(1'*R**,3'*S**)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid



Step A

(1*R**,3*S**)-3-(tert-Butyl-dimethyl-silanyloxy)-cyclopentanol



The title compound was isolated from Example 81, Step A in a 6 % yield.

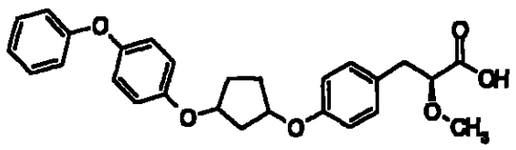
Step B

(2S)-(1'*R**,3'*S**)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared starting from compound from Step A and following the same procedure as in Example 81, to give the final product. MS (ES) for $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450.2, $[M+Na]^+$: 455.23.

Example 83

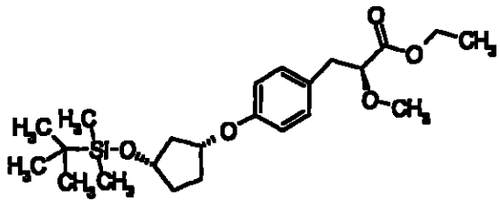
(2S)-(1'*R**,3'*R**)-2-Methoxy-3-{4-[3'-(4-phenoxy-phenoxy)-1'-cyclopentyloxy]-phenyl}-propionic acid



Chiral

Step A.

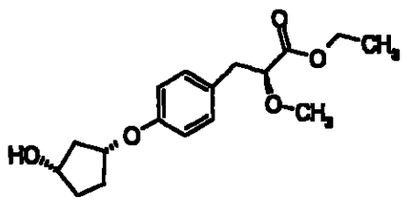
(2S)-(1*R**,3*S**)-3-{4-[3'-(*tert*-Butyl-dimethyl-silanyloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid ethyl ester



A solution of triphenylphosphine (0.634 g, 2.23 mmol) in 15 mL of dry THF was treated at 0° C with diethylazodicarboxylate (0.2.45 mmol) and stirred for 20 min. A solution of (2*S*)-2-methoxy-3-hydroxyphenylpropionic acid ethyl (2.23 mmol) and 1*R**,3*R**-*tert*-butyldimethylsylnalyloxy-cyclopentanol (0.245 mmol) in 5 mL of dry THF was added to the solution, and the mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue was purified by silica gel chromatography.

Step B

(2S)-(1*R**,3*S**)-3-[4-(3'-Hydroxy-1'-cyclopentyloxy)-phenyl]-2-methoxy-propionic acid ethyl ester



The title compound was prepared folowing the Standard Procedure E to give the product.

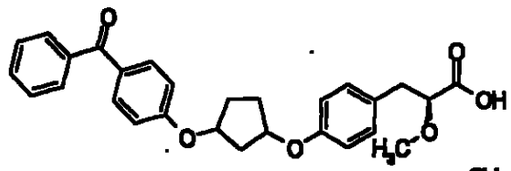
Step C

(2S)-(1'*R**,3'*R**)-2-Methoxy-3-{4-[3'-(4-phenoxy-phenoxy)-1'-cyclopentyloxy]-phenyl}-propionic acid

(2S)-(1*R**,3*S**)-3-[4-(3'-Hydroxy-1'-cyclopentyloxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Step A, was treated with 4-phenoxyphenol under the standard Mitsoumobu coupling procedure B (THF). The product obtained after chromatography was hydrolyzed using the standard hydrolysis procedure C to get the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.34-7.26 (m, 2H), 7.17-7.04 (m, 3H), 7.00-6.92 (m, 4H), 6.88-6.78 (m, 4H), 4.94-4.89 (m, 2H), 3.99 (dd, 1H, J=7.3, 4.3), 3.41 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.6), 2.96 (dd, 1H, J=14.2, 7.3), 2.28 (t, 2H, J=4.8), 2.21-1.89 (m, 4H). *MS (ES)* for $C_{27}H_{28}O_6$ $[M+NH_4]^+$: 466.2, $[M+Na]^+$: 471.2.

Example 84

(2S)-(1'*R**,3'*R**)-3-{4-[3-(4-Benzoyl-phenoxy)-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid

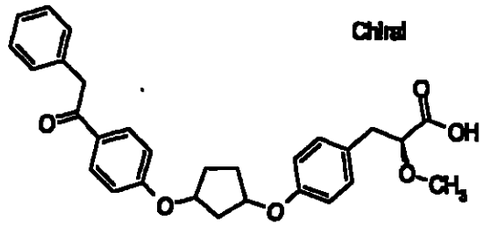


Chiral

The title compound was prepared as manner analogous in Example 83, starting from (1*R**,3*R**)-3-(tert-Butyl-dimethyl-silanyloxy)-cyclopentanol and 4-hydroxy nezophenone. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.83-7.73 (m, 4H), 7.56-7.42 (m, 3H), 7.15 (d, 2H, J=8.3), 6.92 (dd, 2H, J=7.0, 1.9), 6.80 (d, 2H, J=8.6), 5.03-5.01 (m, 1H), 4.96-4.92 (m, 1H), 3.98 (dd, 1H, J=7.3, 4.6), 3.39 (s, 3H), 3.09 (dd, 1H, J=14.5, 4.6), 2.95 (dd, 1H, J=14.2, 7.3), 2.40-1.91 (m, 6H). MS (ES) for $C_{28}H_{28}O_6$ $[M+H]^+$: 461.2, $[M+Na]^+$: 483.2.

Example 85

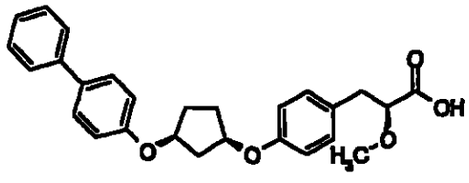
(2S)-(1'R*,3'R*)-2-Methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-cyclopentyloxy]-phenyl}-propionic acid



The title compound was prepared as manner analogous in Example 83, starting from (1*R**,3*R**)-3-(tert-Butyl-dimethyl-silanyloxy)-cyclopentanol and 1-(4-Hydroxy-phenyl)-2-phenyl-ethanone. MS (ES) for $C_{29}H_{30}O_6$ $[M+H]^+$: 475.2, $[M+Na]^+$: 497.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.97 (d, 2H, J=8.9), 7.32-7.23 (m, 5H), 7.15 (d, 2H, J=8.6), 6.91-6.77 (m, 4H), 5.01-4.91 (m, 2H), 4.22 (s, 2H), 3.98 (dd, 1H, J=7.3, 4.6), 3.40 (s, 3H), 3.09 (dd, 1H, J=14.2, 4.6), 2.96 (dd, 1H, J=14.5, 7.3), 2.33-1.92 (m, 6H).

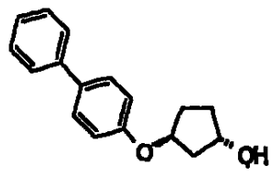
Example 86

(2S)-(1'*R*,3'*S*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid



Step A

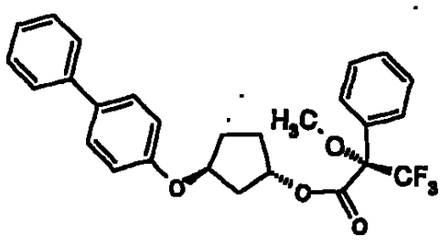
(1S*,3S*)-3-(Biphenyl-4-yloxy)-cyclopentanol



The title compound was prepared starting from (1*R**,3*S**)-3-(tert-Butyl-dimethyl-silanyloxy)-cyclopentanol of Example 82, Step A, and running a Standard Mitsonnobu coupling reaction B (toluene) with 4-phenylphenol. The product then was deprotected by Standard Procedure E to give the compound after purification by chromatography.

Step B

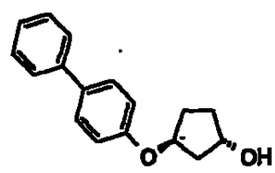
(1'*S*,2*S*,3'*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 3'-(biphenyl-4-yloxy)-1'-cyclopentyl ester



A mixture of (1*S**,3*S**)-3-(Biphenyl-4-yloxy)-cyclopentanol From Step A (1 eq) with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1 eq), DMAP (0.1 eq) and EDCI (1.2 eq) in dichloromethane was stirred at 36° C over night. The reaction mixture was cooled and concentrated to dryness. Reconstituted in ether and washed with HCl 1N, and $NaHCO_3$. Dry over MsSO4 and concentrated in vacuo to give a crude that was purify by silicagel chromatography to give a diastereomeric mixture which was separated using chiral HPLC.

Step C

(1*S*,3*S*)-3-(Biphenyl-4-yloxy)-cyclopentanol



To a solution of compound from Step C in ethanol an excess of NaOH 1N was added and the mixture reaction was stirred at room temperature. The solution was concentrated in vacuo and diluted with brine. Extracted with ether and concentrated to yield the title compound.

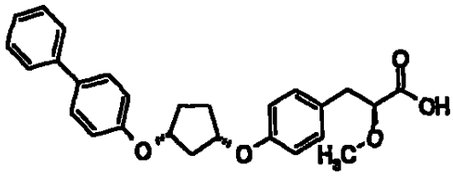
Step D

(2S)-(1'*R*,3'*S*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared using the Standard Procedure for Mitsounobu coupling-hydrolysis A in Toluene to give the final compound. MS (ES) for $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450.2, $[M+Na]^+$: 455.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.56-7.28 (m, 6H), 7.15-7.08 (m, 3H), 6.95 (d, 2H, J=8.9), 6.84-6.73 (m, 2H), 4.81-4.79 (m, 2H), 3.98 (dd, 1H, J=7.0, 4.3), 3.40 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.0), 2.95 (dd, 1H, J=14.2, 7.3), 2.58-2.44 (m, 1H), 2.19-2.02 (m, 5H).

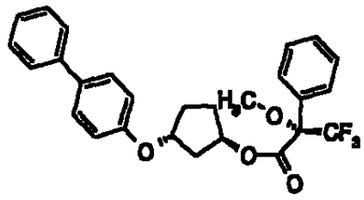
Example 87

(2S)-(1'*S*,3'*R*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxyl-phenyl}-2-methoxy-propionic acid



Step A

(1'R,2S,3'R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 3'-(biphenyl-4-yloxy)-1'-cyclopentyl ester



A mixture of (1S*, 3S*)-3-(Biphenyl-4-yloxy)-cyclopentanol from Step A (1 eq) with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1 eq), DMAP (0.1 eq) and EDCI (1.2 eq) in dichloromethane was stirred at 36 °C over night. The reaction mixture was cooled and concentrated to dryness. Reconstituted in ether and washed with HCl 1N, and $NaHCO_3$. Dry over MsSO4 and concentrated in vacuo to give a crude that was purify by silicagel chromatography to give a diastereomeric mixture which was separated using chiral HPLC.

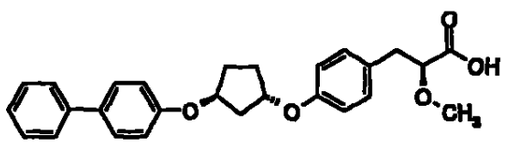
Step B

(2S)-(1'S,3'R)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared using the same procedures as in Example 86, Steps C and D, to give the final compound. MS (ES) for $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450.2, $[M+Na]^+$: 455.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.56-7.28 (m, 6H), 7.15-7.08 (m, 3H), 6.95 (d, 2H, J=8.9), 6.84-6.73 (m, 2H), 4.81-4.79 (m, 2H), 3.98 (dd, 1H, J=7.0, 4.3), 3.40 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.0), 2.95 (dd, 1H, J=14.2, 7.3), 2.58-2.44 (m, 1H), 2.19-2.02 (m, 5H).

Example 88

(2S)-(1'S,3'S)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid

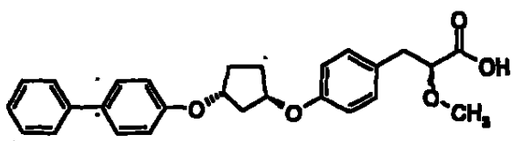


Chiral

The title compound was prepared from (2S)-(1'*R**,2'*R**)3-{4-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid from 0, Step D, which was purified by chiral-HPLC to give the corresponding enantiomer. MS (ES) for $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450.2, $[M+Na]^+$: 455.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.57-7.29 (m, 7H), 7.15 (d, 2H, J=8.6), 6.94 (d, 2H, J=8.9), 6.81 (d, 2H, J=8.6), 4.99-4.91 (m, 2H), 3.99 (dd, 1H, J=7.3, 4.6), 3.41 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.6), 2.96 (dd, 1H, J=14.5, 7.3), 2.31 (t, 2H, J=4.8), 2.26-1.97 (m, 4H).

Example 89

(2S)-(1'*R*,3'*R*)3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid

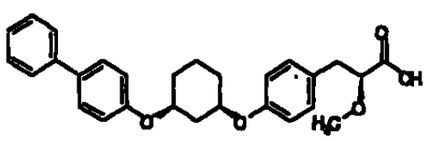


Chiral

The title compound was prepared from (2S)-(1'*R**,2'*R**)3-{4-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid from Example 81, Step D, which was purified by chiral-HPLC to give the corresponding enantiomer. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): d 7.57-7.29 (m, 7H), 7.15 (d, 2H, J=8.6), 6.94 (d, 2H, J=8.9), 6.81 (d, 2H, J=8.6), 4.99-4.91 (m, 2H), 3.99 (dd, 1H, J=7.3, 4.6), 3.41 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.6), 2.96 (dd, 1H, J=14.5, 7.3), 2.31 (t, 2H, J=4.8), 2.26-1.97 (m, 4H). MS (ES) for $C_{27}H_{28}O_5$ $[M+Na]^+$: 455.

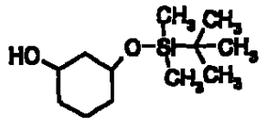
Example 90

(2S)-(1'*R*,3'*S*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid



Step A

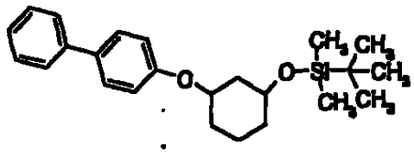
3-(tert-Butyl-dimethyl-silanyloxy)-cyclohexanol



The title compound was prepared following the Standar Procedure D for the monoprotection of diols, to give the product as a colorless oil.

Step B

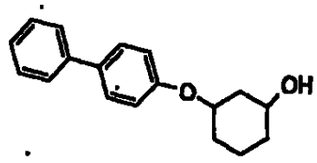
[3-(Biphenyl-4-yloxy)-cyclohexyloxy]-tert-butyl-dimethyl-silane



The title compound was prepared using the Standard Procedure for Mitsonnobu coupling B (Toluene) to give the product as a colorless oil. MS (ES) for $C_{24}H_{34}O_2Si$: $[M+H]^+$: 383.3.

Step C

3-(Biphenyl-4-yloxy)-cyclohexanol

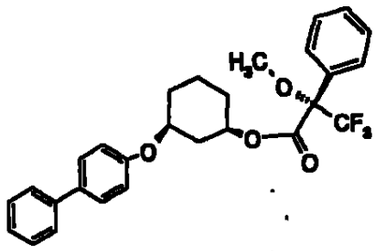


The title compound was prepared by the Standard Procedure E for cleveage the protected alcohols to give a mixture of the four isomers of the compounds. The mixture was purified by silicagel chromatography to give the corresponding two isomers (trans). (1*S**,3*S**)-3-(Biphenyl-4-yloxy)-cyclohexanol ^{1}H-NMR (CDCl3, 500.00 MHz): 7.55 (d, J = 7.3 Hz, 2H); 7.51 (d, J = 8.5 Hz, 2H); 7.41 (t, J = 7.9 Hz, 2H); 7.30 (t, J = 7.3 Hz, 1H); 6.97 (d, J = 8.5 Hz, 2H); 4.74-4.72 (m, 1H); 4.20-4.15 (m, 1H); 2.09-2.04 (m, 1H); 1.86-1.70 (m, 6H); 1.53-1.27 (m, 3H)ppm and (cis)(1R*,3S*)-3-(Biphenyl-4-yloxy)-cyclohexanol ^{1}H-NMR (CDCl3, 500.00

MHz): 7.54 (d, J = 7.6 Hz, 2H); 7.51 (d, J = 8.5 Hz, 2H); 7.41 (t, J = 7.6 Hz, 2H); 7.30 (t, J = 7.3 Hz, 1H); 6.97 (d, J = 8.5 Hz, 2H); 4.39-4.36 (m, 1H); 3.83-3.80 (m, 1H); 2.31 (d, J = 12.3 Hz, 1H); 2.04-1.85 (m, 4H); 1.72-1.34 (m, 10H)ppm.

Step D

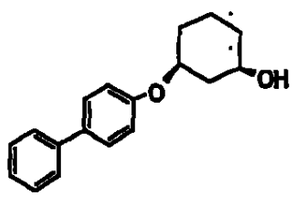
(1*R*,3*S*)-(2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 3-(biphenyl-4-yloxy)-1-cyclohexyl ester



A mixture of (1*R**,3*S**)-3-(Biphenyl-4-yloxy)-cyclohexanol from Step C (1 eq) with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1 eq), DMAP (0.1 eq) and EDCI (1.2 eq) in dichloromethane was stirred at 36°C over night. The reaction mixture was cooled and concentrated to dryness. Reconstituted in ether and washed with HCl 1N, and $NaHCO_3$. Dry over $MaSO_4$ and concentrated in vacuo to give a crude that was purified by silica gel chromatography to give a diastereomeric mixture which was separated using chiral HPLC

Step E

(1R,3S)-3-(Biphenyl-4-yloxy)-cyclohexanol



To a solution of compound from Step D in ethanol an excess of NaOH 1N was added and the mixture reaction was stirred at room temperature. The solution was

concentrated in vacuo and diluted with brine. Extracted with ether and concentrated to yield the title compound.

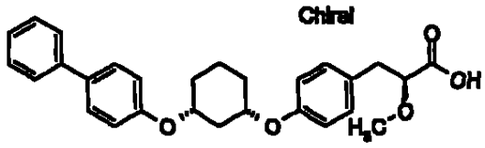
Step F

(2S)-(1'S,3'R)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared using the Standard Procedure for Mitsonobu coupling-hydrolysis A in Toluene to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.73-7.28 (m, 7H), 7.12 (dd, 2H, J=10.2, 8.6), 7.00-6.93 (m, 1H), 6.86-6.73 (m, 2H), 4.34-4.19 (m, 2H), 3.98 (dd, 1H, J=7.3, 4.3), 3.39 (s, 3H), 3.09 (dd, 1H, J=14.2, 4.0), 2.94 (dd, 1H, J=14.5, 7.3), 2.67-2.61 (m, 1H), 2.27-2.18 (m, 1H), 1.96-1.93 (m, 1H), 1.71-1.54 (m, 1H), 1.46-1.37 (m, 3H).

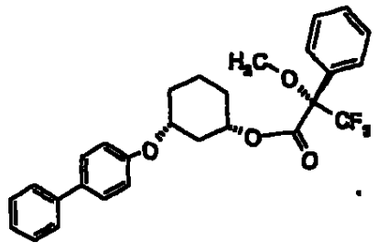
Example 91

(2S)-(1'S,3'R)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid



Step A

(1S,3R)-(2S)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 3-(biphenyl-4-yloxy)-1-cyclohexyl ester

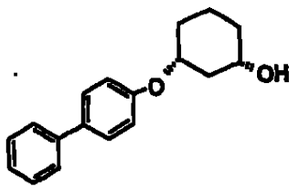


A mixture of (1R*, 3S*)-3-(Biphenyl-4-yloxy)-cyclohexanol from Example 90, Step C (1 eq) with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1 eq),

DMAP (0.1 eq) and EDCI (1.2 eq) in dichloromethane was stirred at 36°C over night. The reaction mixture was cooled and concentrated to dryness. Reconstituted in ether and washed with HCl 1N, and $NaHCO_3$. Dry over $MaSO_4$ and concentrated in vacuo to give a crude that was purified by silicagel chromatography to give a diastereomeric mixture which was separated using chiral HPLC.

Step B

(1*S*,3*R*)-3-(Biphenyl-4-yloxy)-cyclohexanol



The compound was prepared using the same procedure as in Example 90, Step B.

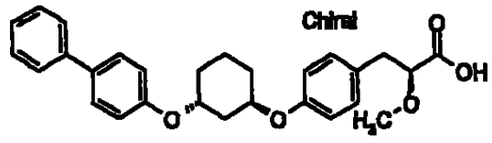
Step C

(2S)-(1'*S*,3'*R*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared using the Standard Procedure for Mitsonobu coupling-hydrolysis A in toluene to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.73-7.28 (m, 7H), 7.12 (dd, 2H, J=10.2, 8.6), 7.00-6.93 (m, 1H), 6.86-6.73 (m, 2H), 4.34-4.19 (m, 2H), 3.98 (dd, 1H, J=7.3, 4.3), 3.39 (s, 3H), 3.09 (dd, 1H, J=14.2, 4.0), 2.94 (dd, 1H, J=14.5, 7.3), 2.67-2.61 (m, 1H), 2.27-2.18 (m, 1H), 1.96-1.93 (m, 1H), 1.71-1.54 (m, 1H), 1.46-1.37 (m, 3H).

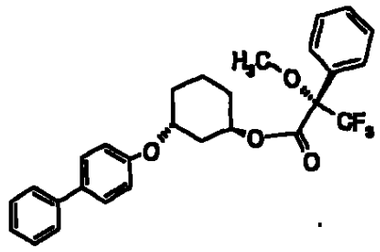
Example 92

(2S)-(1'*R*,3'*R*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid



Step A

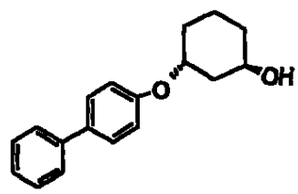
(1R,3R)-(2S)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 3-(biphenyl-4-yloxy)-1-cyclohexyl ester



A mixture of (1R*,3R*)-3-(Biphenyl-4-yloxy)-cyclohexanol (trans), from Example 90, Step C (1 eq) with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1 eq), DMAP (0.1 eq) and EDCI (1.2 eq) in dichloromethane was stirred at 36°C over night. The reaction mixture was cooled and concentrated to dryness. Reconstituted in ether and washed with HCl 1N, and $NaHCO_3$. Dry over MsSO4 and concentrated in vacuo to give a crude that was purify by silicagel chromatography to give a diastereomeric mixture which was separated using chiral HPLC.

Step B

(1R,3R)-3-(Biphenyl-4-yloxy)-cyclohexanol



The compound was prepared using the same procedure as in Example 90, Step E.

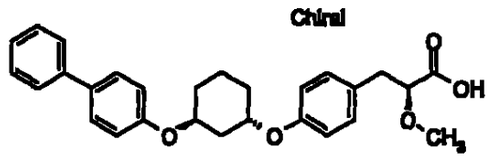
Step C

(2S)-(1'R,3'R)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared using the Standard Procedure for Mitsonnobu coupling-hydrolysis A in toluene to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.57-7.27 (m, 7H), 7.13 (d, 2H, J=8.6), 6.96 (dd, 2H, J=6.7, 2.1), 6.83 (d, 2H, J=8.9), 4.75-4.72 (m, 2H), 4.00-3.95 (m, 1H), 3.38 (s, 3H), 3.09 (dd, 1H, J=14.8, 4.3), 2.94 (dd, 1H, J=14.5, 7.5), 2.12-2.05 (m, 3H), 1.80-1.78 (m, 5H).

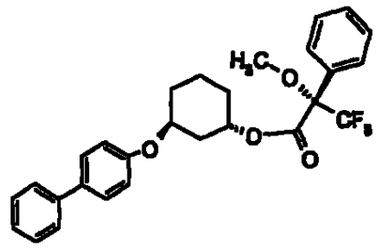
Example 93

(2S)-(1'S,3'S)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid



Step A

(1S,3S)-(2S)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 3-(biphenyl-4-yloxy)-1-cyclohexyl ester

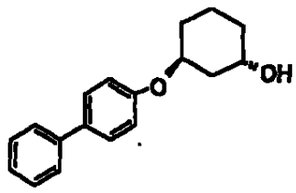


A mixture of (1R*,3R*)-3-(Biphenyl-4-yloxy)-cyclohexanol (trans), from Example 90, Step C (1 eq) with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1 eq), DMAP (0.1 eq) and EDCI (1.2 eq) in dichloromethane was stirred at 36°C over night. The reaction mixture was cooled and concentrated to dryness. Reconstituted in ether and washed with HCl 1N, and $NaHCO_3$. Dry over MaSO4 and concentrated

in vacuo to give a crude that was purify by silicagel chromatography to give a diastereomeric mixture which was separated using chiral HPLC.

Step B

(1*S*,3*S*)-3-(Biphenyl-4-yloxy)-cyclohexanol



The compound was prepared using the same procedure as in Example 90, Step E.

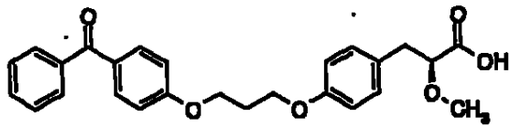
Step C

(2*S*)-(1'*S*,3'*S*)-3-{4-[3'-(Biphenyl-4-yloxy)-1'-cyclohexyloxyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared using the Standard Procedure for Mitsoumobu coupling-hydrolysis A in toluene to give the final compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.57-7.27 (m, 7H), 7.13 (d, 2H, J=8.6), 6.96 (dd, 2H, J=6.7, 2.1), 6.83 (d, 2H, J=8.9), 4.75-4.72 (m, 2H), 4.00-3.95 (m, 1H), 3.38 (s, 3H), 3.09 (dd, 1H, J=14.8, 4.3), 2.94 (dd, 1H, J=14.5, 7.5), 2.12-2.05 (m, 3H), 1.80-1.78 (m, 5H).

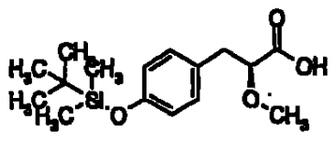
Example 94

(2*S*)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxyl-phenyl}-2-methoxy-propionic acid



Step A

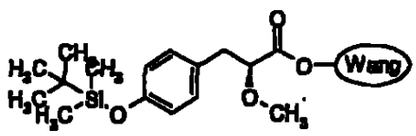
(2*S*)-3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-2-methoxy-propionic acid



To a solution of (2S)-3-hydroxyphenyl-2-methoxy-propionic acid (7.30 g, 37.2 mmol) in 40 mL of dry DMF was added *tert*-butyldimethylsilyl chloride (11.80 g, 78.2 mmol) and imidazole (5.32 g, 78.2 mmol). The solution was stirred at room temperature overnight. Water (40 mL) was added, and the aqueous phase was extracted with hexanes (40 mL). The organic layer was washed with water (50 mL), dried ($MgSO_4$), and concentrated. The crude material was dissolved in THF (20 mL), and saturated $NaHCO_3$ solution (20 mL) was added. The resulting mixture was stirred for 2 hours at room temperature. The aqueous layer was extracted with ethyl acetate (40 mL), acidified to pH 3, and extracted again with ethyl acetate (3 x 40 mL). The combined organic layers were washed with brine (60 mL) and dried ($MgSO_4$), and concentrated to a yellow oil (11.5 g, 99%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.09 (d, 2H, *J*=8.3), 6.76 (d, 2H, *J*=8.6), 3.97 (dd, 1H, *J*=7.5, 4.3), 3.38 (s, 3H), 3.09 (dd, 1H, *J*=14.5, 4.3), 2.93 (dd, 1H, *J*=14.2, 7.3), 0.97 (s, 9H), 0.18 (6H, s).

Step B

Preparation of (2S)-3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin

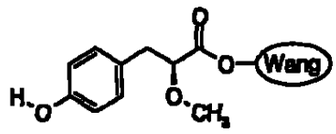


The reaction was carried out in a polypropylene syringe equipped with a polypropylene frit. Wang's resin (1 eq, ca. 1.2 mmol/g resin) was suspended in dichloromethane (0.05 M) and (2S)-3-[4-(*tert*-butyldimethylsilanyloxy) phenyl]-2-methoxypropionic acid (1.5 eq), diisopropylcarbodiimide (2.0 eq), and a catalytic amount of dimethylaminopyridine were added. The mixture was shaken at room temperature overnight. The reaction solvent was removed, and the resin was washed sequentially with CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), methanol, and CH_2Cl_2 (2x). The resin was dried under vacuum for 5 hours. The resin was suspended in CH_2Cl_2 (0.05 M) and treated with acetic anhydride (5 eq) and a catalytic amount of dimethylaminopyridine for 2 hours. The solvent was removed and the resin washed

sequentially with a mixture of 1:1 acetic acid/CH_2Cl_2 (3x), CH_2Cl_2 (2x), methanol, CH_2Cl_2 (2x) and dried under vacuum overnight to give (2S)-3-[4-(*tert*-butyldimethylsilanyloxy)phenyl]-2-methoxypropionic acid linked to Wang's Resin.

Step C

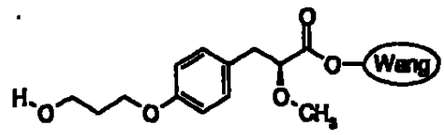
Preparation of (2S)-3-(4-Hydroxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin



The reaction was carried out in a polypropylene syringe equipped with a polypropylene frit. To a suspension of (2S)-3-[4-(*tert*-butyldimethylsilanyloxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (1 eq) in dichloromethane (0.05 M) was added tetrabutylammonium fluoride (ca 5 eq). The mixture was shaken at room temperature for 3 hours. The solvent was removed, and the resin was washed sequentially with CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), methanol, and CH_2Cl_2 (2x). The resin was dried under vacuum overnight to produce (2S) 3-(4-hydroxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin. Cleavage of 20 mg of the resin in TFA/CH_2Cl_2 1:1 followed by evaporation of the solvent produced (*S*)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid as an oil. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.10 (d, 2H, *J*=8.6), 6.76 (d, 2H, *J*=8.6), 3.99 (dd, 1H, *J*=7.0, 4.6), 3.41 (s, 3H), 3.10 (dd, 1H, *J*=14.5, 4.6), 2.95 (dd, 1H, *J*=14.5, 7.5).

Step D

Preparation of (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin



The title compound was prepared from (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin via Mitsunobu coupling (Standard Procedure

F) to produce (2S)-3-[4-(3-hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin. Cleavage of 20 mg of the resin in TFA/CH_2Cl_2 1:1 followed by evaporation of the solvent produced (2S)-3-[4-(3-hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid as an oil. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.16 (d, 2H, *J*=8.6), 6.82 (d, 2H, *J*=8.6), 4.56 (t, 1H, *J*=6.2), 4.09 (2H, dd, *J*=13.2, 5.9), 3.99 (dd, 1H, *J*=6.7, 4.0), 3.90 (1H, t, *J*=5.9), 3.40 (s, 3H), 3.10 (dd, 1H, *J*=14.2, 4.0), 2.96 (dd, 1H, *J*=14.2, 7.3), 2.22 (qn, 1H, *J*=5.9), 2.05 (qn, 1H, *J*=5.9).

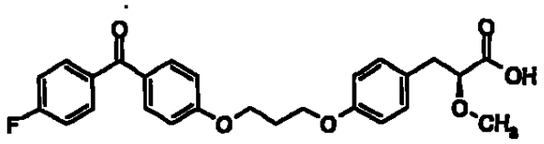
Step E

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-[4-(3-hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin via the Mitsunobu coupling-cleavage from the resin procedure (Standard Procedure G) to give 1.6 mg of a white solid (6%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.82-7.72 (m, 4H), 7.57-7.43 (m, 3H), 7.14 (d, 2H, *J*=8.8), 6.96 (d, 2H, *J*=8.8), 6.84 (d, 2H, *J*=8.8), 4.25 (t, 2H, *J*=6.0), 4.14 (t, 2H, *J*=6.0), 4.00 (dd, 1H, *J*=6.8, 4.6 Hz), 3.41 (s, 3H), 3.10 (dd, 1H, *J*=14.1, 4.6), 2.97 (dd, 1H, *J*=14.1, 6.8), 2.28 (qn, 2H, *J*=6.0).

Example 95

(2S)-3-{4-[3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

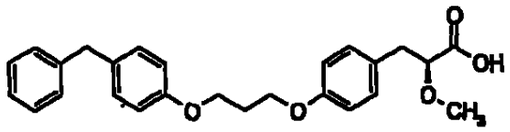


The title compound was prepared from (2S)-3-[4-(3-hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-hydroxybenzophenone and cleavage from the resin (Standard Procedure G) gave an oil (7%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.82-7.73 (m, 4H), 7.19-7.10 (m, 4H), 6.96 (d, 2H, *J*=8.9), 6.84 (d, 2H, *J*=8.9), 4.25 (t, 2H, *J*=6.0), 4.15 (t, 2H, *J*=6.0), 4.00 (dd, 1H, *J*=6.7, 4.6), 3.41 (s, 3H), 3.10 (dd, 1H,

J=14.1, 4.6), 2.97 (dd, dd, J=14.1, 6.8), 2.28 (qn, 2H, J=6.0). MS (ES) for $C_{26}H_{25}FO_6$ $[M+H]^+$: 453.2, $[M+Na]^+$: 475.2.

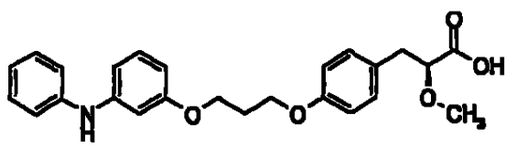
Example 96

(2S)-3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-hydroxydiphenylmethane and cleavage from the resin (Standard Procedure G) produced a white solid (5%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.29-7.13 (m, 6H), 7.08 (d, 2H, J=8.9), 6.82 (d, 2H, J=8.6), 4.12 (t, 4H, J=6.2), 3.97 (dd, 1H, J=6.6, 4.0), 3.39 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.0), 2.95 (dd, 1H, J=14.2, 6.6), 2.22 (qn, 2H, J=6.2).

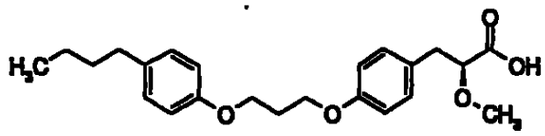
Example 97(2S)-2-Methoxy-3-{4-[3-(3-phenylamino-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 3-hydroxydiphenylamine and cleavage from the resin (Standard Procedure G) gave an oily solid (4%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.31-6.81 (m, 8H), 6.83 (d, 2H, J=8.6), 6.65-6.62 (m, 2H), 6.48 (dd, 1H, J=8.2, 2.1), 4.12 (t, 4H, J=6.2), 3.99 (dd, 1H, J=7.0, 4.4), 3.40 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.4), 2.95 (dd, 1H, J=14.2, 7.0), 2.22 (qn, 2H, J=6.2).

Example 98

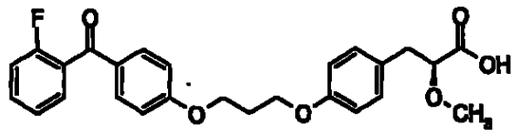
(2S)-3-{4-[3-(4-Butyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-n-butylphenol and cleavage from the resin (Standard Procedure G) gave an oily solid (7%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.11 (dd, 4H, *J*=12.7, 8.6), 6.82 (dd, 4H, *J*=8.6, 3.2), 4.12 (t, 4H, *J*=6.2), 3.97 (dd, 1H, *J*=7.7, 4.4), 3.38 (s, 3H), 3.30 (dd, 1H, *J*=14.5, 4.4), 2.94 (dd, 1H, *J*=14.5, 7.7), 2.54 (t, 2H, *J*=7.7), 2.23 (qn, 2H, *J*=6.2), 1.63-1.48 (m, 2H), 1.42-1.24 (m, 2H), 0.91 (t, 3H, *J*=7.2).

Example 99

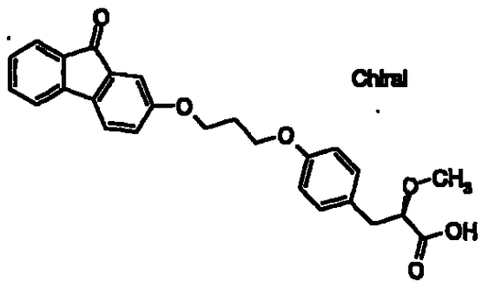
(2S)-3-{4-[3-[4-(2-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 2-fluoro-4'-hydroxybenzophenone and cleavage from the resin (Standard Procedure G) gave an oily solid (7%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.81 (dd, 2H, *J*=8.8, 1.3), 7.54-7.45 (m, 2H), 7.28-7.09 (m, 4H), 6.94 (d, 2H, *J*=8.6), 6.83 (d, 2H, *J*=8.6), 4.24 (t, 2H, *J*=6.2), 4.14 (t, 2H, *J*=6.2), 3.98 (dd, 1H, *J*=7.0, 4.6), 3.40 (s, 3H), 3.09 (dd, 1H, *J*=14.2, 4.6), 2.96 (dd, 1H, *J*=14.2, 7.0), 2.28 (qn, 2H, *J*=6.2).

Example 100

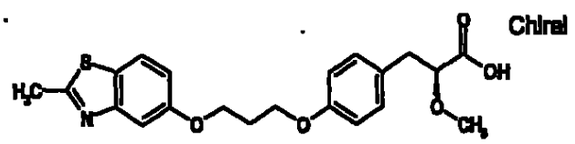
(2S)-2-Methoxy-3-{4-[3-(9-oxo-9H-fluoren-2-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 2-hydroxy-9-fluorenone and cleavage from the resin (Standard Procedure G) gave an oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.59 (d, 1H, J= 7.0); 7.43-7.37 (m, 3H); 7.26-7.13 (m, 4H); 6.98 (dd, 1H, J= 8.1, 2.4); 6.85 (d, 2H, J= 8.6); 4.17 (qui, 4H, J= 5.6); 3.99 (dd, 1H, J= 7.0, 4.6); 3.40 (s, 3H); 3.10 (dd, 1H, J= 14.2, 4.6); 2.96 (dd, 1H, J= 14.2, 7.0); 2.32-2.23 (m, 4H) ppm.

Example 101

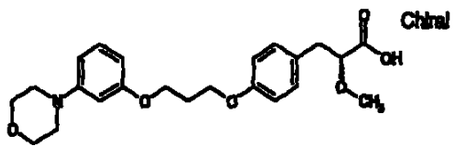
(2S)-2-Methoxy-3-{4-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 2-methyl-5-benzothiazolol and cleavage from the resin (Standard Procedure G) to give an oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.65 (d, 1 H, J=8.9), 7.36-7.35 (m, 1 H), 7.16 (d, 2 H, J=8.9), 7.03 (dd, 1 H, J=8.9, 2.4), 6.86 (dd, 2 H, J=6.5, 1.9), 4.22 (t, 2 H, J=5.9), 4.18 (t, 2 H, J=6.2), 4.01 (dd, 2 H, J=6.4, 5.4), 3.43 (s, 3 H), 3.14-2.94 (m, 2 H), 2.87 (s, 3 H), 2.27 (qn, 2 H, J=6.2) ppm.

Example 102

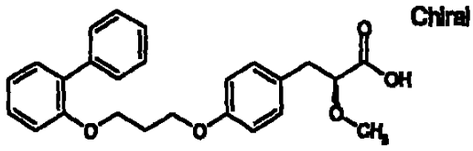
(2S)-2-Methoxy-3-{4-[3-(3-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2*S*)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 3-(4-morpholino) phenol and cleavage from the resin (Standard Procedure G) gave an oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.32-7.23 (m, 1 H), 7.14-7.10 (m, 2 H), 6.84-6.69 (m, 5 H), 4.14 (q, 4 H, J=5.6), 4.02-3.94 (m, 5 H), 3.40 (s, 3 H), 3.33-3.28 (m, 4 H), 3.13-2.91 (m, 2 H), 2.23 (qn, 2 H, J=5.9) ppm.

Example 103

(2S)-3-{4-[3-(Biphenyl-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

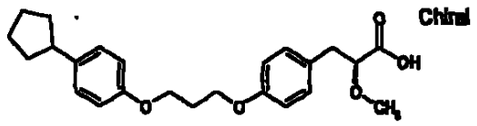


The title compound was prepared from (2*S*)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 2-phenylphenol and cleavage from the resin (Standard Procedure G) to give the title compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.51-7.43 (m, 2 H), 7.38-7.29 (m, 5 H), 7.15-6.98 (m, 4 H), 6.79-6.72 (m, 2 H), 4.15 (t, 2 H, J = 5.9 Hz), 4.04-3.96 (m, 3 H), 3.39 (s, 3 H), 3.15-2.90 (m, 2 H), 2.15 (qn, 2 H, J = 5.9 Hz) ppm.

211 20

Example 104

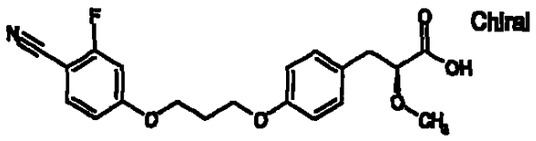
(2S)-3-{4-[3-(4-Cyclopentyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-cyclopentylphenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 105

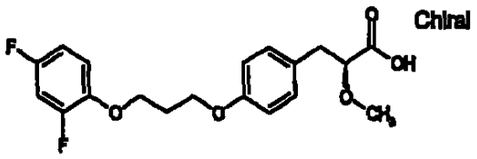
(2S)-3-{4-[3-(4-Cyano-3-fluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 2-fluoro-4-hydroxybenzonitrile and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 106

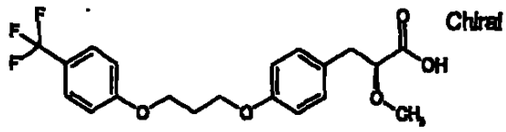
(2S)-3-{4-[3-(2,4-Difluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 2,4-difluorophenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 107

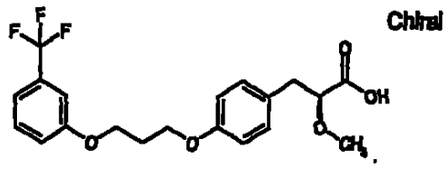
(2S)-2-Methoxy-3-{4-[3-(4-trifluoromethyl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-trifluoromethylphenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 108

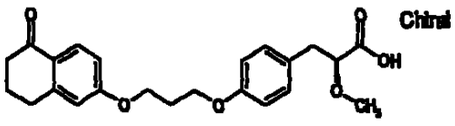
(2S)-2-Methoxy-3-{4-[3-(3-trifluoromethyl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 3-trifluoromethylphenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 109

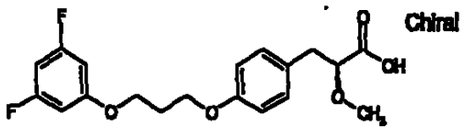
(2S)-2-Methoxy-3-{4-[3-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 6-hydroxy-1,2,3,4-tetrahydronaphtalenone and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 110

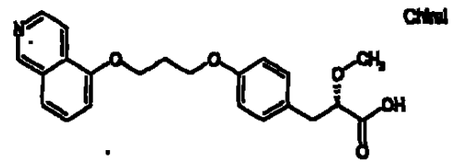
(2S)-3-{4-[3-(3,5-Difluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 3,5-difluorophenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 111

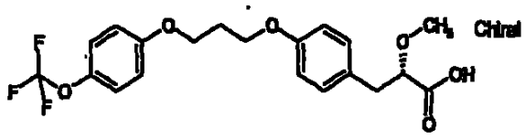
(2S)-3-{4-[3-(Isoquinolin-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 5-hydroxyisoquinolyne and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 112

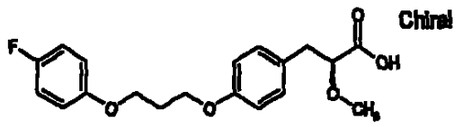
(2S)-2-Methoxy-3-{4-[3-(4-trifluoromethoxy-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-trifluoromethoxyphenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 113

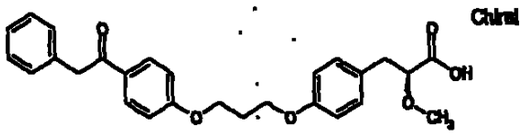
(2S)-3-{4-[3-(4-Fluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-fluorophenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 114

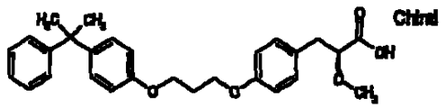
(2S)-2-Methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with benzyl-4-hydroxyphenylketone and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 115

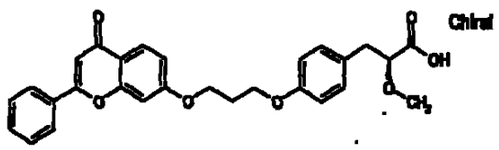
(2S)-2-Methoxy-3-{4-[3-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-propoxy}-phenyl]-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-cumylphenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 116

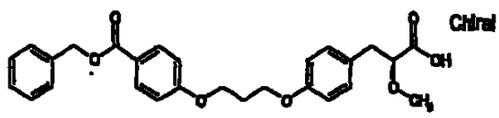
(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 7-hydroxyflavone and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 117

4-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid benzyl ester

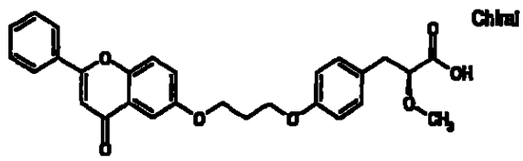


The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via

Mitsunobu coupling with benzyl 4-hydroxybenzoate and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 118

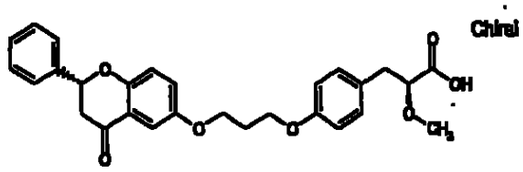
(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-chroman-6-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 6-hydroxyflavone and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 119

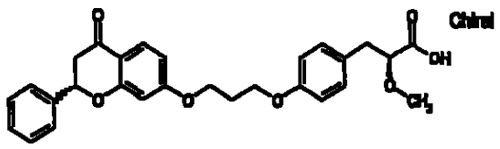
(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-chroman-6-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 6-hydroxyflavanone and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 120

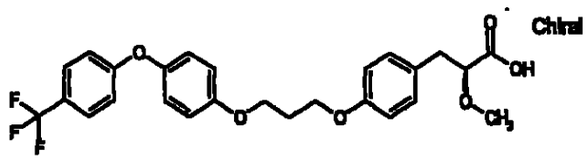
(2S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-chroman-7-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 7-hydroxyflavanone and cleavage from the resin (Standard Procedure G) gave an oily solid.

Example 121

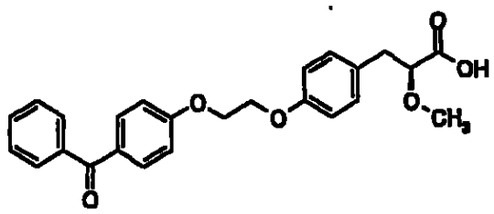
(2S)-2-Methoxy-3-(4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-propoxy}-phenyl)-propionic acid



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via Mitsunobu coupling with 4-(4-trifluoromethyl)phenoxyphenol and cleavage from the resin (Standard Procedure G) gave an oily solid.

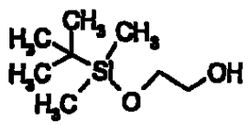
Example 122

(2S)-3-{4-[2-(4-benzoyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



Step A

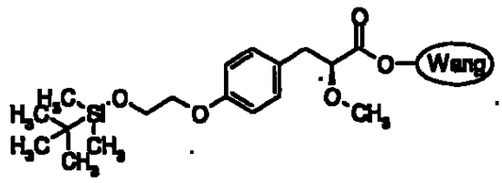
2-(*tert*-Butyl-dimethyl-silanyloxy)-ethanol



To a solution of ethylene glycol (1.00 g, 16.1 mmol) in THF (80 mL) was added NaH (0.65 mg, 16.1 mmol, 60% oil dispersion) at 0 °C. The reaction was stirred 1 hour, *tert*-butyldimethylsilyl chloride (2.35 g, 16.1 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After 3 hours at room temperature, Na_2CO_3 saturated solution (80 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (80 mL) and brine (80 mL), dried over ($MgSO_4$), and concentrated under vacuum. The reaction crude was purified by silica gel column chromatography (silica gel, hexanes/ethyl acetate, 2:3) to produce 1.93 g (85%) of a yellow oil. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 3.74-3.59 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H).

Step B

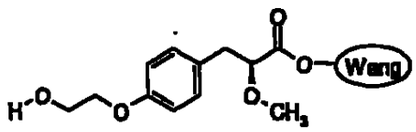
Preparation of (2S)-3-{4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethoxyl-phenyl}-2-methoxy-propanoic acid linked to Wang's Resin



The title compound was prepared from (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step D) via the Mitsunobu coupling procedure with 2-(*tert*-butyldimethylsilanyloxy)ethanol (Standard Procedure B).

Step C

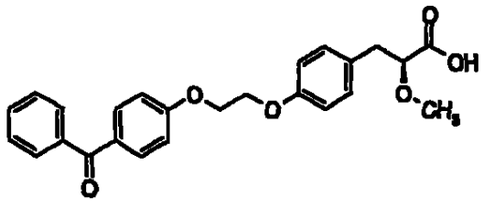
Preparation of (2S)-3-[4-[2-Hydroxyethoxyl-phenyl}-2-methoxy-propanoic acid linked to Wang's Resin



The title compound was prepared from 3-{4-[2-(*tert*-butyl-dimethylsilanyloxy)ethoxy]-phenyl}-2-methoxy-propanoic acid linked to Wang's Resin when treated with tetrabutylammonium fluoride in THF as described in Standard Procedure E. Cleavage of 20 mg of the resin in TFA/CH_2Cl_2 (1:1) followed by evaporation of the solvent produced (2S)-3-[4-[2-hydroxy-ethoxy]-phenyl}-2-methoxy-propanoic acid as an oil. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.16 (d, 2H, *J*=8.6), 6.85 (d, 2H, *J*=8.9), 4.09-3.93 (m, 5H), 3.41 (s, 3H), 3.11 (dd, 1H, *J*=14.5, 4.0), 2.97 (dd, 1H, *J*=14.5, 7.2).

Step D

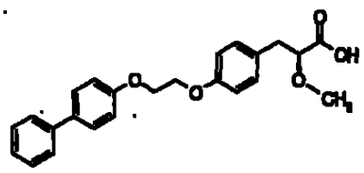
(2S)-3-{4-[2-(4-Benzoyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin via Mitsunobu coupling Standard Procedure G. Cleavage from the resin gave an oily solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.84-7.72 (m, 4H), 7.60-7.41 (m, 3H), 7.18 (d, 2H, *J*=8.6), 6.99 (d, 2H, *J*=8.9), 6.87 (d, 2H, *J*=8.7), 4.43-4.32 (m, 4H), 3.96 (dd, 1H, *J*=7.5, 4.6), 3.65 (s, 3H), 3.09 (dd, 1H, *J*=14.2, 4.2), 2.95 (dd, 1H, *J*=14.2, 7.8)ppm.

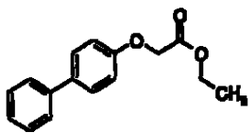
Example 123

(2S)-3-{4-[2-(Biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



Step A

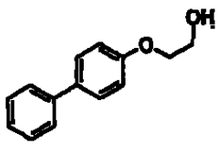
(Biphenyl-4-yloxy)-acetic acid ethyl ester



To a solution of 4-phenylphenol (1.02 g, 5.99 mmol) in 10 mL of DMF at -20 °C was added sodium hydride (0.24 g, 5.99 mmol, 60% oil dispersion) and the mixture stirred at 0°C for 30 min. 2-bromoethyl acetate (0.66 mL, 5.99 mmol) was added and the mixture stirred at room temperature overnight. The solution was diluted with water (50 mL) and extracted with diethyl ether (3 x 20 mL). The combined extracts were washed with water (4 x 20 mL), dried ($MgSO_4$) and concentrated under vacuum. 0.63 g (41 %). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.57-7.50 (m, 4H), 7.45-7.26 (m, 3H), 6.98 (dd, 2H, J=6.4, 2.1), 4.66 (s, 2H); 4.29 (q, 2H, J=7.3), 1.31 (t, 5H, J=7.3) ppm.

Step B

2-(Biphenyl-4-yloxy)-ethanol



To a solution of (Biphenyl-4-yloxy)-acetic acid ethyl ester (0.63 g, 2.46 mmol) in dry toluene (15 mL) at –78°C was added DIBAL-H 1M in toluene (4.92 mL, 4.92 mmol). The solution was stirred at –78°C for 1 hour, warmed to room temperature and quenched with mixture of a solution of sodium tartrate in water and ethyl acetate for 1 hour. The layers were separated and the aqueous phase further extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated under

vacuum and the residue purified bu column chromatography (silica gel, hexanes/Ethyl acetate 4:1, R_f 0.1), 48%. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.58-7.26 (m, 8H); 7.00 (d, 2H, *J*=8.6), 4.14 (t, 2H, *J*=4.6), 4.02-3.98 (m, 2H); 2.04 (t, 1H, *J*=5.4).

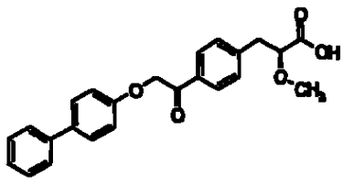
Step C

(2S)-3-{4-[2-(Biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from 2-(Biphenyl-4-yloxy)-ethanol and (2S)-2-Methoxy-3-hydroxyphenyl propionic acid ethyl ester using the general procedure A (34%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.55-7.49 (m, 4H); 7.43-7.35 (m, 2H); 7.29 (d, 1H, *J*=7.3); 7.15 (d, 2H, *J*=8.8); 7.00 (d, 2H, *J*=8.8); 6.88 (d, 2H, *J*=8.8); 4.36-4.29 (m, 4H); 3.98 (dd, 1H, *J*=7.0, 4.4); 3.39 (s, 3H); 3.10 (dd, 1H, *J*=14.3, 4.4); 2.95 (dd, 1H, *J*=14.3, 7.3)ppm. MS (ES) for $C_{24}H_{24}O_5$ $[M+NH_4]^+$: 410.

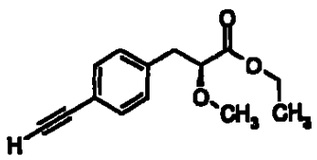
Example 124

(2S)-3-{4-[2-(Biphenyl-4-yloxy)-acetyl]-phenyl}-2-methoxy-propionic acid



Step A

(2S) 3-(4-Ethynyl-phenyl)-2-methoxy-propionic acid ethyl ester

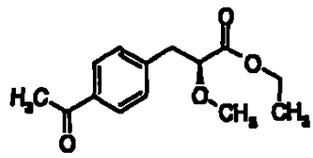


To a solution of (2S) 2-Methoxy-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid ethyl ester (0.100 g, 0.29 mmol)(Example 1, Step A) in 10 mL of degassed piperidine, was added (trimethylsilyl)acetylene (99,6 mg, 1.015 mmol),

tetrakis(triphenylphosphine) Palladium (0) (0.017 g, 0.015 mmol), triphenylphosphine (7.7 mg, 0.029 mmol) and cooper (I) Iodide (5.5 mg, 0.029 mmol). The solution was stirred for 2 hours at 120°C and then cooled to room temperature. The solvent was evaporated under vacuum. The residue was dissolved in dry THF and 0,4 mL of a solution of tetrabutylamonium fluoride (1.0 M in THF) and 0.02 mL of water were added. The mixture was stirred at room temperature for 5 min. The solvent was evaporated under vacuum and the residue partitioned between water (20 ml) and diethyl ether (20 mL). The layers were separated and the aqueous solution extracted twice with 20 ml of diethylether. The combined organic layers were washed with 10% Na_2CO_3 (6 x 20 ml) and brine (20 ml) and dried ($MgSO_4$). Concentration produced a yellow oil (38 mg, 56 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.95 (d, 1H, *J*=7.3), 7.25 (d, 1H, *J*=7.3), 4.18 (q, 2H, *J*=7.0), 3.97 (dd, 1H, *J*=7.3, 5.6), 3.36 (s, 3H), 3.05 (d, 1H, *J*=5.3), 3.02 (d, 1H, *J*=2.4 Hz), 1.22 (t, 3H, *J*=7.25).

Step B

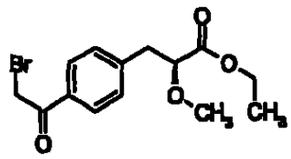
(2S) 3-(4-Acetyl-phenyl)-2-methoxy-propionic acid ethyl ester



To (2S) 3-(4-Ethynyl-phenyl)-2-methoxy-propionic acid ethyl ester (36 Mg, 0.15 mmol) (Example 29, Step A) were added 4 ml of formic acid. The solution was stirred for 1 hour at 100°C and then cooled to room temperature. The mixture was taken up with methylene chloride and the solution was washed with water, sodium carbonate, and water, dried ($MgSO_4$) and the solvent was evaporated under vacuum. Obtained a brown liquid (0.035 g, 95 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.43 (d, 1H, *J*=7.3), 7.12 (d, 1H, *J*=7.3), 4.18 (q, 2H, *J*=7.0), 3.97 (dd, 1H, *J*=7.3, 5.6), 3.32 (s, 3H), 3.06 (s, 1H), 3.03 (d, 1H, *J*=2.4 Hz), 2.56 (s, 2H), 1.22 (t, 3H, *J*=7.25).

Step C

(2S) 3-[4-(2-Bromo-acetyl)-phenyl]-2-methoxy-propionic acid ethyl ester



Powdered cupric bromide (62 mg, 0.28 mmol) was added portionwise to a solution of (2S) 3-(4-Acetyl-phenyl)-2-methoxy-propionic acid ethyl ester (35 mg, 0.14 mmol) in $CHCl_3$ (5ml) and ethyl acetate (5 mL). The solution was stirred for 1 hour at 65°C and then cooled to room temperature. The mixture was filtered and the solvent evaporated under vacuum. The residue was purified by chromatography (silica gel, hexanes/Ethyl Ether 8:2, R_f 0.20) to produce a colorless oil (25 mg, 54%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.935 (d, 1H, *J*=7.3), 7.38 (d, 1H, *J*=7.3), 4.50 (s, 2H), 4.12 (q, 2H, *J*=7.0), 3.97 (dd, 1H, *J*=7.3, 5.6), 3.38 (s, 3H), 3.10 (s, 1H), 3.06 (d, 1H, *J*=2.4 Hz), 1.22 (t, 3H, *J*=7.25).

Step D

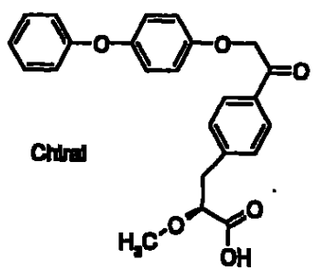
(2S) 3-{4-[2-(Biphenyl-4-yloxy)-acetyl]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from a solution of (2S) 3-[4-(2-Bromo-acetyl)-phenyl]-2-methoxy-propionic acid ethyl ester (25 mg, 0.076 mmol) in acetonitrile (5 ml). 4-phenylphenol (29 mg, 0.152 mmol) and K_2CO_3 (31,5 mg, 0.23 mmol) were added. The solution was stirred for 30 min at 80°C and then cooled to room temperature. The mixture was concentrated to dryness under vacuum and chromatographed in silica gel (hexanes/Ethyl ether 8:2 to 7:3). Fractions corresponding to the coupled compound were collected (R_f0.27)and concentrated to dryness. The mixture thus obtained was dissolved in 4 mL of NaOH 1N and 12 mL of Methanol and stirred at room temperature until TLC indicates the disappearance of starting material. The methanol was eliminated under vacuum and the aqueous solution diluted with 20 mL of brine and washed with diethyl ether (3 x 15 mL). The aqueous phase was acidulated with HCl 1N (until pH 3); extracted with ethyl acetate (3 x 15 mL) and the organic layer dried ($MgSO_4$) and concentrated under vacuum. Obtained a colorless oil (9.6 mg, 32 %). ^{1}H-NMR (200.15 MHz, $CDCl_3$):

δ 7.96 (d, 2H, J=8.4), 7.55-7.23 (m, 9H), 6.99 (d, 2H, J=8.8), 5.26 (s, 2H), 4.03 (dd, 1H, J=7.3, 5.6), 3.39 (s, 3H) 3.22 (dd, 1H, J=14.3, 5,5), 3.03 (dd, 1H, J=14.3, 7.2).

Example 125

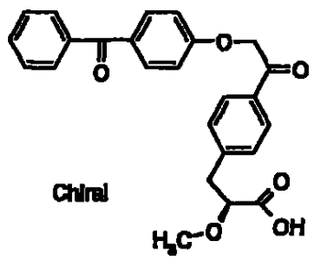
(2S)-2-Methoxy-3-{4-[2-(4-phenoxy-phenoxy)-acetyl]-phenyl}-propionic acid



The title compound was prepared from a solution of (2S) 3-[4-(2-Bromo-acetyl)-phenyl]-2-methoxy-propionic acid ethyl ester (0.076 mmol) from Example 124, Step C in acetonitrile (5 ml). 4-phenoxyphenol (0.152 mmol) and K_2CO_3 (0.23 mmol) were added. The solution was stirred for 30 min at 80°C and then cooled to room temperature. The mixture was concentrated to dryness under vacuum and chromatographed in silica gel (hexanes/Ethyl ether 8:2 to 7:3). Fractions corresponding to the coupled compound were collected (R_f: 0.27) and concentrated to dryness. The mixture thus obtained was dissolved in 4 mL of NaOH 1N and 12 mL of Methanol and stirred at room temperature until TLC indicates the disappearance of starting material. The methanol was eliminated under vacuum and the aqueous solution diluted with 20 mL of brine and washed with diethyl ether (3 x 15 mL). The aqueous phase was acidulated with HCl 1N (until pH 3); extracted with ethyl acetate (3 x 15 mL) and the organic layer dried ($MgSO_4$) and concentrated under vacuum. Obtained a colourless oil. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.96 (d, 2H, J=8.4), 7.55-7.33 (m, 5H), 7.04-6.83 (m, 6H), 5.24 (s, 2H), 4.08 (dd, 1H, J=7.4, 4.4), 3.40 (s, 3H) 3.22 (dd, 1H, J=14.3, 4.4), 3.15 (dd, 1H, J=14.3, 7.2).

Example 126

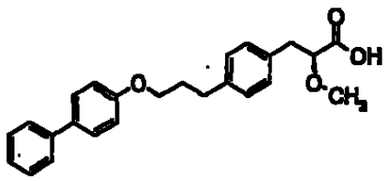
(2S)-3-{4-[2-(4-Benzoyl-phenoxy)-acetyl]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from a solution of (2*S*) 3-[4-(2-Bromo-acetyl)-phenyl]-2-methoxy-propionic acid ethyl ester (0.076 mmol) from Example 124, Step C in acetonitrile (5 ml). 4-hydroxybenzophenone (0.152 mmol) and K_2CO_3 (0.23 mmol) were added. The solution was stirred for 30 min at 80°C and then cooled to room temperature. The mixture was concentrated to dryness under vacuum and chromatographed in silica gel (hexanes/Ethyl ether 8:2 to 7:3). Fractions corresponding to the coupled compound were collected (R_f 0.27) and concentrated to dryness. The mixture thus obtained was dissolved in 4 mL of NaOH 1N and 12 mL of Methanol and stirred at room temperature until TLC indicates the disappearance of starting material. The methanol was eliminated under vacuum and the aqueous solution diluted with 20 mL of brine and washed with diethyl ether (3 x 15 mL). The aqueous phase was acidulated with HCl 1N (until pH 3); extracted with ethyl acetate (3 x 15 ml) and the organic layer dried ($MgSO_4$) and concentrated under vacuum. Obtained a colorless oil. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.96-7.71 (m, 6H), 7.57-7.46 (m, 5H), 6.97 (d, 2H, J=8.1), 5.35 (s, 2H), 4.08 (dd, 1H, J=7.4, 4.2), 3.26 (s, 3H) 3.20 (dd, 1H, J=14.1, 4.1), 3.09 (dd, 1H, J=14.1, 7.2).

Example 127

(2S)-3-{4-[3-(Biphenyl-4-yloxy)-propyl]-phenyl}-2-methoxy-propionic acid

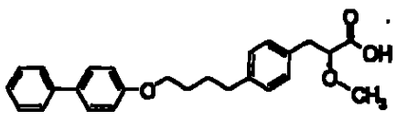


The title compound was prepared as follows: (2*S*) 3-{4-[3-(Biphenyl-4-yloxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid (0, Step C) (0.0325 g, 0.08 mmol) was

dissolved in methanol (10 mL). Palladium 10% on activated carbon (0.004 g, 0.004 mmol) was added and the solution saturated with hydrogen (1 Atm) and stirred for 5 hours. The mixture was filtered through a pad of celite and concentrated under vacuum. The residue was purified by column chromatography (silica gel, hexanes/Ethyl acetate-Acetic acid 50:50:1, R_f 0.23) (85%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.56-7.24 (m, 11H), 6.94 (d, 2H, J=8.8), 4.02-3.95 (m, 3H), 3.38 (s, 3H), 3.11 (dd, 1H, J=14.3, 4.4), 2.98 (dd, 1H, J=14.3, 7.3), 2.79 (t, 2H, J=8.1), 2.16-2.03 (m, 3H).MS (ES) for $C_{25}H_{26}O_4$ $[M+NH_4]^+$: 408.2, $[M+Na]^+$: 413.2.

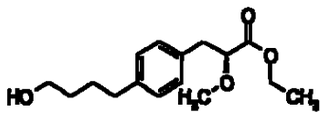
Example 128

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-butyl]-phenyl}-2-methoxy-propionic acid



Step A

(2S)-3-[4-(4-Hydroxy-butyl)-phenyl]-2-methoxy-propionic acid ethyl ester



(2S)-3-[4-(3-Hydroxy-prop-1-ynyl)-phenyl]-2-methoxy-propionic acid ethyl ester (0.294 g, 1.06 mmol) was dissolved in ethyl acetate (50 mL). Palladium 10% on activated carbon (0.057 g, 0.05 mmol) was added and the solution saturated with hydrogen (1 Atm) and stirred for 2 hours. The mixture was filtered through a pad of celite and concentrated under vacuum. (100%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.12 (dd, 4H, *J*=11.3, 8.6), 4.17 (q, 2H, *J*=7.0), 3.94 (dd, 1H, *J*=7.0, 6.2), 3.65 (t, 2H, *J*=5.9); 3.35 (s, 3H), 3.00 (s, 1H), 2.97 (s, 1H), 2.61 (t, 2H, *J*=7.3), 1.73-1.60 (m, 4H), 1.22 (t, 3H, *J*=7.0).

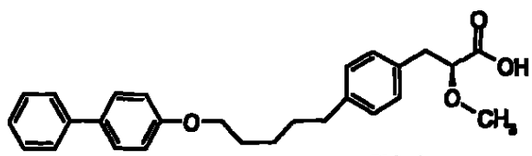
Step B

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-butyl]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S) 3-[4-(4-Hydroxy-butyl)-phenyl]-2-methoxy-propionic acid ethyl ester and 4-phenylphenol following the Standard Procedure of coupling-hydrolysis A. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.55-7.23 (m, 7H); 7.14 (d, 4H, *J*=1.1); 6.93 (d, 2H, *J*=8.4); 4.02-3.96 (m, 3H); 3.37 (s, 3H); 3.11 (dd, 1H, *J*=14.3, 4.4); 2.97 (dd, 1H, *J*=14.3, 7.3); 2.66 (t, 2H, *J*=7.0); 1.83-1.80 (m, 4H). MS (ES) for $C_{26}H_{28}O_4$ $[M+NH_4]^+$: 422.2, $[M+Na]^+$: 427.2.

Example 129

(2S)-3-{4-[5-(Biphenyl-4-yloxy)-pentyl]-phenyl}-2-methoxy-propionic acid

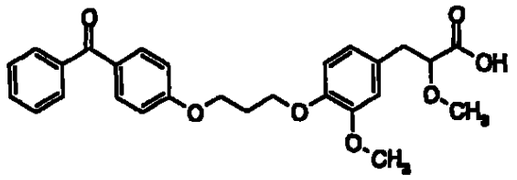


Chiral

The title compound was prepared as follows: (2S)-3-{4-[5-(Biphenyl-4-yloxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid from Example 21 (0.08 mmol) was dissolved in methanol (10 mL). Palladium 10% on activated carbon (0.004 g, 0.004 mmol) was added and the solution saturated with hydrogen (1 Atm) and stirred for 5 hours. The mixture was filtered through a pad of celite and concentrated under vacuum. The residue was purified by column chromatography. MS (ES) for $C_{27}H_{30}O_4$ $[M-H]^-$: 417.3.

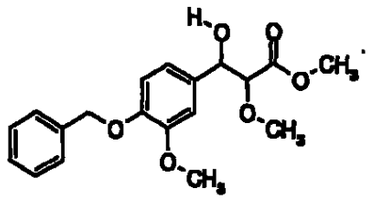
Example 130

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methoxy-propionic acid



Step A

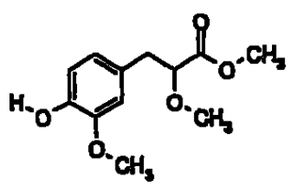
3-(4-Benzyloxy-3-methoxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester



A solution of 4-benzyloxy-3-methoxy-benzaldehyde (0.44 g, 1.92 mmol) and methyl methoxyacetate (0.19 mL, 1.92 mmol) in THF (10 mL) at –78°C was added dropwise to sodium bis(trimethylsilyl)amide (20 mL, 2.11 mmol, 1N in THF) at –78°C. The reaction mixture was stirred for 3 h and quenched with 1N HCl (5 mL). The mixture was allowed to warm to room temperature, diluted with water (15 mL), and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (silica gel, hexanes/ethyl acetate, 1:1) to produce 3-(4-benzyloxy-3-methoxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester as an oil (350 mg, 52%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.45-7.20 (m, 5H), 6.9 (s, 1H), 6.8 (b, 2H), 5.1 (s, 2H), 4.90-4.80 (m, 1H), 4.10 (m, 1H), 3.90 (s, 3H), 3.65 (s, 3H), 3.31 (s, 3H), 3.10-2.90 (m, 1H).

Step B

3-(4-Hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid methyl ester

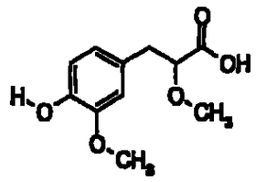


Trifluoroacetic anhydride (0.62 mL, 4.36mmol) and triethylamine (0.62 mL, 4.36 mmol) were added to a solution of 3-(4-benzyloxy-3-methoxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester (1.01 g, 2.91 mmol) in methylene chloride (30 mL) at 0°C. The resulting mixture was stirred for 4 hours at room temperature and was concentrated under vacuum. The residue was dissolved in ethyl acetate (30 mL), and 10% palladium on carbon (0.3 g) was added to the solution. The mixture was stirred under hydrogen pressure (4 atm) for 16 hours. The mixture was filtered through Celite and concentrated under vacuum. The residue was purified by silica

gel column chromatography (silica gel, hexanes/ethyl acetate 7:3) to produce 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid methyl ester as an oil (598 mg, 86%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 6.80 (d, 1H, *J*=7.8), 6.7 (s, 1H), 6.62 (d, 1H, *J*=7.8), 3.96 (dd, 1H, *J*=7.8, 4.0), 3.80 (s, 3H), 3.68 (s, 3H), 3.30 (s, 3H), 3.09 (dd, 1H, *J*=14.2, 4.0), 2.91 (dd, 1H, *J*=14.2, 7.8).

Step C

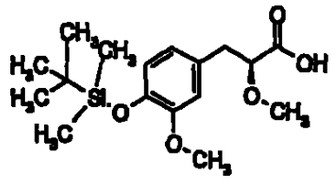
3-(4-Hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid



A 1N aqueous lithium hydroxide solution was added to a solution of 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid methyl ester (280 mg, 1.17mmol) in THF at room temperature, and the reaction mixture stirred overnight. The aqueous phase was extracted with ethyl acetate (20 mL), acidified to pH 2, and extracted with ethyl acetate (3 x 15 mL). The later organic layers were combined and washed with water (15 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to produce 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid as an oil (183 mg, 74%). ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ 6.83 (1H, d, *J*=7.8), 6.74 (1H, s), 6.72 (1H, d, *J*=7.8), 3.99 (1H, dd, *J*=7.8, 4.0), 3.85 (s, 3H), 3.40 (s, 3H), 3.09 (1H, dd, *J*=14.2, 4.0), 2.91 (1H, dd, *J*=14.2, 7.8).

Step D

3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methoxy-phenyl]-2-methoxy-propionic acid

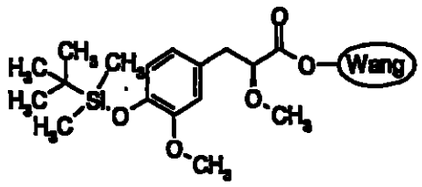


To a solution of 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid (1.02 g, 4.87 mmol) in CH_2Cl_2-DMF (20 mL = 10:1) was added *tert*-butyl-dimethylsilyl

chloride (1.75 g, 11.68 mmol) and imidazole (0.70 g, 10.24 mmol). The resulting solution was stirred at room temperature overnight. Water (15 mL) was added, and the aqueous phase was extracted with hexanes (30 mL). The hexanes layer was washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in ethyl acetate (10 mL), and a saturated solution of K_2CO_3 (5 mL) was added. The resulting mixture was stirred for 2 hours at room temperature. The aqueous layer was extracted with ethyl acetate (10 mL), acidified to pH 3, and extracted again with ethyl acetate (3 x 10 mL). The later organic layers were combined and washed with brine (20 mL), dried ($MgSO_4$), and concentrated to a yellow oil (1.2 g, 77%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 6.78-6.67 (m, 3H), 3.96 (dd, 1H, *J*=7.8, 4.0), 3.78 (s, 3H), 3.35 (s, 3H), 3.09 (dd, 1H, *J*=14.2, 4.0), 2.91 (dd, 1H, *J*=14.2, 7.8), 0.98 (s, 9H), 0.13 (6H, s).

Step E

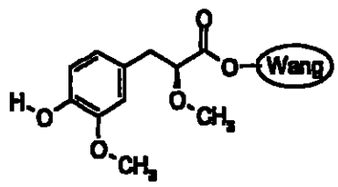
Preparation of 3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methoxy-phenyl]-2-methoxy-propionic acid linked to Wang's Resin



The title compound was prepared following the procedure as in Example 95, Step B.

Step F

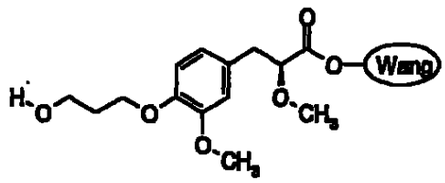
Preparation of 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin



The title compound was prepared following the procedure as in Example 95, Step C.

Step G

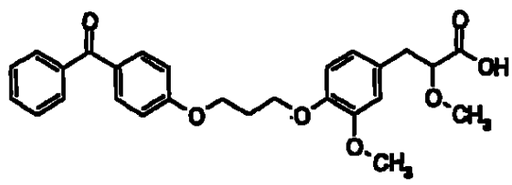
Preparation of 3-[4-(3-hydroxy-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid linked to Wang's Resin.



The title compound was prepared from 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin via Mitsunobu coupling (Standard Procedure F) to produce 3-[4-(3-hydroxy-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid linked to Wang's Resin.

Step H

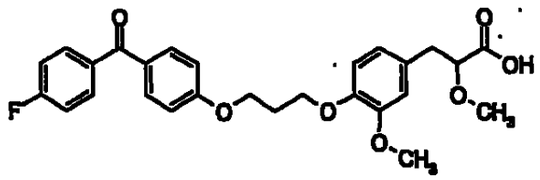
3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid



The title compound was prepared from 3-(4-(3-hydroxy-propoxy)-3-methoxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin via the Mitsunobu coupling-cleavage from the resin procedure (Standard Procedure G) to produce an oily solid (4%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.81-7.72 (m, 4H), 7.57-7.43 (m, 3H), 6.96 (d, 2H, *J*=8.9), 6.81-6.73 (m, 3H), 4.28 (t, 2H, *J*=6.2), 4.20 (t, 2H, *J*=6.2), 4.01 (dd, 1H, *J*=7.0, 4.6), 3.83 (s, 3H), 3.42 (s, 3H), 3.09 (dd, 1H, *J*=14.5, 4.0), 2.97 (dd, 1H, *J*=14.5, 7.0), 2.33 (qn, 2H, *J*=6.2).

Example 131

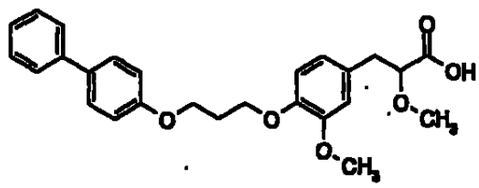
3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-3-methoxy-phenyl)-2-methoxy-propionic acid



The title compound was prepared from 3-(4-(3-hydroxy-propoxy)-3-methoxy-phenyl)-2-methoxy-propionic acid linked to Wang's Resin via the Mitsunobu coupling-cleavage from the resin procedure (Standard Procedure G) to produce an oily solid (4%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.83-7.74 (m, 4H), 715 (t, 2H, *J*=8.6 Hz), 6.96 (d, 2H, *J*=8.6), 6.85-6.74 (m, 3H), 4.28 (t, 2H, *J*=6.2), 4.20 (t, 2H, *J*=6.2), 4.01 (dd, 1H, *J*=7.0, 4.6), 3.84 (s, 3H), 3.42 (s, 3H), 3.10 (dd, 1H, *J*=14.2, 4.6), 2.97 (dd, 1H, *J*=14.2, 7.0), 2.33 (qn, 2H, *J*=6.2).

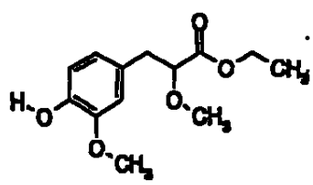
Example 132

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid



Step A

3-(4-Hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid ethyl ester



To a solution of 3-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-methoxy-phenyl]-2-methoxy-propionic acid (356 mg, 1.05 mmol) in absolute ethanol (8 mL) was added concentrated sulfuric acid (0.033 mL, 0.63 mmol). The reaction mixture was allowed to stir at room temperature for 17 hours. The solution was concentrated

under vacuum, and water (10 mL) and solid $NaHCO_3$ were added to neutralize the residue. The aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried (MgSO4), filtered, and concentrated to produce 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid ethyl ester (260 mg, 98%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 6.83 (d, 1H, *J*=8.1 Hz), 6.76-6.69 (m, 2H), 4.19 (q, 2H, *J*=7.3 Hz), 3.97-3.90 (m, 1H), 3.87 (s, 3H), 3.36 (s, 3H), 2.96-2.92 (m, 2H), 1.25 (t, 3H, *J*=7.3 Hz).

Step B

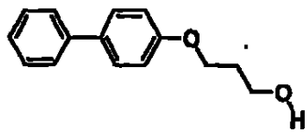
[1.3.2]Dioxathiane 2,2-dioxide



To a solution of 1,3-propanodiol (30 g, 394 mmol) in CCl_4 (278 mL) was added thionyl chloride (36 mL, 491 mmol) via syringe. The resulting mixture was heated at reflux for 1.5 h and was cooled to 0°C to evaporate the solvent under vacuum. The residue was dissolved in a mixture of $CCl_4/CH_3CN/H_2O$ (2:2:3=500 mL) and cooled to 0°C. Ruthenium trichloride trihydrate (0.556 g, 2.68 mmol) was added, followed by addition of solid $NaIO_4$ (14.35 g, 197 mmol). The mixture was stirred at room temperature for 1 h, H_2O (1 L) was added, and the aqueous phase was extracted with diethyl ether (4 x 300mL). The combined organic layers were washed with brine (2 x 100 mL), dried (MgSO4), and filtered through a pad of silica gel to remove the ruthenium salts. The solvent was evaporated and hexanes (200 mL) was added to the resulting oil. After cooling, a gray solid precipitated. The solid was filtered and washed with hexanes. Recrystallization from hexanes/ether yielded a white, crystalline solid (18.15 g, 33%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 4.73 (t, 4H, *J*=5.6), 2.13 (qn, 2H, *J*=5.6).

Step C

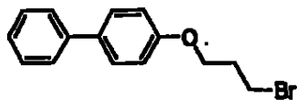
3-(Biphenyl-4-yloxy)-propan-1-ol



A solution of 4-phenylphenol (4.9 g, 29.0 mmol) and potassium *tert*-butoxide (3.64 g, 30.3 mmol) in THF (100 mL) was stirred at room temperature for 30 min. The solution was cooled at 0°C and [1,3,2]dioxathiane 2,2-dioxide (3.6 g, 26.34 mmol) in THF (25 mL) was added. The resulting mixture was stirred at room temperature for 5 hours, and the solvent was removed under vacuum. The residue was dissolved in 6N HCl (15 mL) and heated at 100°C for 16 hours. The mixture was cooled to room temperature, and the aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with H_2O (3 x 25 mL) and brine (25 mL), dried (MgSO4), filtered, and concentrated to produce 3-(biphenyl-4-yloxy)-propan-1-ol as a white solid (4.16 g, 63%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.49 (m, 4H), 7.45-7.37 (m, 3H), 6.98 (dd, 2H, *J*=6.72, 2.14), 4.17 (t, 2H, *J*=5.9), 3.88 (q, 2H, *J*=5.9), 2.07 (qn, 2H, *J*=5.9).

Step D

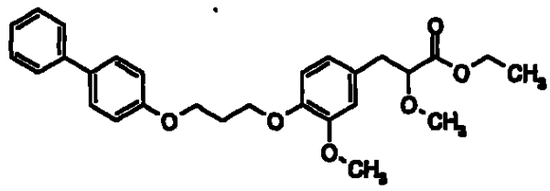
4-(3-Bromo-propoxy)-biphenyl



To a solution of 3-(biphenyl-4-yloxy)-propan-1-ol (1.00 g, 4.38 mmol) in CH_2Cl_2 (20 mL) at 0°C was added triphenylphosphine (1.61 g, 6.14 mmol) and carbon tetrabromide (1.81 g, 5.47 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 1 hour, and extracted with ethyl acetate (50 mL). The organic layer was washed with H_2O (3 x 50 mL) and brine (3 x 25 mL), dried (MgSO4), filtered and concentrated. The crude product was purified by silica gel column chromatography (silica gel, hexanes/ethyl acetate, 9:1) to produce 4-(3-bromo-propoxy)-biphenyl (1.22 g, 95%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.29 (m, 7H), 6.98 (dd, 2H, *J*=6.72, 1.88), 4.15 (t, 2H, *J*=5.92), 3.62 (t, 2H, *J*=6.44), 2.34 (qn, 2H, *J*=5.92).

Step E

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid ethyl ester



To a solution of 3-(4-hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid ethyl ester (Example 132, Step A) (0.080 g, 0.31 mmol) in acetonitrile (10 mL) was added 4-(3-bromo-propoxy)-biphenyl (Example 132, Step D) (0.101 g, 0.35 mmol) and potassium carbonate (0.115 g, 0.945 mmol). The resulting suspension was stirred at 85°C overnight. After cooling, the reaction mixture was diluted with ethyl acetate (10 mL), and water (10 mL) was added. The organic layer was washed with water (10 mL) and brine (10 mL), dried (MgSO4), and concentrated. The crude product was purified by silica gel column chromatography (silica gel, hexanes/ethyl acetate, 7:3) to produce 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid ethyl ester (0.086 g, 59%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.26 (m, 7H), 6.98 (d, 2H, *J*=8.6), 6.87-6.73 (m, 3H), 4.25-4.17 (m, 6H), 3.91 (dd, 1H, *J*=7.0, 5.6), 3.83 (s, 3H), 3.35 (s, 3H), 2.97-2.93 (m, 2H), 2.31 (qn, 2H, *J*=5.9), 1.24 (t, 3H, *J*=7.3).

Step F

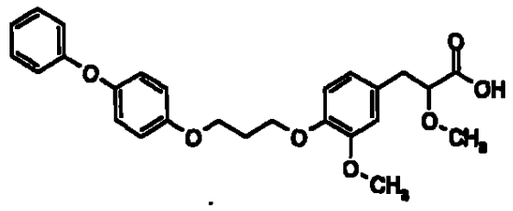
3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid

The title compound was prepared from 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid ethyl ester following the hydrolysis procedure described in Example 130, Step C. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.56-7.25 (m, 7H), 6.97 (d, 2H, *J*=8.9), 6.89-6.79 (m, 3H), 5.07 (b, 1H), 4.17 (q, 4H, *J*=5.6), 3.95 (dd, 1H, *J*=7.5, 3.5), 3.82 (s, 3H), 3.32 (s, 3H), 3.11-2.86 (m, 2H), 2.28 (qn, 2H, *J*=6.2).

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Example 133

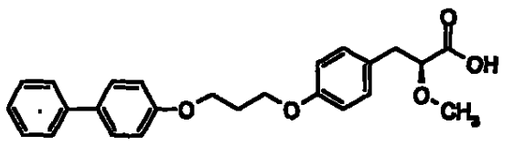
2-Methoxy-3-{3-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared following the procedure described for Example 132 (Steps A-E). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.32-7.24 (m, 2H), 7.06-6.75 (m, 10H), 4.16 (q, 4H, *J*=6.2), 3.97 (dd, 1H, *J*=7.8, 4.3), 3.82 (s, 3H), 3.37 (s, 3H), 3.08 (dd, 1H, *J*=14.2, 4.0), 2.94 (dd, 1H, *J*=14.5, 7.8); 2.27 (qn, 2H, *J*=6.2).

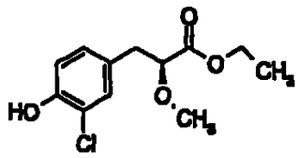
Example 134

(2S)-3-(4-[3-(Biphenyl-4-yloxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid



Step A

(2S)-3-(3-Chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester



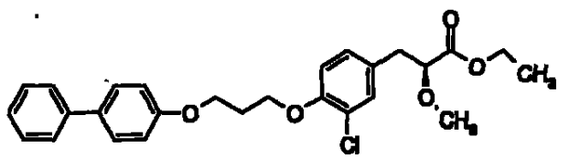
To a solution of 3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (0.113 g, 0.5 mmol) in CH_3CN (3 mL) cooled to 0°C, N-chlorosuccinimide (0.067 g, 0.5 mmol,) was added in various portions. The mixture was allowed to warm to room temperature and was stirred for 8 hours. The mixture was concentrated under vacuum, and the resulting oil was washed with CCl_4 (4 mL). The precipitate which

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formed was filtered, and the filtrate was concentrated to give a mixture of 3-(3-chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester and 3-(3,5-Dichloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester as a brown oil which was purified by ultraviolet-directed HPLC. A colorless oil was obtained (0.020 g, 14%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.18 (d, 1H, *J*=2.15), 7.02 (dd, 1H, *J*=8.32, 2.15), 6.91 (d, 1H, *J*=8.32), 4.18 (q, 2H, *J*=7.25), 3.88 (dd, 1H, *J*=7.24, 5.62), 3.35 (s, 3H), 2.92 (dd, 2H, *J*=6.31, 2.42), 1.24 (t, 3H, *J*=7.2).

Step B

(2S)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid ethyl ester



3-(3-Chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (0.020 g, 0.077 mmol) was dissolved in CH_3CN (3 mL) and 4-(3-bromo-propoxy)-biphenyl (Example 132, Step D), (0.025 g 0.085 mmol) and K_2CO_3 (0.032 g, 0.23 mmol) were added. The mixture was heated to 85°C and stirred for 5 hours. After cooling, water (2 mL) was added. The mixture was extracted in EtOAc (3 x 10 mL), washed with H_2O (2 x 5 mL) and brine (2 x 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (silica gel, hexanes/ethyl acetate 9:1) to produce 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid ethyl ester (0.017 mg, 48%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.24 (m, 9H), 7.02-6.89 (m, 3H), 4.28-4.12 (m, 5H), 3.89 (dd, 1H, *J*=7.24, 5.62), 3.62 (t, 1H, *J*=6.44), 3.36 (s, 3H), 2.93 (dd, 2H, *J*=6.31, 2.42), 2.32 (qn, 2H, *J*=5.10), 1.25 (t, 3H, *J*=7.2).

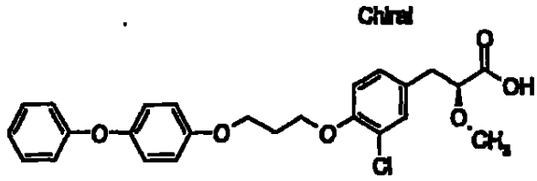
Step C

(2S) 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid

The title compound was prepared as follows: 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid ethyl ester (0.017 g, 0.037 mmol) was dissolved in 0.25 M ethanolic NaOH solution (0.3 mL, 0.075 mmol). The mixture was stirred 16 hours at room temperature and water was added. The aqueous layer was extracted with Et_2O (3 x 5 mL). The aqueous layer was acidified to pH=1 with 1 N HCl and extracted with Et_2O (5 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give the title compound as a yellow oil (0.006 mg, 38%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-7.25 (m, 9H), 7.0-6.86 (m, 3H), 4.23 (q, 4H, *J*=6.18), 3.96 (dd, 1H, *J*=7.24, 4.28), 3.40 (s, 3H), 3.06 (dd, 1H, *J*=14.5, 4.28), 2.92 (dd, 1H, *J*=14.5, 7.24), 2.32 (qn, 2H, *J*=5.92).

Example 135

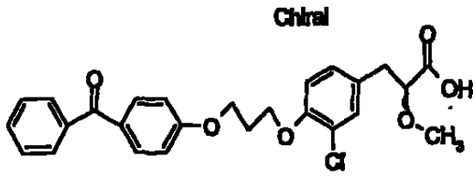
3-{3-Chloro-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared as a same manner in Example 134, but using 4-(3-bromopropoxy)-1-phenoxybenzene as material for the coupling reaction.

Example 136

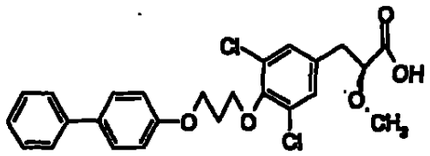
3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionic acid



The title compound was prepared as a same manner in Example 134, but using [4-(3-Bromo-propoxy)-phenyl]-phenyl-methanoneas material for the coupling reaction.

Example 137

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3,5-dichloro-phenyl}-2-methoxy-propionic acid



Chiral

Step A

3-(3,5-Dichloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester

To a solution of 3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (0.113 g, 0.5 mmol) in CH_3CN (3 mL) cooled to 0°C, N-chlorosuccinimide (0.067 g, 0.5 mmol,) was added in various portions. The mixture was allowed to warm to room temperature and was stirred for 8 hours. The mixture was concentrated under vacuum, and the resulting oil was washed with CCl_4 (4 mL). The precipitate which formed was filtered, and the filtrate was concentrated to give a mixture of 3-(3-chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester and 3-(3,5-Dichloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester as a brown oil which was purified by ultraviolet-directed HPLC.

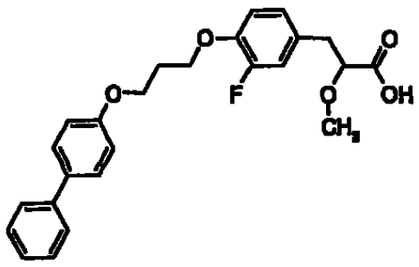
Step B

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3,5-dichloro-phenyl}-2-methoxy-propionic acid

The title compound was prepared starting from compound from Step A and using the same procedure as in 0.

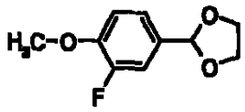
Example 138

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-2-methoxy-propionic acid



Step A

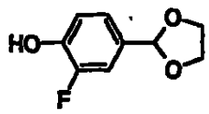
2-(3-Fluoro-4-methoxy-phenyl)-[1,3]-dioxolane



A solution of 3-fluoro-4-methoxy-benzaldehyde (463 mg, 3 mmol), ethylene glycol (0.86 mL, 15 mmol) and PPTs (75 mg, 0.3 mmol) in toluene (15 mL) was heated at reflux with azeotropic removal of water for 6 hours. The solvent was evaporated and the residue was diluted with methylene chloride (20 mL), washed with water (2x10 mL) and dried ($MgSO_4$). Concentration produced 2-(3-Fluoro-4-methoxy-phenyl)-[1,3]-dioxolane as a colorless oil (550 mg, 92%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 7.24-7.15 (m, 2H), 6.92 (t, 1H, *J*=8.5), 5.71 (s, 1H), 4.10-3.98 (m, 4H), 3.86 (s, 3H).

Step B

4-[1,3]Dioxolan-2-yl-2-fluoro-phenol

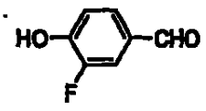


A solution of 2-(3-Fluoro-4-methoxy-phenyl)-[1,3]-dioxolane (250 mg, 1.26 mmol) and Sodium thiomethoxide (106 mg, 1.51 mmol) in dry *N,N*-dimethylformamide (3.5 mL) was heated at 100°C under nitrogen for 4 hours. Then a saturated solution

of ammonium chloride (15 mL) was added and the aqueous layer extracted with methylene chloride (4x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 7:3) to produce 4-[1,3]dioxolan-2-yl-2-fluoro-phenol as a pale brown oil (120 mg, 52%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 7.24-7.01 (m, 2H), 6.88 (t, 1H, *J*= 8.4), 6.07 (s, 1H), 5.71 (s, 1H), 4.13-3.95 (m, 4H).

Step C

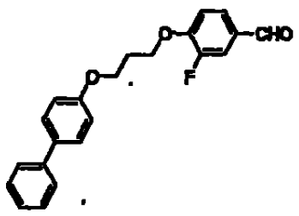
3-Fluoro-4-hydroxy-benzaldehyde



A solution of 1N HCl (1 mL) and 4-[1,3]dioxolan-2-yl-2-fluoro-phenol (250 mg, 1.35 mmol) in THF (2 mL) was stirred, at room temperature for 1 hour. The mixture was diluted with water and extracted with methylene chloride (4x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 1:1) to produce 3-Fluoro-4-hydroxy-benzaldehyde as a white solid (180 mg, 95%). ^{1}H-NMR (CDCl3, 200.15 MHz): 9.84 (d, 1H, *J*=2.4), 7.68-7.59 (m, 2H), 7.15 (t, 1H, *J*=8.5), 6.5 (s, 1H).

Step D

4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-benzaldehyde



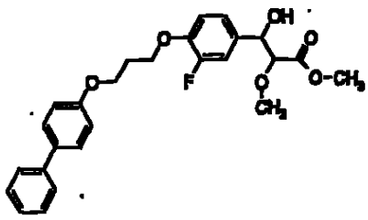
Potassium tert-butoxide (198 mg, 1.76 mmol) was added, at 0°C, to a solution of 3-Fluoro-4-hydroxy-benzaldehyde (235 mg, 1.68 mmol) in dry *N,N*-dimethylformamide (2 mL). The mixture was stirred for 10 minutes. 4-(3-Bromo-

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propoxy)-biphenyl (example 23, Step D) (539 mg, 1.84 mmol) was added and the reaction was stirred for 24 hours at room temperature. The mixture was diluted with water (15 mL) and extracted with ethyl acetate (4x15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum to produce a solid which was washed with hexanes to produce 4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-benzaldehyde as a pale brown solid (490 mg, 83%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 9.83 (d, 1H, *J*=2.2), 7.64-7.23 (m, 9H), 7.09 (t, 1H, *J*=8.2), 6.96 (d, 2H, *J*=8.8), 4.32 (t, 2H, *J*=5.9), 4.21 (t, 2H, *J*=5.9), 2.35 (qn, 2H, *J*=5.9).

Step E

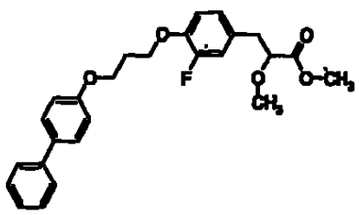
3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-3-hidroxy-2-methoxy-propionic acid methyl ester



To a solution of sodium bis(trimethylsilyl)amide 1N (0.71 mL, 0.71 mmol)in dry THF (5 mL), was added dropwise methyl methoxyacetate (57 µL, 0.57 mmol) at -78°C. The solution was stirred for 1 hour. 4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-benzaldehyde (220 mg, 0.626 mmol) was added and the mixture warmed to 0°C and stirred for 3 additional hours. The mixture was quenched with 1N HCl (2 mL), diluted with water (20 mL) and extracted with dichloromethane (4 X 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 7:3) to produce 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-3-hidroxy-2-methoxy-propionic acid methyl ester as a colourless oil (62 mg, 24%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 7.55-7.25 (m, 8H), 7.15-6.89 (m, 5H), 4.91-4,79 (m, 1H), 4.24-4.18 (m, 4H), 3.92 and 3.81 (2d, 1H, *J*=5.86 and 5.48), 3.67 and 3.64 (2s, 3H), 3.40 and 3.36 (2s, 3H), 3.01 and 2.94 (2d, 1H, *J*=5.12 and 5.12), 2.29 (qn, 2H, *J*=5.9).

Step F

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-2-methoxy-propionic acid methyl ester



Trifluoroacetic anhydride (0.056 mL, 0.395 mmol) and pyridine (0,048 mL, 18.9 mmol) were added to a solution of 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-3-hidroxy-2-methoxy-propionic acid methyl ester (90 mg, 0.197 mmol) in methylene chloride (2 mL) at 0°C. The mixture was stirred for 4 hours at room temperature and quenched with 1N HCl (10 mL). The layers were separated and the aqueous extracted with methylene chloride (3 x 20 mL). The combined organic layers were evaporated and the residue dissolved in ethyl acetate (50 mL). 10% palladium on carbon (90 mg) was added to the solution and mixture was stirred under hydrogen pressure (5 atm) for 16 hours, filtered through a pad of celite and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 4:1) to produce 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-2-methoxy-propionic acid methyl ester as a colorless oil (40 mg, 46%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 7.58-7.49 (m, 4H), 7.46-7.37 (m, 2H), 7.34-7.24 (m, 1H), 7.01-6.90 (m, 5H), 4.22 (t, 4H, *J*=5.9), 3.93 (dd, 1H, *J*=7.3, 5.3), 3.73 (s, 3H), 3.37 (s, 3H), 2.97-2.92 (m, 2H), 2.31 (qn, 2H, *J*=5.9).

Step G

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-2-methoxy-propionic acid

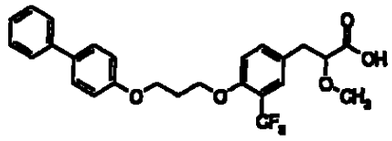
The title compound was prepared from 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-fluoro-phenyl}-2-methoxy-propionic acid methyl ester following the Standard Procedure E: white solid (38mg, 98%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 7.58-7.49 (m, 4H), 7.46-7.37 (m, 2H), 7.34-7.24 (m,1H), 7.01-6.90 (m, 5H), 4.23 (t, 2H,

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J=5.9), 4.22 (t, 2H, J=5.9), 3.97 (dd, 1H, J=7.4, 4.4), 3.4 (s, 3H), 3.12-2.89 (m, 2H), 2.31 (qn, 2H, J=5.9).

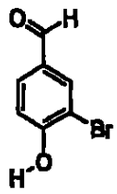
Example 139

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-trifluoromethyl-phenyl}-2-methoxy-propionic acid



Step A

3-Bromo-4-hydroxy-benzaldehyde

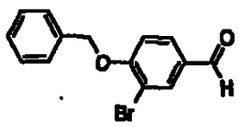


A solution of bromine (0.88 mL, 17.18 mmol) in chloroform (20 mL) was added dropwise at room temperature to a solution of 4-hydroxybenzaldehyde (2 g, 16.36 mmol) in chloroform (40 mL) and the mixture was stirred for 0.5 hour at room temperature and 1 more hour at 40°C. A saturated solution of $NaHCO_3$ (30 mL) was added and the organic layer separated. The aqueous layer was extracted with methylene chloride (3 x 20 mL). Thee combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was chromatographed (silica gel, methylene chloride-methanol 98:2) to affored 3-Bromo-4-hydroxy-benzaldehyde as a white solid (1.1 g, 34%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 9.80 (s, 1H), 8.02 (d, 1H, J=1.8), 7.75 (dd, 1H, J=8.4, 1.8), 7.12 (d, 1H, J=8.4), 6.19 (s, 1H).

Step B

4-Benzyloxy-3-bromo-benzaldehyde

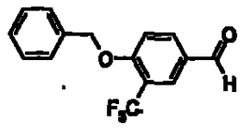
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3-Bromo-4-hydroxy-benzaldehyde (1.9 g, 9.45 mmol) was added slowly, at 0°C, to a suspension of NaH 95% (290 mg, 11.34 mmol) in dry *N,N*-dimethylformamide (45 mL). The mixture was stirred for 0.5 hours. Benzyl chloride (1.3 mL, 11.34 mmol) was added and the reaction stirred at room temperature overnight. 1N HCl (40 mL) was added and the layers separated. The aqueous layer was extracted with diethyl ether (5x50 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 9:1) to produce 4-Benzyloxy-3-bromo-benzaldehyde as a white solid (2.47 g, 90%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 9.82 (s, 1H), 8.09 (d, 1H, *J*=1.8), 7.76 (dd, 1H, *J*=8.4, 1.8), 7.47-7.32 (m, 5H), 7.02 (d, 1H, *J*=8.4), 5.24 (s, 2H).

Step C

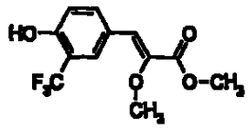
4-Benzyloxy-3-trifluoromethyl-benzaldehyde



Methyl 2,2-difluoro-2-(fluorosulfonyl)-acetate (1.25 mL, 9.78 mmol) was added to a suspension of dry CuI (745 mg, 3.91 mmol) and 4-Benzyloxy-3-bromo-benzaldehyde (570 mg, 1.96 mmol) in dry *N,N*-dimethylformamide (10 mL). The mixture was stirred under nitrogen at 120°C for 6 hours in a sealed tube. The reaction mixture was cooled to room temperature and diluted with water (20 mL). The aqueous layer was extracted with diethyl ether (4x20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 9:1) to produce 4-Benzyloxy-3-trifluoromethyl-benzaldehyde as a white solid (120 mg, 22%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 9.88 (s, 1H), 8.11 (d, 1H, *J*=1.8), 7.98 (dd, 1H, *J*=8.6, 1.8), 7.44-7.31 (m, 5H), 7.14 (d, 1H, *J*=8.6), 5.27 (s, 2H).

Step D

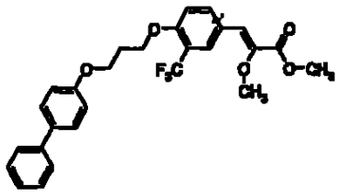
3-(4-hydroxy-3-trifluoromethyl-phenyl)-2-methoxy-acrylic acid methyl ester



To a solution of sodium bis(trimethylsilyl)amide 1N (0.8 mL, 0.8 mmol)in THF (4 mL), was added dropwise methyl methoxyacetate (0.066 mL, 0.66 mmol) at -78°C. After allowing the mixture to stir for 1 hour, 4-Benzyloxy-3-trifluoromethyl-benzaldehyde (185 mL, 0.66 mmol) was added dropwise. When the addition was finished the mixture was warmed to room temperature and stirred for 3 additional hours. Trifluoroacetic anhydride (0.28 mL, 1.98 mmol) was added and the mixture was stirred at room temperature for 4 hours. The solvent was evaporated and the residue dissolved in ethyl acetate (50 mL). 10% palladium on carbon (200 mg) was added to the solution and the mixture stirred under hydrogen pressure (5 atm) for 16 hours, filtered through a pad of celite and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 4:1) to produce 3-(4-hydroxy-3-trifluoromethyl-phenyl)-2-methoxy-acrylic acid methyl ester as a white solid (72 mg, 40%). ^{1}H-NMR ($(CD_3)_2CO$, 200.15 MHz): δ 9.65 (b, 1H), 8.02 (d, 1H, J=1.8), 7.87 (dd, 1H, J=8.4, 1.8), 7.08 (d, 1H, J=8.4), 6.90 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H).

Step E

3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-trifluoromethyl-phenyl}-2-methoxy-acrylic acid methyl ester

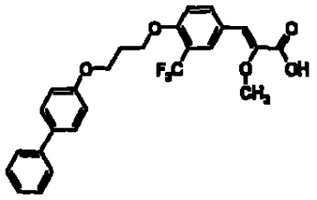


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Potassium tert-butoxide (15 mg, 0.13 mmol) was added at 0°C to a solution of 3-(4-hydroxy-3-trifluoromethyl-phenyl)-2-methoxy-acrylic acid methyl ester (35 mg, 0.126 mmol) in dry *N,N*-dimethylformamide (0.6 mL). The mixture was stirred for 0.5 hours and 4-(3-Bromo-propoxy)-biphenyl (example 23, Step D) (45 mg, 0.15 mmol) was added. The reaction was stirred for 6 hours at room temperature and quenched with a saturated solution of ammonium chloride (10 mL). The aqueous layer was separated and extracted with methylene chloride (5x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was chromatographed (silica gel, hexanes/ethyl acetate 8:2) to produce 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-trifluoromethyl-phenyl}-2-methoxy-acrylic acid methyl ester as a colorless oil (35 mg, 57%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 8.00 (d, 1H, *J*=1.6), 7.89 (dd, 1H, *J*=8.6, 1.6), 7.46-7.26 (m, 7H), 7.05-6.93 (m, 4H), 4.33-4.20 (m, 4H), 3.86 (s, 3H), 3.79 (s, 3H), 2.33 (qn, 2H, *J*=5.9).

Step F

3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-trifluoromethyl-phenyl}-2-methoxy-acrylic acid



The title compound was prepared 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-trifluoromethyl-phenyl}-2-methoxy-acrylic acid methyl ester (35 mg, 0.072 mmol) following the Standard Procedure E: white solid (31mg, 92%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 8.02 (d, 1H, *J*=1.8), 7.88 (dd, 1H, *J*=8.6, 1.8), 7.57-7.28 (m, 7H), 7.08-6.96 (m, 4H), 4.35-4.21 (m, 4H), 3.81 (s, 3H), 2.34 (qn, 2H, *J*=5.8).

Step G

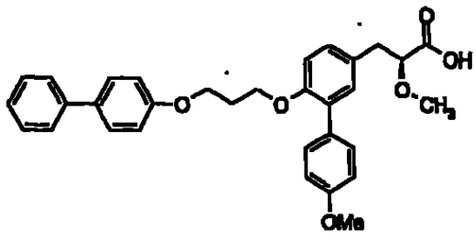
3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-trifluoromethoxy-phenyl}-2-methoxy-propionic acid

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The title compound was prepared as follows: A mixture of 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-trifluoromethyl-phenyl}-2-methoxy-acrylic (20 mg, 0.041 mmol) and magnesium (20 mg, 0.82 mmol) in methanol (1 mL) was stirred at room temperature for 80 hours. The reaction mixture was quenched with 1N HCl (10 mL). The aqueous layer was extracted with methylene chloride (5x10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-3-trifluoromethoxy-phenyl}-2-methoxy-propionic acid as a white solid (7 mg, 35%). ^{1}H-NMR (CDCl3, 200.15 MHz): δ 7.57-7.32 (m, 9H), 7.00-6.95 (m, 3H), 4.27-4.19 (m, 4H), 3.97 (dd, 1H, *J*=7.3, 4.3), 3.41 (s, 3H), 3.16-2.93 (m, 2H), 2.31 (qn, 2H, *J*=5.8).

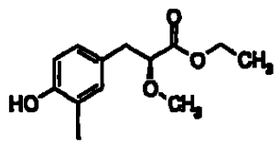
Example 140

(2S)-3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-4'-methoxy-biphenyl-3-yl}-2-methoxy-propionic acid



Step A

(4-Hydroxy-3-iodide-)-2-methoxy dihidrocinnamic acid



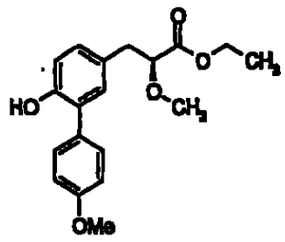
(4-Hydroxy)-2-methoxy dihydrocinnamic acid (1 g, 4.4 mmol) was dissolved in 30 mL of CH_3CN and cooled to –20°C. NIS was added (0.99 g, 4.43 mmol) and the mixture was stirred for 8 hours. The solvent was evaporated under vacuum and the crude oil was washed with CCl_4 with formation of a white solid. The solid was removed by filtration, and the filtrate was concentrated and purified by column chromatography (silica gel, dichloromethane/MeOH 0.5%) Yellow oil (924 mg,

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60%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.49 (d, 1H, *J*=2), 7.04 (dd, 1H, *J*=2, 8.2), 6.80 (d, 1H, *J*=8.2), 6.03 (bs, 1H), 4.17 (q, 2H, *J*=7.2), 3.88 (dd,1H, *J*=5.6, 7), 3.33 (s, 3H), 2.88 (dd, 2H, *J*=2.4, 5.0), 1.21 (t, 3H, *J*=7.2)

Step B

(2S)-3-(6-Hydroxy-4'-methoxy-biphenyl-3-yl)-2-methoxy-propionic acid

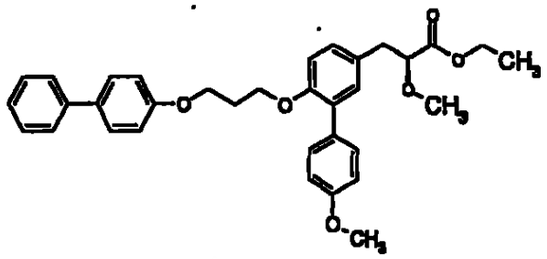


A solution of (2S)(4-Hydroxy-3-iodide-)-2-methoxy dihidrocinnamic acid (197 mg, 0.56 mmol), 4-methoxyphenyl boronic acid (170.7 mg, 1.12 mmol) and tetrakis(triphenylphosphine)-palladium (0) (8.7 mg, 0.5 mmol) in 11 mL of a mixture 20:1 toluene/ethanol together with 2 mL of a 2N Na_2CO_3 was heated to 120° for 16 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and dilute with ethyl acetate (20 mL). It was washed with H_2O (3 x 5mL) and brine (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resultant crude was purified by column chromatography (silica gel, hexanes/ethyl acetate 8:2). Colorless oil (123 mg, 67%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.39 (dd, 2H, *J*=2.1, 6.4), 7.08-7.03 (m, 2H), 6.97 (dd, 2H, *J*=2.1, 6.7), 6.85 (dd, 1H, *J*=1.3, 7.5), 5.60 (s, 1H), 4.17 (q, 2H, *J*=7.0), 3.95 (dd, 1H, *J*=5.9, 6.4), 3.82 (s, 3H), 3.35 (s, 3H), 2.97 (d, 2H, *J*=6.4), 1.22 (t, 3H, *J*=7.2)

Step C

(2S)-3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-4'-methoxy-biphenyl-3-yl}-2-methoxy-propionic acid ethyl ester

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3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-4'-methoxy-biphenyl-3-yl}-2-methoxy-propionic acid ethyl ester was prepared following the Standard Procedure B (THF). The residue was purified by chromatography (silica gel, hexanes/ethyl acetate 8:2). White solid (13 mg, 17%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57 (m, 10H), 7.14 (dd, 2H, *J*=2.1, 7.8), 6.94-6.87 (m, 4H), 4.24-4.04 (m, 6H), 3.94 (dd,1H, *J*=5.9, 6.9), 3.81 (s, 3H), 3.36 (s, 3H), 2.99 (d, 2H, *J*=6.9), 2.18 (qn, 2H, *J*=5.9), 1.22 (t, 3H, *J*=7.2).

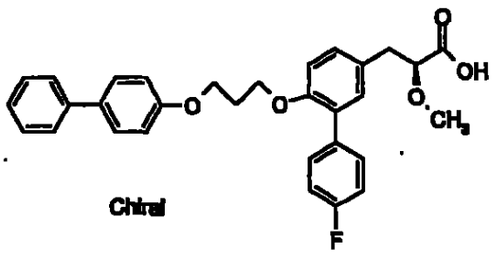
Step D

(2S)-3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-4'-methoxy-biphenyl-3-yl}-2-methoxy-propionic acid

The title compound was prepared following the procedure described in example 25 (Step C). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-6.87 (m, 16 H), 4.15 (t, 2H, *J*=6.1), 4.07 (t, 2H, *J*=6.1), 4.01 (dd, 1H, *J*=7.2, 4.5), 3.80 (s, 3H), 3.41 (s, 3H), 3.13 (dd, 1H, *J*=4.5, 14.4), 2.99 (dd, 1H, *J*=7.1, 14.4), 2.21 (qn, 2H, *J*=5.9).

Example 141

3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-4'-fluoro-biphenyl-3-yl}-2-methoxy-propionic acid

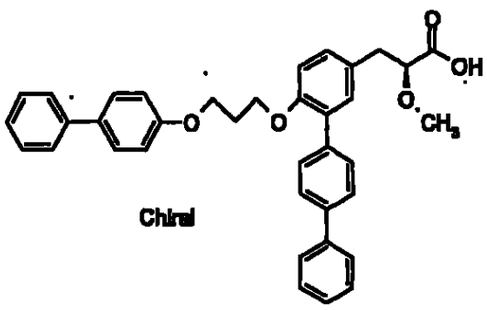


Chiral

The title compound was prepared as in Example 140, with 4-fluorophenyl boronic acid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.57-6.87 (m, 16 H), 4.15 (t, 2H, *J*=5.9), 4.04 (t, 2H, *J*=5.9), 4.02 (dd, 1H, *J*=7.2, 4.5), 3.41 (s, 3H), 3.13 (dd, 1H, *J*=4.5, 14.2), 3.00 (dd, 1H, *J*=7.5, 14.2), 2.17 (qn, 2H, *J*=5.9).

Example 142

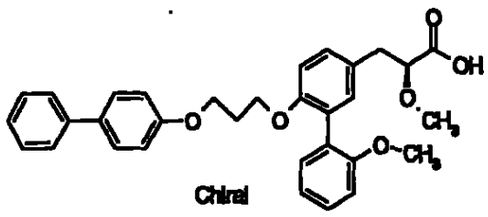
3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-[1,1';4',1"] terphenyl-3-yl}-2-methoxy-propionic acid



The title compound was prepared as in Example 140, with 4-phenylphenyl boronic acid.

Example 143

3-{6-[3-(Biphenyl-4-yloxy)-propoxy]-2'-methoxy-biphenyl-3-yl}-2-methoxy-propionic acid

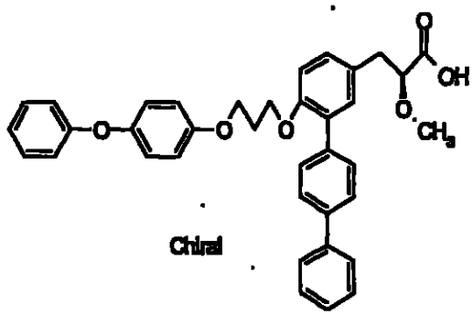


The title compound was prepared as in Example 140, with 2-methoxyphenyl boronic acid.

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Example 144

2-Methoxy-3-{6-[3-(4-phenoxy-phenoxy)-propoxy]-[1,1';4',1"]terphenyl-3-yl}-propionic acid



The title compound was prepared as in Example 140, with 4-diphenyl boronic acid.

Example 145

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-styryl-phenyl}-2-methoxy-propionic acid

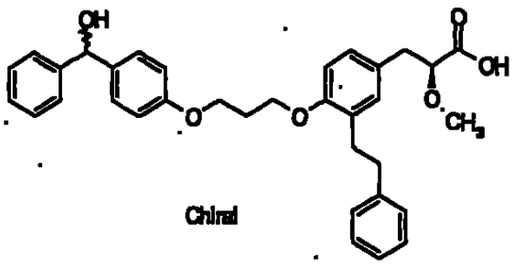


The title compound was prepared as in Example 140, with trans-2-phenylvinyl boronic acid

Example 146

3-(4-{3-[4-(Hydroxy-phenyl-methyl)-phenoxy]-propoxy}-3-phenethyl-phenyl)-2-methoxy-propionic acid

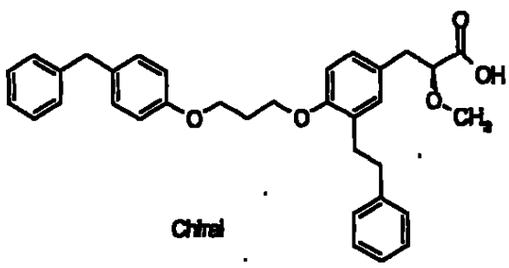
253



A solution of 3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-styryl-phenyl}-2-methoxy-propionic acid ethyl ester from Example 145, was dissolved in ethanol and treated with H_2 under balloon pressure. Filtered through a pad of celite and concentrated to dryness. The compound thus obtained was treated under standard hydrolysis procedure C to give the title compound.

Example 147

3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-3-phenethyl-phenyl}-2-methoxy-propionic acid

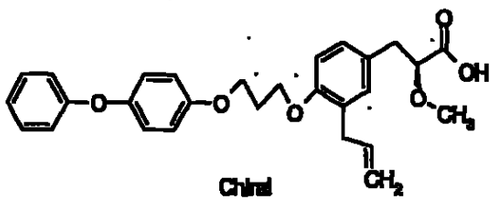


The title compound was obtained as a secondary product of the reduction of 3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-styryl-phenyl}-2-methoxy-propionic acid ethyl ester (from Example 145) as in Example 146, and was hydrolyzed under the standard hydrolysis procedure C to afford the product.

Example 148

(2S)-3-{3-Allyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

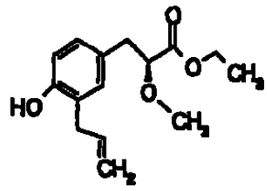
254



Chiral

Step A

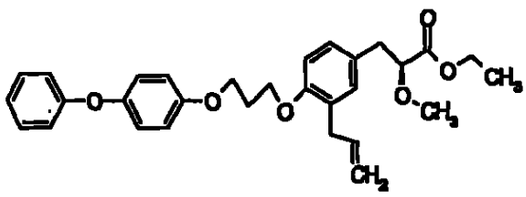
(2S)-3-(3-Allyl-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester



To a solution of 3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (1 eq) in acetone, K_2CO_3 (2 eq) and allyl bromide (1.2 eq) were added and the mixture reaction was stirred at 55°C over night. Quenched with water and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give 3-(4-allyloxy-phenyl)-2-methoxy-propionic acid ethyl ester. This crude product was dissolved in Me_2NPh and heated to reflux for 6 hours and then stirred at room temperature over 3 days. Refluxed again for 8 hours and then poured into and ice-cold HCl 1M solution, extracted with ethyl acetate and washed with water. Dried and concentrated to give a crude product which was purified by chromatography to give the title product.

Step B

(2S)-3-{3-Allyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



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(2S)-3-(3-Allyl-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester from Step A was allowed to react with 4-(3-bromopropoxy)-1-phenoxybenzene under the Standard Procedure I to give the title compound.

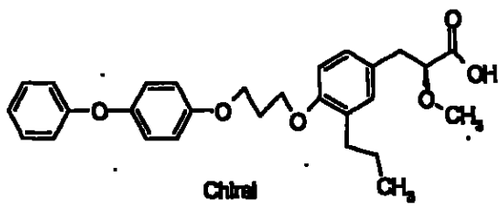
Step C

(2S)-3-{3-Allyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2S)-3-{3-Allyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester from Step B was hydrolyzed under the standard hydrolysis procedure C to afford the product.

Example 149

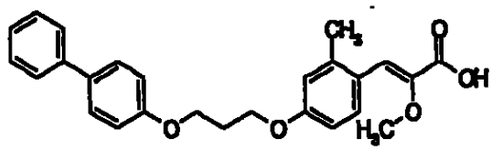
(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-3-propyl-phenyl}-propionic acid



A solution of (2S)-3-{3-Allyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester, from Example 148, Step B, was dissolved in ethanol and treated with H_2 under balloon pressure. Filtered through a pad of celite and concentrated to dryness. The compound thus obtained was treated under standard hydrolysis procedure C to give the title compound.

Example 150

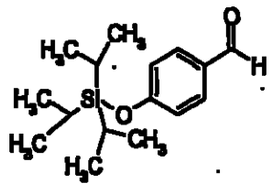
3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-acrylic acid



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Step A

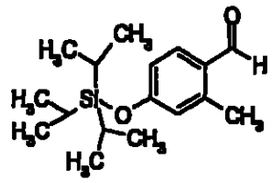
4-Triisopropylsilanyloxy-benzaldehyde



4-hydroxybenzaldehyde (3 g, 24.57 mmol), triisopropylsilyl chloride (5.52 mL, 25.79 mmol) and imidazol (2g, 29.48 mmol) were dissolved in 60 mL of DMF and the solution stirred at room temperature overnight. Water (120 mL) was added to the solution and the mixture extracted with diethyl ether (3 x 50 mL). The combined extracts were washed with water (5 x 30 mL), saturated ammonium chloride (2 x 30 mL) and brine (20 mL) and dried ($MgSO_4$). Concentration produced an oil that was purified by chromatography (silica gel, hexanes/Ethyl acetate 20:1, R_f 0.4) (75 %). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 9.85 (s, 1H), 7.75 (d, 2H, J=8.8), 6.95 (d, 2H, J=8.4), 1.31-1.20 (m, 3H), 1.10 (s, 18H).

Step B

2-Methyl-4-triisopropylsilanyloxy-benzaldehyde

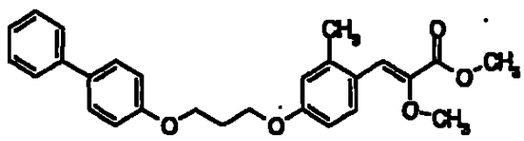


To a solution of trimethylethylenediamine (0.45 mL, 3.48 mmol) in THF (9 mL) at –20°C was added Butyllithium 1.6M in hexanes (2.11 mL, 3.38 mmol). The solution was stirred at –20°C for 15 min. A solution of 4-Triisopropylsilanyloxy-benzaldehyde (0.922 g, 3.31 mmol) was added dropwise and the solution stirred for 15 min at –20°C. Butyllithium 1.6M in hexanes (6.21 ml, 9.93 mmol) was added dropwise and the solution kept in the freezer at –20°C for 26 hours. The solution was cooled to –40°C and methyl iodide (3.71 mL, 59.60 mmol) was added. The solution was allowed to reach room temperature and further stirred 30 min. The

reaction was quenched with saturaded ammoninm chloride (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried ($MgSO_4$), concentrated under vacuum and purified by column chromatography (silica gel, hexanes/Ethyl acetate 20:1, R_f 0.085) (49%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 10.1 (s, 1H), 7.69 (d, 1H, *J*=8.3), 6.80 (dd, 1H, *J*=8.6, 2.4), 6.72 (s, 1H), .61 (s, 3H), 1.33-1.19 (m, 3H), 1.12 (s,18H).

Step C

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-acrylic acid methyl ester



Methyl 2-methoxyacetate (0.450 mL, 4.53 mmol) was added to a solution of NaHDMS (4.74 mmol) in 40 mL of THF cooled to –78°C. The mixture was stirred at –78°C for 30 min and then a solution of 2-Methyl-4-triisopropylsilanyloxy-benzaldehyde (1.26 g, 4.3 mmol) in 20 mL of THF was added dropwise. The solution was allowed to warm to 0°C and stirred for 2.5 hours. The mixture was quenched with HCl 1N (50 mL) at 0°C, extracted with dichloromethane (3 x 40 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was dissolved in dichlorometane (50 mL) and cooled to 0°C. To the solution was added trifluoroacetic anhidride (0.82 mL, 5.84 mmol), N,N-dimethylaminopyridine (0.025 g, 0.21 mmol), and pyridine (0.379 mL, 4.59 mmol). And stirred at room temperature for 4 hours. The volatiles were eliminated under vacuum and the residue dissolved in 100 mL of ethyl acetate. Palladium 10% on activated carbon (0.9 g) was added and the mixture hydrogenated at room temperature (5 Atm H_2) for 14 hours. The solution was filtered through a pad of celite and concentrated under vacuum. The residue was purified by column chromatography (silica gel, hexanes/Ethyl acetate 3:1) the fractions with R_f 0.08 were collected and concentrated under vacuum (0.249 g containing 3-(4-Hydroxy-2-methyl-phenyl)-2-methoxy-acrylic acid c.a. 85% pure by NMR). The residue was added to a solution

of 4-(3-Bromo-propoxy)-biphenyl (example 23, Step D) (0.359 g, 1.23 mmol), sodium iodide (0.05 g) and potassium tert-butoxide (126 mg, 1.12 mmol) in 5 mL of dimethylformamide. The solution was stirred at room temperature 24 hours, diluted with water and extracted with diethylether (3 x 30 mL). The combined organic layers were washed with water (5 x 30 ml), dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate 6:1, R_f 0.22). (0.18 mg, 10%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.98 (d, 1H, J=8.6), 7.57-7.25 (m, 7H), 7.16 (s, 1H); 6.98 (dd, J=6.7, 2.1), 6.80-6.76 (m, 2H), 4.20 (t, 4H, J=5.9), 3.85 (s, 3H), 3.69 (s, 3H), 2.36 (s, 3H), 2.29 (t, 2H, J=6.2).

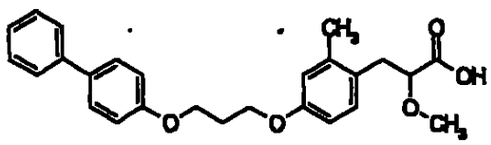
Step D

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-acrylic acid

The title compound was prepared from 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-acrylic acid methyl ester following the general procedure B. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.97 (d, 1H, J=8.4), 7.55-7.47 (m, 4H), 7.43-7.27 (m, 4H), 6.96 (dd, 2H, J=6.6, 2.2), 6.79-6.75 (m, 2H), 4.19 (t, 4H, J=6.2), 3.69 (s, 3H), 2.35 (s, 3H), 2.27 (t, 2H, J=6.2).

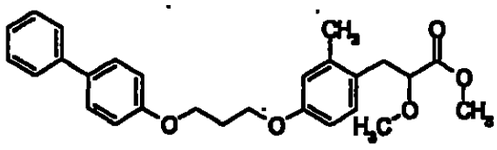
Example 151

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-propionic acid



Step A

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-propionic acid methyl ester



Magnesium turnings (0.101 g, 4.17 mmol) was added to a solution of 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-acrylic acid methyl ester (Example 37, Step C) (0.09 g, 0.21 mmol) in methanol (2 mL) and diethyl ether (2 mL). The mixture was stirred at room temperature overnight and then quenched with HCl 3N until pH 7. A saturated solution of ammonium chloride (10 mL) was added and the mixture extracted with ethyl ether (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (Silica Gel, hexanes/Ethyl acetate 4.5:1, R_f 0.31) (48%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.57-7.29 (m, 7H), 7.07 (d, 1H, J=8.1); 6.98 (dd, 2H, J=6.7, 2.1), 6.73 (s, 1H); 6.71 (d, 1H, J=11.8); 4.18 (dt, 4H, J=9.7, 6.2), 3.91 (dd, 1H, J=7.3, 6.2), 3.72 (s, 3H), 3.32 (s, 3H), 2.97 (d, 2H, J=6.4), 2.31 (s, 3H); 2.27 (t, 2H, J=6.2).

Step B

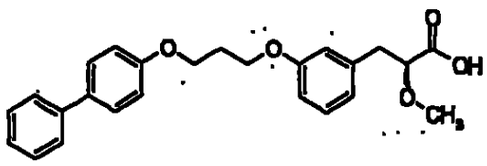
3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared from 3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methyl-phenyl}-2-methoxy-propionic acid methyl ester following the general procedure B. (71%). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.55-7.27 (m, 7H); 7.09 (d, 1H, *J*=8.1); 6.96 (d, 2H, *J*=9.2); 6.71-6.67 (m, 2H); 4.15 (dt, 4H, *J*=9.1, 6.2); 3.92 (dd, 1H, *J*=8.4, 4.4); 3.31 (s, 3H); 3.08 (dd, 1H, *J*=14.6, 4.4); 2.93 (dd, 1H, *J*=14.3, 8.4); 2.30 (s, 3H); 2.25 (qn, 2H, *J*=6.2).

Example 152

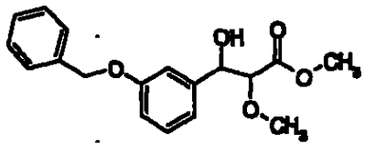
3-{3-[3-(Biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

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Step A

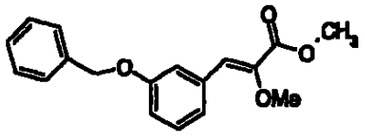
3-(3-Benzyloxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester



To a solution of NaHMDS (1.1 eq) in dry THF at -78°C a mixture of 3-benzyloxy-benzaldehyde (1 eq) and methoxy-acetic acid methyl ester (1.25 eq) in THF were added dropwise and the mixture reaction at this temperature over 1.5 hours. Then the reaction was quenched with HCl 3N and allowed to rise room temperature. Washed with brine and extracted with ether. The organic layer was dried and concentrated to dryness to give after chromatography in silicagel the title product.

Step B

3-(3-Benzyloxy-phenyl)-2-methoxy-acrylic acid methyl ester

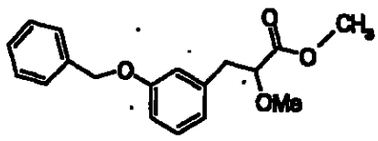


A mixture of 3-(3-Benzyloxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester (1 eq), mesylchloride (1 eq) triethylamine (4 eq) and a catalytic amount of DMAP (0.1 eq) in dichloromethane was stirred at room temperature overnight. The reaction mixture was diluted with ether and washed with HCl 1N. Dried and concentrated in vacuo to give a residue which was chromatographed in silicagel to yield the title compound.

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Step C

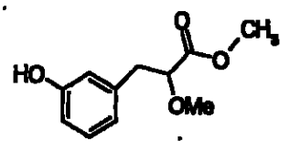
3-(3-Benzyloxy-phenyl)-2-methoxy-propionic acid methyl ester



Compound from Step B was dissolved in methanol and treated with magnesium. The flask was placed in an ice bath for 5 min and then the reaction mixture was stirred at room temperature for 4 hours. Washed with HCl 3N and extracted with ether. Dry and concentrated to dryness to get the title compound.

Step D

3-(3-Hydroxy-phenyl)-2-methoxy-propionic acid methyl ester



A solution of 3-(3-Benzyloxy-phenyl)-2-methoxy-propionic acid methyl ester in methanol was treated with a catalytic amount of C-Pd (0.1 eq) and then H_2 was bubbled through the mixture and stirred overnight. The mixture reaction was concentrated and reconstituted in ethyl acetate, filtered through a pad of celite and concentrated in vacuo to give the title compound.

Step E

3-{3-[3-(Biphenyl-4-yloxy)-propoxyl-phenyl}-2-methoxy-propionic acid

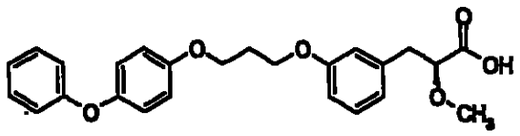
A mixture of 3-(3-Hydroxy-phenyl)-2-methoxy-propionic acid methyl ester (1 eq) from Step D, Cesium Carbonate (3 eq) and 4-(3-bromopropoxy)biphenyl (1 eq) in DMF and in a 10 mL tube was shaked in an orbital agitator over a weekend. The mixture was filtered through a hydrofobic syringer and evaporated in a speed-vac apparatus. Then diluted with NaOH 1N-Ethanol and stirred overnight. Then HCl 3N was added and the reaction mixture was concentrated to remove the ethanol in vacuo, reconstituted in dichloromethane and filtered through a hydrofobic syringe.

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The organic layer was evaporated to give the title compound. MS (ES) for $C_{25}H_{26}O_5$ $[M+NH_4]^+$: 424.2, $[M+Na]^+$: 429.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.57-7.17 (m, 9H), 6.98 (dd, 2H, J=6.7, 1.9), 6.84-6.81 (m, 3H), 4.19 (dd, 4H, J=14.0, 6.4), 4.03 (dd, 1H, J=7.3, 4.3), 3.40 (s, 3H), 3.13 (dd, 1H, J=14.2, 4.6), 2.98 (dd, 1H, J=14.0, 7.5), 2.28 (qui, 2H, J=5.9)ppm.

Example 153

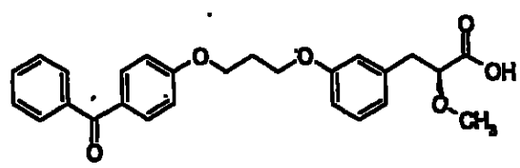
2-Methoxy-3-{3-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from 3-(3-Hydroxy-phenyl)-2-methoxy-propionic acid methyl ester from Example 152, Step D with 4-(3-bromopropoxy)1-phenoxybenzene in a manner analogous as in Example 152, Step E. MS (ES) for $C_{25}H_{26}O_6$ $[M+NH_4]^+$: 440.2, $[M+Na]^+$: 445.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.33-7.17 (m, 3H), 7.07-6.78 (m, 10H), 4.15 (dt, 4H, J=1.9, 6.2), 4.03 (dd, 1H, J=7.3, 4.3), 3.40 (s, 3H), 3.13 (dd, 1H, J=14.2, 4.6), 2.98 (dd, 1H, J=14.0, 7.5), 2.25 (qui, 2H, J=5.9)ppm.

Example 154

3-{3-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

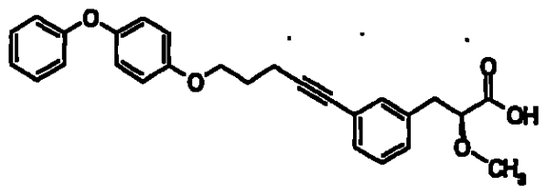


The title compound was prepared from 3-(3-Hydroxy-phenyl)-2-methoxy-propionic acid methyl ester from Example 152, Step D with [4-(3-Bromo-propoxy)-phenyl]-phenyl-methanone in a manner analogous as in Example 152, Step E. MS (ES) for $C_{26}H_{26}O_6$ $[M+H]^+$: 435.2, $[M+Na]^+$:457.2. 1H-NMR (CDCl3, 200.15 MHz): 7.83-7.72 (m, 4H), 7.56-7.42 (m, 3H), 7.21 (dd, 2H, J=9.1, 7.0), 6.97 (d, 2H, J=8.9), 6.82 (d, 1H, J=14.2), 6.82 (s, 2H), 4.25 (t, 2H, J=6.2), 4.16 (t, 2H, J=5.9), 4.02 (dd, 1H,

J=7.5, 4.3), 3.40 (s, 3H), 3.12 (dd, 1H, J=14.0, 4.3), 2.98 (dd, 1H, J=14.2, 7.5), 2.29 (qui, 2H, J=5.9).

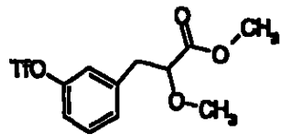
Example 155

2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid



Step A

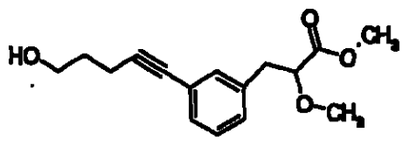
2-Methoxy-3-(3-trifluoromethanesulfonyloxy-phenyl)-propionic acid methyl ester



The title compound was prepared using the same procedure as in Example 1, Step A starting from 3-(3-Hydroxy-phenyl)-2-methoxy-propionic acid methyl ester.

Step B

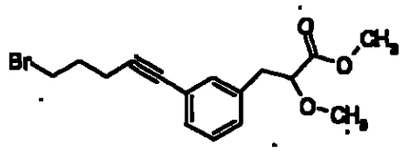
3-[3-(5-Hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid methyl ester



The title compound was prepared from 4-butyn-1-ol following the procedure described in Example 1, Step B.

Step C

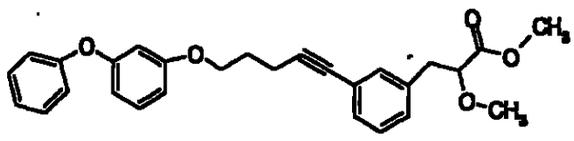
3-[3-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid methyl ester



To a solution of 3-[3-(5-Hydroxy-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid methyl ester, and CBr4 dissolved in dichloromethane at 0°C, triphenylphosphine was added and the mixture reaction was stirred at room temperature over 5 hours. The reaction then was diluted with water and extracted with ether. Chromatographied to give the title compound.

Step D

2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid methyl ester



A mixture of 3-[3-(5-Bromo-pent-1-ynyl)-phenyl]-2-methoxy-propionic acid methyl ester (1 eq), 4-phenoxyphenol (1 eq) and Cesium carbonate (3 eq), in DMF was stirred overnight. Then diluted in water and extracted with ether to give after dry in vacuo the title compound.

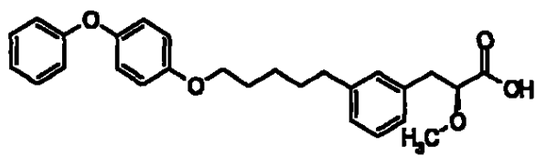
Step E

2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid

The title compound was prepared following the Standard Hydrolysis Procedure C and starting from 2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid methyl ester from Step D. MS (ES) for $C_{27}H_{26}O_5$ $[M+NH^4]^+$: 448.2, $[M+Na]^+$:453.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.33-7.17 (m, 7H), 7.07-6.88 (m, 7H), 4.11 (t, 2H, J=6.2), 4.00 (dd, 1H, J=7.5, 4.0), 3.39 (s, 3H), 3.11 (dd, 1H, J=14.0, 4.3), 2.96 (dd, 1H, J=14.5, 7.8), 2.63 (t, 2H, J=7.0), 2.08 (qui, 2H, J=6.7).

Example 156

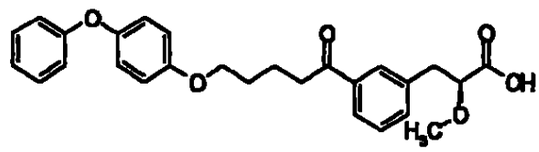
2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pentyl]-phenyl}-propionic acid



The title compound was prepared from 2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid of Example 155, Step E, and treated with Pd-C (0.1 eq) in ethyl acetate and H_2. Filtered through celite and concentrated to give the compound. MS (ES) for $C_{27}H_{30}O_5$ $[M+H]^+$: 435.2, $[M+NH_4]^+$:452.2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.34-7.19 (m, 3H), 7.09-6.84 (m, 10H), 4.02 (dd, 1H, J=7.5, 4.6), 3.94 (t, 2H, J=6.5), 3.39 (s, 3H), 3.13 (dd, 1H, J=14.0, 4.3), 3.00 (dd, 1H, J=14.0, 7.5), 2.63 (t, 2H, J=7.8), 1.88-1.45 (m, 6H)ppm.

Example 157

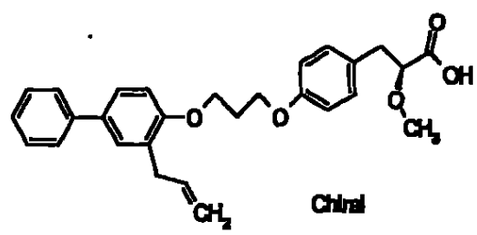
2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pentanoyl]-phenyl}-propionic acid



The title compound was prepared from 2-Methoxy-3-{3-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid methyl ester,(Example 155, Step D) and following the same procedure as in Example 57, and a standard hydrolysis procedure C to get the compound.

Example 158

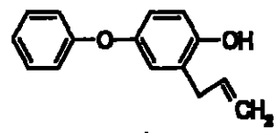
3-{4-[3-(3-Allyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Chiral

Step A

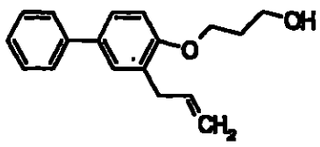
2-Allyl-4-phenoxy-phenol



To a solution of 4-phenylphenol (1 eq) in acetone, K_2CO_3 (2 eq) and allyl bromide (1.2 eq) were added and the mixture reaction was stirred at 55°C overnight. Quenched with water and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give 4-allyloxybiphenyl. This crude product was dissolved in Me_2NPh and heated to reflux for 6 hours and then stirred at room temperature over 3 days. Refluxed again for 8 hours and then poured into and ice-cold HCl 1M solution, extracted with ethyl acetate and washed with water. Dried and concentrated to give a crude product which was purified by chromatography to give the title product.

Step B

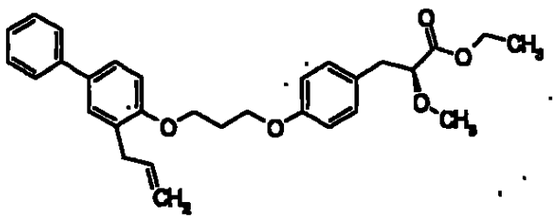
3-(3-Allyl-biphenyl-4-yloxy)-propan-1-ol



The product obtained in Step A (1.1 eq) was dissolved in THF and treated with t-BuOK (1.15 eq) and allowed to react for 2 hours. Then a solution of [1,3,2]Dioxathiolane 2,2-dioxide (1.0 eq) was added and the mixture reaction was stirred overnight, quenched with HCl 6N and refluxed the reaction overnight. Extracted with ethyl acetate, washed with brine and concentrated to give the title compound.

Step C

3-{4-[3-(3-Allyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



A solution of compound from Step B in dichloromethane was treated with CBr_4 (1.12 eq) and PPh_3 (1.4 eq) and allow to react for 1.5 hours. The product isolated after chromatography of this reaction was treated under Standard Procedure I with (2S)-3-(4-hydroxy-phenyl)-2-methoxypropionic acid ethyl ester to give the title compound.

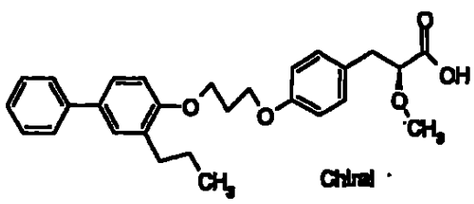
Step D

3-{4-[3-(3-Allyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared by using the standard Hydrolysis Procedure (NaOH) C.

Example 159

(2S)-2-Methoxy-3-{4-[3-(3-propyl-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid

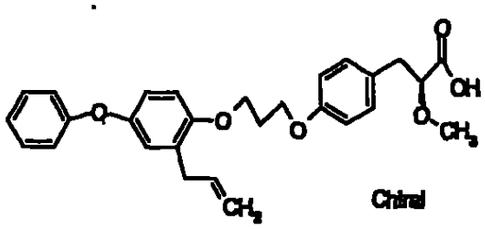


3-{4-[3-(3-Allyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid from Example 158, Step D dissolved in ethyl acetate was treated with Pd(C) 10% under balloon pressure for 6 hours. Filtered through celite and concentrated to dryness to give the title compound.

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Example 160

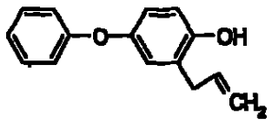
(2S)-3-{4-[3-(2-Allyl-4-phenoxy-phenoxy)-propoxy]- phenyl}-2-methoxy-propionic acid



Chiral

Step A

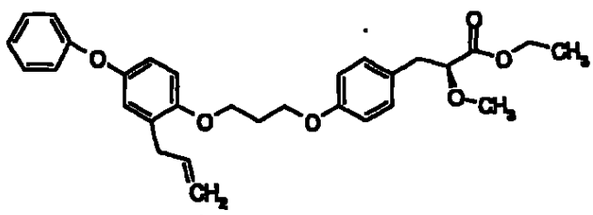
2-Allyl-4-phenoxy-phenol



The title compound was prepared in a same manner as in Example 158, Step A, starting from 4-phenoxyphenol.

Step B

2-{4-[3-(2-Allyl-4-phenoxy-phenoxy)-propoxy]-phenyl}-3-methoxy-propionic acid ethyl ester



3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester and 2-Allyl-4-phenoxy-phenol from Step A were allowed to react under Standard Procedure I to give the title compound.

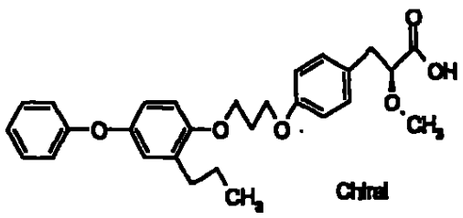
Step C

(2S)-3-{4-[3-(2-Allyl-4-phenoxy-phenoxy)-propoxy]- phenyl}-2-methoxy-propionic acid

The title compound was prepared by using the standard Hydrolysis Procedure C (NaOH) to yield the compound.

Example 161

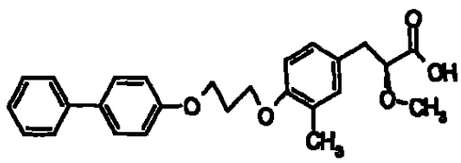
(2S)-2-Methoxy-3-{4-[3-(4-phenoxy-2-propyl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from 2-{4-[3-(2-Allyl-4-phenoxy-phenoxy)-propoxy]-phenyl}-3-methoxy-propionic acid ethyl ester from Example 160, Step B which was treated in ethyl acetate with Pd(C) and H_2 in balloon presure to give after filtration the corresponding reduced product which was hydrolyzed under Standard Procedure C to give the title compound.

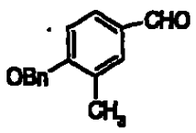
Example 162

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid



Step A

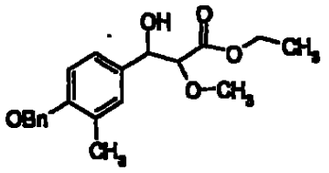
4-Benzyloxy-3-methyl-benzaldehyde



A mixture of benzyl bromide and 4-hydroxy-3-methylbenzaldehyde were treated under Standard Procedure I to give the title product.

Step B

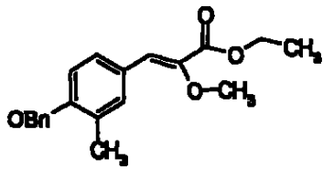
3-(4-Benzyloxy-3-methyl-phenyl)-3-hydroxy-2-methoxy-propionic acid ethyl ester



To a solution of NaHMDS (1.1 eq) in dry THF at -78°C a mixture of 4-Benzyloxy-3-methyl-benzaldehyde (1 eq) and Methoxy-acetic acid methyl ester (1.25 eq) in THF were added dropwise and the mixture reaction at this temperature over 1.5 hours. Then the reaction was quenched with HCl 3N and allowed to rise room temperature. Washed with brine and extracted with ether. The organic layer was dried and concentrated to dryness to give after chromatography in silicagel the title product.

Step C

3-(4-Benzyloxy-3-methyl-phenyl)-2-methoxy-acrylic acid ethyl ester

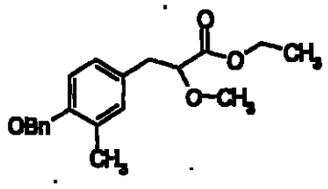


A mixture of 3-(4-Benzyloxy-3-methyl-phenyl)-3-hydroxy-2-methoxy-propionic acid ethyl ester (1 eq), Mesylchloride (1 eq) triethylamine (4 eq) and a catalytic amount of DMAP (0.1 eq) in dichloromethane was stirred at room temperature over night. The reaction mixture was diluted with ether and washed with HCl 1N. Dried

and concentrated in vacuo to give a residue which was chromatographed in silicagel to yield the title compound.

Step D

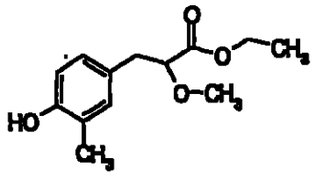
3-(4-Benzyloxy-3-methyl-phenyl)-2-methoxy-propionic acid ethyl ester



Compound from Step C was dissolved in methanol and treated with magnesium. The flask was placed in an ice bath for 5 min and then the reaction mixture was stirred at room temperature for 4 hours. Washed with HCl 3N and extracted with ether. Dry and concentrated to dryness to get the title compound.

Step E

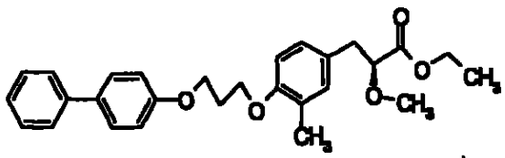
3-(4-Hydroxy-3-methyl-phenyl)-2-methoxy-propionic acid ethyl ester



A solution of 3-(4-Benzyloxy-3-methyl-phenyl)-2-methoxy-propionic acid ethyl ester in ethyl acetate was treated with a catalytic amount of C-Pd (0.1 eq) and then H_2 was bubbled through the mixture and stirred 2 hours. The mixture reaction was filtered through a pad of celite and concentrated in vacuo to give the title compound.

Step F

(2S)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid ethyl ester



A mixture of 3-(4-Hydroxy-3-methyl-phenyl)-2-methoxy-propionic acid ethyl ester and from Step E and 4-(3-bromopropoxy)biphenyl were treated under standard condition I to give the title product.

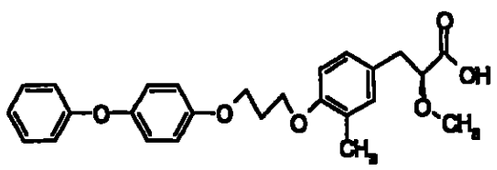
Step G

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared from compound from Step F under Standard hydrolysis procedure C using NaOH.

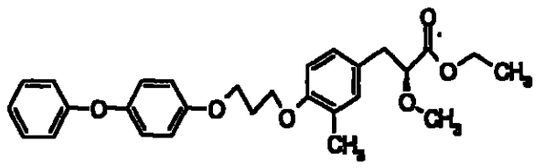
Example 163

2-Methoxy-3-{3-methyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid



Step A

2-Methoxy-3-{3-methyl-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester



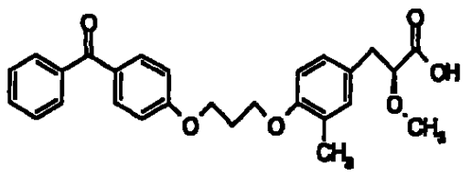
A mixture of 3-(4-Hydroxy-3-methyl-phenyl)-2-methoxy-propionic acid ethyl ester and from Example 162, Step E and 4-(3-bromopropoxy)phenoxyphenyl were treated under standard condition I to give the title product.

Step B

The title compound was prepared from compound from Step A under Standard hydrolysis procedure C using NaOH.

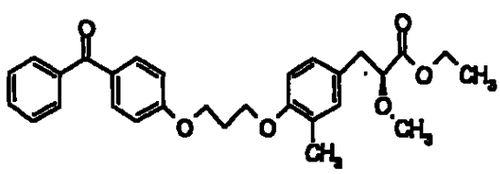
Example 164

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid



Step A

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid ethyl ester



A mixture of 3-(4-Hydroxy-3-methyl-phenyl)-2-methoxy-propionic acid ethyl ester and from Example 162, Step E and [4-(3-Bromo-propoxy)-phenyl]-phenyl-methanone were treated under standard condition I to give the title product.

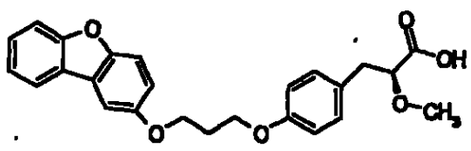
Step B

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared from compound from Step A under Standard hydrolysis procedure C using NaOH.

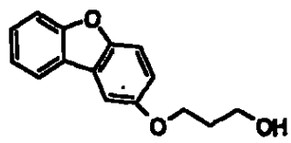
Example 165

(2S)-3-{4-[3-(Dibenzofuran-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

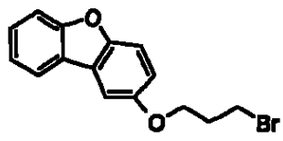
3-(Dibenzofuran-2-yloxy)-propan-1-ol



A solution of 2-hydroxydibenzofuranne, potassium *tert*-butoxide and [1,2,3]dioxathiane-2,2-dioxide were treated as the same manner as in Example 132, Step C, to give the title product.

Step B

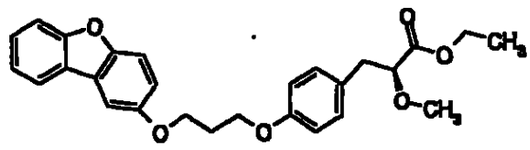
2-(3-Bromo-propoxy)-dibenzofuran



Starting from compound of Step A and following the procedure described in Example 132, Step D we obtained the title compound.

Step C

3-{4-[3-(Dibenzofuran-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



A mixture of 2-(3-Bromo-propoxy)-dibenzofuran and (2S)-3-(4-hydroxy-phenyl)-2-methoxy propionic acid ethyl ester were allowed to react under the Standard Procedure I to give the title compound.

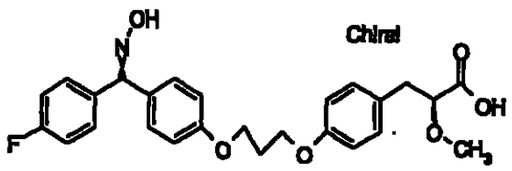
Step D

(2S)-3-{4-[3-(Dibenzofuran-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from Step C using the standard hydrolysis procedure C (NaOH).

Example 166

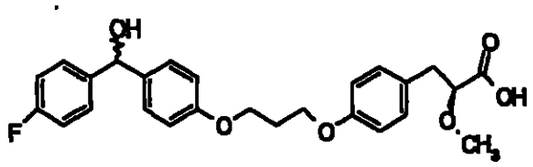
(2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxyimino-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Example 95),and was treated under the same conditions as in Example 61, to give the title compound.

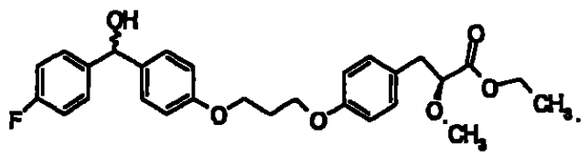
Example 167

(2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxy-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid



Step A

(2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxy-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester (Example 95) which was dissolved in methanol and treated at 0°C with $NaBH_4$ (2 eq) for 6 hours. Washed with water and extracted with dichloromethane to give after purification by chromatography the title compound.

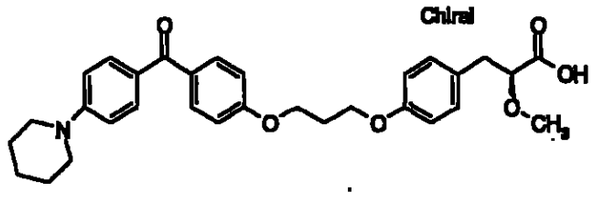
Step B

2S)-3-[4-(3-{4-[(4-Fluoro-phenyl)-hydroxy-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid

The title compound was prepared from Step A by standard hydrolysis procedure C (NaOH).

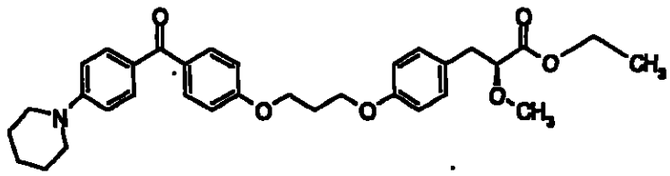
Example 168

(2S)-2-Methoxy-3-(4-{3-[4-(4-piperidin-1-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

(2S)-2-Methoxy-3-(4-{3-[4-(4-piperidin-1-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid ethyl ester



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To a solution of (2*S*)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester (Example 95) in DMSO, piperydine (3 eq) was added and the mixture reaction was heated to 140°C for 2 days. The reaction was extracted with ethyl acetate and washed (several times) with water. Concentrated to dryness and chromatographied to give the title compound.

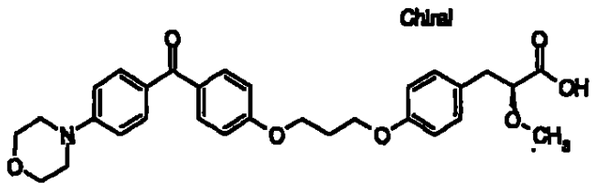
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-piperidin-1-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid

The title compound was prepared from Step A by standard hydrolysis procedure C (LiOH). MS (ES) for $C_{31}H_{35}NO_6$ $[M+H]^+$: 518.

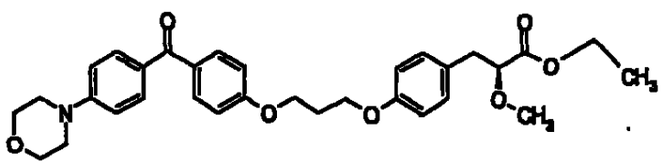
Example 169

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-morpholin-4-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-morpholin-4-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid ethyl ester



To a solution of (2*S*)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester (Example 95) in DMSO, morpholyne (3 eq) was added and the mixture reaction was heated to 140°C for 2 days. The reaction was

extracted with ethyl acetate and washed (several times) with water. Concentrated to dryness and chromatographed to give the title compound

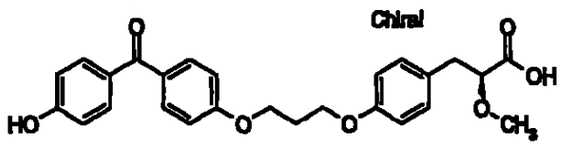
Step B

(2S)-2-Methoxy-3-(4-{3-[4-(4-morpholin-4-yl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid

The title compound was prepared from Step A by standard hydrolysis procedure C (LiOH). MS (ES) for $C_{30}H_{33}NO_7$ $[M+H]^+$: 520.

Example 170

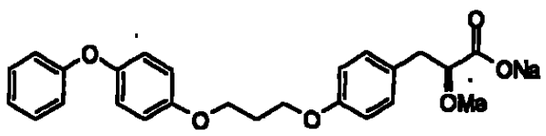
(2S)-3-(4-{3-[4-(4-Hydroxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



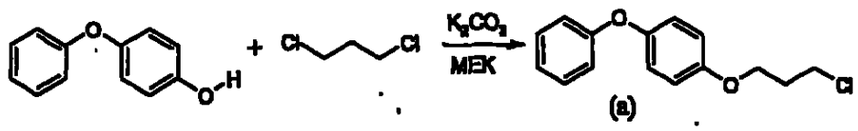
A solution of (2S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (85 mg) (Example 95) and KOH (100mg) in chlorobenzene (0.3 ml) with water (1 ml) were heated in sealed tube at 200°C for 3 days. Extracted with ethyl acetate, dried and concentrated to dryness to give a crude product which was purified by chromatography to give the title compound. MS (ES) for $C_{26}H_{26}O_7$ $[M+H]^+$: 451.

Example 171

2S-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid sodium salt

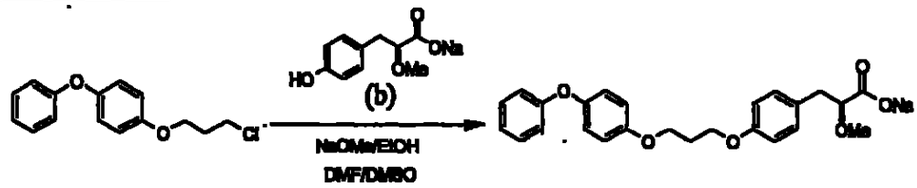


Step 1: 1-chloro-3-(4-phenoxyphenyl)propane (a)



The compound of 4-phenoxyphenol (81.03g, 435.15mmol) was dissolved in 810 ml MEK at ambient temperature under Nitrogen. Powdered potassium carbonate (577.16g, 4,176.27mmol) was added followed by 1,3-dichloropropane (300.00g, 2,655.1mmol), and the resulting solution was heated to reflux for 15.5 hours. The solution was cooled to room temperature, filtered and washed with 750ml MEK. The filtrate was concentrated under vacuum to give a crude orange liquid. The crude liquid was dissolved in 260ml absolute MeOH at ambient temperature and stirred 5minutes, which was then cooled in an ice/acetone/water bath for 1.5 hours. White precipitate was filtered off and washed with 480ml cold absolute MeOH. The white solid was collected and dried under vacuum at 30°C for16 hours to afford about 81.87g of compound (a).

Step 2: 2S-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}-propanoic acid sodium salt

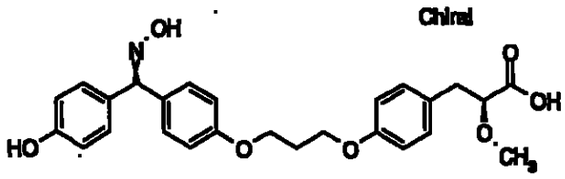


The compound (b) (10.9g, 50mmol) was dissolved in 50ml absolute ethanol at ambient temperature. Sodium methoxide (4.05g, 75mmol) was added all at once, and the resulting solution was heated to reflux for 30 minutes. The solution was cooled to 40°C and the compound (a) (15.72g, 75mmol) was added all at once followed by 50ml DMF and 50ml DMSO. The clear red solution was heated to reflux for 30 minutes, and cooled to ambient temperature. The ethanol was removed under vacuum at 60°C, and a mixture 100ml of water and 100ml MTBE was added. The top organic layer was separated and discarded. Fresh MTBE (100ml) was added and crystallization occurred. The biphasic slurry was stirred at ambient temperature for 30 minutes, filtered and washed with 250ml MTBE. The white solid

was dried under vacuum at 60°C for 16 hours to afford about 15.34g of the title compound.

Example 172

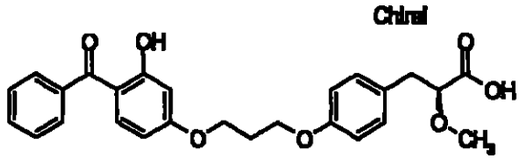
(2S)-3-[4-(3-{4-[Hydroxyimino-(4-hydroxy-phenyl)-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-(4-{3-[4-(4-Hydroxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (Example 170), and was treated under the same conditions as in Example 61, to give the title compound. MS (ES) for $C_{26}H_{27}NO_7$ $[M-H]^-$: 464.

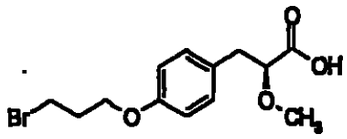
Example 173

(2S)-3-{4-[3-(4-Benzoyl-3-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

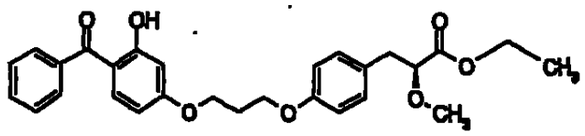
(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 171, Step B, and following the procedure described in Example 132, Step D we obtained the title compound.

Step B

3-{4-[3-(4-Benzoyl-3-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



A mixture of (2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Step A and 2,4-dihydroxybenzophenone were allowed to react under the Standard Procedure I to get to title compound.

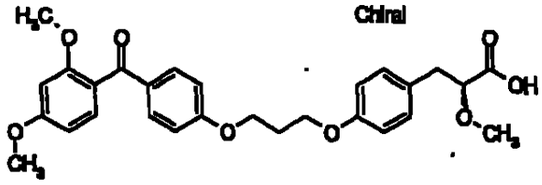
Step C

(2S)-3-{4-[3-(4-Benzoyl-3-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from Step B by standard hydrolysis procedure C (LiOH). MS (ES) for $C_{26}H_{26}O_7$ $[M-H]^-$: 449.

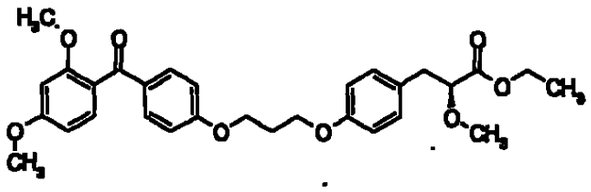
Example 174

(2S)-3-{4-{3-[4-(2,4-Dimethoxy-benzoyl)-phenoxy]-propoxy}-phenyl}-2-methoxy-propionic acid



Step A

3-{4-{3-[4-(2,4-Dimethoxy-benzoyl)-phenoxy]-propoxy}-phenyl}-2-methoxy-propionic acid ethyl ester



A mixture of (2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from 0, Step A and 2,4-dimethoxy-4'hydroxybenzophenone were allowed to react under the Standard Procedure I to get to title compound.

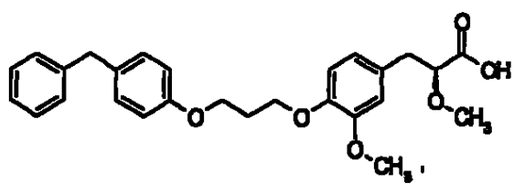
Step B

(2S)-3-{4-[3-[4-(2,4-Dimethoxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

The title compound was prepared from Step A by standard hydrolysis procedure C (LiOH). MS (ES) for $C_{28}H_{30}O_8$ [M-H]$^-$: 493.

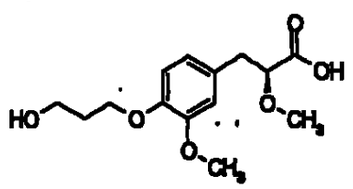
Example 175

3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid



Step A

3-[4-(3-Hydroxy-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid

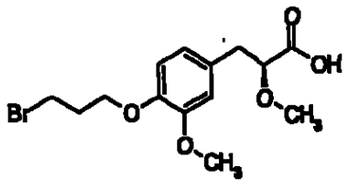


A mixture of 3-(4-Hydroxy-3-methoxy-phenyl)-2-methoxy-propionic acid ethyl ester (Example 130, Step A) and 3-(tert-Butyl-dimethyl-silanyloxy)-propan-1-ol were treated under Mitsonnobu coupling standard conditions B using DIAD and

toluene. The product fims obtained was treated under Standard Procedure E for cleavage protected alcohols to give the title product.

Step B

3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(3-Hydroxy-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid and following the procedure described in Example 132, Step D we obtained the title compound.

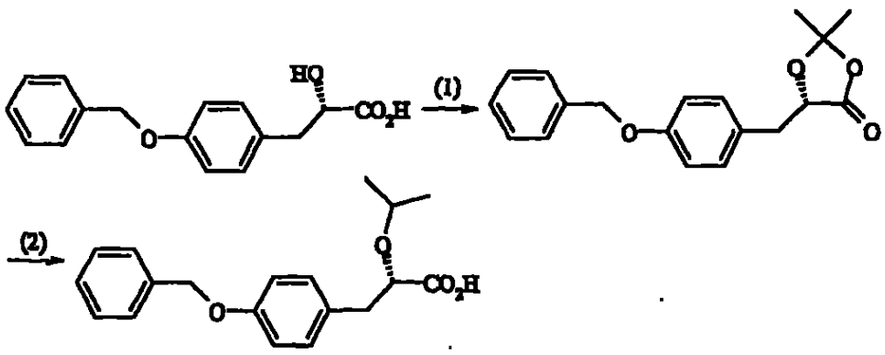
Step C

3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid

The title compound was prepared from 3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid and 4-benzylphenol following the Standard Procedure J. MS (ES) for $C_{27}H_{30}O_6$ $[M+NH_4]^+$: 468, $[M+Na]^+$: 473.

Example 176

(S)-3-(4-benzyloxy-phenyl)-2-isopropoxy-propionic acid



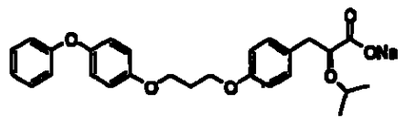
Step 1: A solution containing (*S*)-5-(4-benzyloxy-benzyl)-2,2-dimethyl-[1,3]dioxolan-4-one (*S*)-3-(4-benzyloxy-phenyl)-2-hydroxy-propionic acid (2.0 g, 7.34 mmol), 2,2-dimethoxypropane (18.63 g, 0.179 mol) and pyridiidium *p*-toluene sulfonate (0.92 g, 3.66 mmol) in chloroform (80 mL) was heated to reflux for 40 minutes under N_2. The reaction was cooled, diluted with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give crude product which was purified by a flash chromatography using 10:1 hexanes:acetone to afford about 2.01g (88%) of (*S*)-5-(4-benzyloxy-benzyl)-2,2-dimethyl-[1,3]dioxolan-4-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.29 (m, 5H), 7.17 (d, 2H, *J* = 8.80 Hz), 6.91 (d, 2H, *J* = 8.80 Hz), 5.04 (s, 2H), 4.61 (dd, 1H, *J* = 6.36 Hz, *J* = 4.40 Hz), 3.12 (dd, 1H, *J* = 14.67 Hz, *J* = 4.40 Hz), 2.99 (dd, 1H, *J* = 14.67 Hz, *J* = 6.36 Hz), 1.49 (s, 3H), 1.36 (s, 3H). MS (ES^+) *m/z* exact mass calculated for $C_{19}H_{20}O_4$ (M +NH_4) 330. Found *m/z* 330.

Step 2: (*S*)-3-(4-benzyloxy-phenyl)-2-isopropoxy-propionic acid

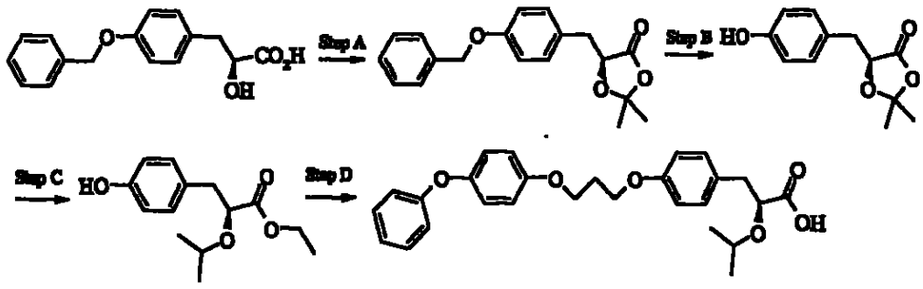
A -78^{0}C solution of (*S*)-5-(4-benzyloxy-benzyl)-2,2-dimethyl-[1,3]dioxolan-4-one (0.20 g, 0.64 mmol) and triethylsilane (0.223 g, 1.92 mmol) in CH_2Cl_2 (8 mL) was treated dropwise with a 1 molar solution of $TiCl_4$ in CH_2Cl_2 (0.64 mL, 0.64 mmol) under N_2. The solution was stirred at -78 ^{0}C for 15 minutes and then quenched with water. The mixture was extracted with EtOAc, and the organic layer was dried (Na_2SO_2). The organic layer was filtered, and the solvent was removed *in vacuo* to give crude product which was purified by a flash chromatography using 5:1 hexanes:acetone to afford 0.171 g (85%) (*S*)-3-(4-benzyloxy-phenyl)-2-isopropoxy-propionic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (bs, 1H), 7.42-7.27 (m, 5H), 7.12 (d, 2H, *J* = 8.80 Hz), 6.88 (d, 2H, *J* = 8.80 Hz), 5.02 (s, 2H), 3.96 (dd, 1H, *J* = 7.83 Hz, *J* = 4.89 Hz), 3.47 (hp, 1H, *J* = 5.87 Hz), 2.83 (dd, 1H, *J* = 13.69 Hz, *J* = 4.89 Hz), 2.71 (dd, 1H, *J* = 13.69 Hz, *J* = 8.31 Hz), 1.02 (d, 2H, *J* = 5.87 Hz), 0.86 (d, 2H, *J* = 5.87 Hz). IR (KBr) 3012, 2977, 2931, 1767, 1722, 1610, 1511, 1380, 1240, 1116, 1020. HRMS (TOF ES$^-$) *m/z* exact mass calculated for $C_{19}H_{21}O_4$ (M-1) 313.1440. Found *m/z* 313.1434.

Example 176A

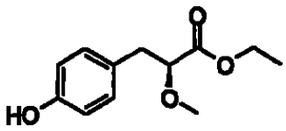
2S-2-isopropoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid sodium salt



Scheme

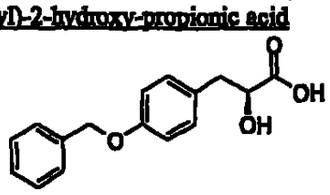


(*S*)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester



A solution of (*S*)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid (20 g, 100 mmol) in 3A ethanol (140 mL) was treated dropwise with concentrated sulfuric acid (5.7 mL)) and stirred at room temperature overnight. The solution was concentrated and water (110 mL) was added. Sodium bicarbonate was added to bring the pH to 7-8. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with 20% NaCl solution (50 ml), dried ($MgSO_4$), filtered, and concentrated to a golden oil (18 g, 80%). ^{1}H-NMR ($CDCl_3$): 7.1(d, 2H); 6.7(d, 2H); 4.2(m, 2H); 3.9(m, 1H); 3.6(s, 3H); 2.95(m, 2H); 1.25(t, 3H). MS (ES): 223.2 (M-1).

(*S*)-3-(4-benzyloxy-phenyl)-2-hydroxy-propionic acid



(*S*)-2-Hydroxy-3-(4-hydroxy-phenyl)-propionic acid (121 g, 0.664 mol) (Wang et al. *Tetrahedron Lett.* 1998, 39, 5501) in absolute EtOH (2L) was treated with potassium carbonate (184 g, 1.33 mol) and benzyl chloride 169 g, 1.34 mol). The mixture was heated at reflux overnight and concentrated to about half the volume under vacuum. Aqueous 5N NaOH (100 mL) was added, and the mixture was stirred at ambient temperature overnight and then concentrated. The residue was acidified with concentrated HCl. The yellow solid was collected by filtration and dried overnight under vacuum at 50°C. The crude product in isopropanol (1.8L) was heated at reflux for about 30 minutes, cooled to ambient temperature, and stirred for about 16 hours. The slurry was filtered and dried under vacuum at 70°C overnight to give the title compound as a white solid (137 g, 76%).

Step A: (*S*)-5-(4-benzyloxy-benzyl)-2,2-dimethyl-[1,3]dioxolan-4-one

(*S*)-3-(4-Benzyloxy-phenyl)-2-hydroxy-propionic acid (2.0 g, 7.34 mmol), 2,2-dimethoxypropane (18.63 g, 0.179 mol) and pyridinium *p*-toluene sulfonate (0.92 g, 3.66 mmol) in chloroform (80 mL) was heated to reflux for 40 minutes under N_2. The mixture was cooled, diluted with water, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give crude product that was purified by flash chromatography using 10:1 hexanes:acetone to afford the title compound (2.01 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.29 (m, 5H), 7.17 (d, 2H, J = 8.80 Hz), 6.91 (d, 2H, J = 8.80 Hz), 5.04 (s, 2H), 4.61 (dd, 1H, J = 6.36 Hz, J = 4.40 Hz), 3.12 (dd, 1H, J = 14.67 Hz, J = 4.40 Hz), 2.99 (dd, 1H, J = 14.67 Hz, J = 6.36 Hz), 1.49 (s, 3H), 1.36 (s, 3H). MS (ES^+) *m/z* calc'd for $C_{19}H_{20}O_4$ ($M+NH_4$) 330. Found *m/z* 330.

Step B: (*S*)-5-(4-hydroxy-benzyl)-2,2-dimethyl-[1,3]dioxolan-4-one

(*S*)-5-(4-benzyloxy-benzyl)-2,2-dimethyl-[1,3]dioxolan-4-one (1.0 g, 3.2 mmol) was combined with 10% Pd/C (0.75 g) in EtOAc (40 mL) and purged with N_2 then H_2 and then stirred under a hydrogen balloon for 3 hours. Sodium sulfate was added, and the mixture was filtered through Celite. The solvent was removed *in vacuo* to afford the title compound (0.747 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, 2H, J = 8.31 Hz), 6.76 (d, 2H, J = 8.31 Hz), 4.93 (bs, 1H), 4.61 (dd, 1H, J = 6.36 Hz, J = 4.40 Hz), 3.11 (dd, 1H, J = 14.67 Hz, J = 4.40 Hz), 2.98 (dd, 1H, J = 14.67 Hz, J = 5.86 Hz), 1.49 (s, 3H), 1.36 (s, 3H). MS (ES$^-$) *m/z* mass calc'd for $C_{12}H_{14}O_4$ (M-1) 221. Found *m/z* 221.

Step C: (*S*)-3-(4-hydroxy-phenyl)-2-isopropoxy-propionic acid ethyl ester

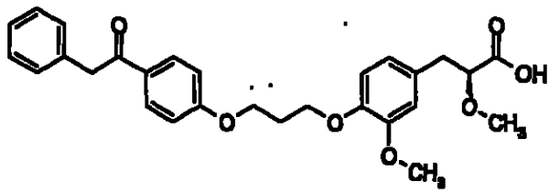
A 0°C solution of (*S*)-5-(4-hydroxy-benzyl)-2,2-dimethyl-[1,3]dioxolan-4-one (0.20 g, 0.90 mmol) and triethylsilane (1.05 g, 9.02 mmol) in CH_2Cl_2 (10 mL) was treated dropwise with $TiCl_4$ (0.90 mL, 0.90 mmol, 1M CH_2Cl_2) under N_2. The solution was stirred at 0°C for about 15 min and warmed to room temperature. After about 45 minutes, the mixture was quenched with water and extracted with EtOAc. The organic layer was dried (Na_2SO_2), filtered, and concentrated *in vacuo* to give of crude product (0.32 g). This material was combined with ethanol (25 mL) and conc. H_2SO_2 (1 mL) and stirred for 17 hours at room temperature under N_2. The mixture was concentrated and partitioned between EtOAc and water. The organic layer was dried (Na_2SO_2), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5:1 hexanes:acetone to afford the title compound (0.158 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, 2H, J = 8.31 Hz), 6.76 (d, 2H, J = 8.31 Hz), 4.79 (bs, 1H), 4.20-4.12 (m, 2H), 3.99 (dd, 1H, J = 8.56 Hz, J = 4.89 Hz), 3.49 (hp, 1H, J = 6.36 Hz), 2.94-2.83 (m, 2H), 1.23 (t, 3H, J = 6.85 Hz), 1.14 (d, 3H, J = 6.36 Hz), 0.96 (d, 3H, J = 6.36 Hz). MS (ES$^-$) *m/z* calc'd for $C_{14}H_{20}O_4$ (M-1) 251. Found *m/z* 251.

Step D: (*S*)-2-isopropoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid

The synthesis of 2S-2-isopropoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid sodium salt was completed according to procedures described in Example 171. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, 3 H, *J*= 5.9 Hz), 1.09 (d, 3 H, *J*= 6.3 Hz), 2.22 (quartet, 2 H, *J* = 5.9 Hz), 2.82 (dd, 1 H, *J* = 9.3 Hz, 13.7 Hz), 3.01 (dd, 1 H, *J* = 2.5 Hz, 13.7 Hz), 3.43 (q, 1 H, *J* = 5.9 Hz), 4.01 (dd, 1 H, *J* = 3.4 Hz, 8.8 Hz), 4.11 (q, 4 H, *J* = 6.4 Hz), 6.80 (d, 2 H, *J*= 8.3 Hz), 6.88 (d, 2 H, *J*= 8.8 Hz), 6.90-7.00 (m, 4 H), 7.01-7.05 (m, 1 H), 7.17 (d, 2 H, *J*= 8.3 Hz), 7.28 (d, 2 H, *J*= 8.8 Hz). MS: 451.2 (MH^+).

Example 177

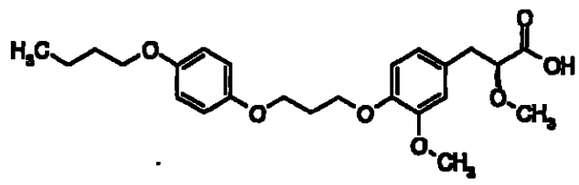
2-Methoxy-3-{3-methoxy-4-[3-(4-phenylacetyl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from 3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid (Example 175, Step B) and 1-(4-Hydroxy-phenyl)-2-phenyl-ethanone following the Standard Procedure J. MS (ES) for $C_{28}H_{30}O_7$ $[M+H]^+$: 479.

Example 178

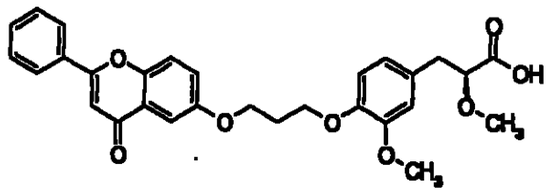
3-{4-[3-(4-Butoxy-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid (Example 175, Step B) and 4-Butoxy-phenol following the Standard Procedure J. MS (ES) for $C_{24}H_{32}O_7$ $[M+Na]^+$: 455.

Example 179

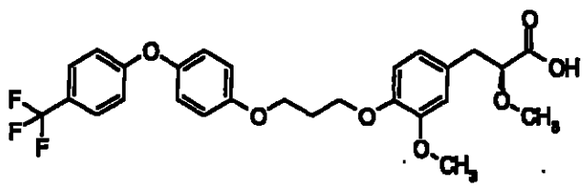
2-Methoxy-3-{3-methoxy-4-[3-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from 3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid (Example 175, Step B) and 6-Hydroxy-2-phenyl-chromen-4-one following the Standard Procedure J. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 8.0-7.9 (m, 2H), 7.6-7.5 (m, 5H), 7.30 (dd, 1H, J=9.0, 3.0), 6.9-6.8 (m, 4H), 4.3-4.2 (m, 4H), 4.00 (dd, 1H, J=7.2, 4.6), 3.83 (s, 3H), 3.41 (s, 3H), 3.09 (dd, 1H, J=14.2, 4.6), 2.96 (dd, 1H, J=14.2, 7.2), 2.33 (qn, 2H, J=6.2) ppm.

Example 180

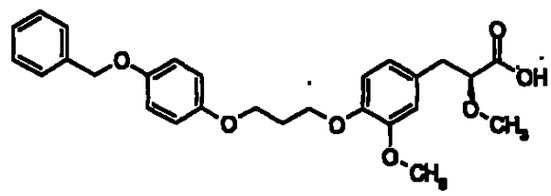
2-Methoxy-3-{3-methoxy-4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-propoxy}-phenyl}-propionic acid



The title compound was prepared from 3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid (Example 175, Step B) and 4-(4-Trifluoromethyl-phenoxy)-phenol following the Standard Procedure J. MS (ES) for $C_{27}H_{27}F_3O_7$ $[M+Na]^+$: 543.

Example 181

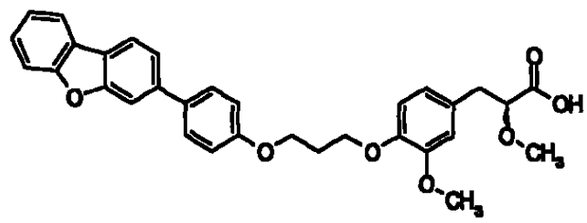
3-{4-[3-(4-Benzyloxy-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid (Example 175, Step B) and 4-Benzyloxy-phenol following the Standard Procedure J. MS (ES) for $C_{27}H_{30}O_7$ $[M+Na]^+$: 489.

Example 182

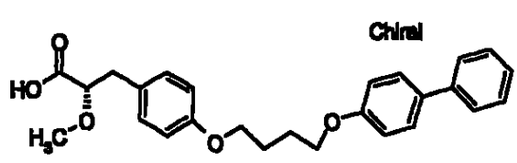
3-{4-[3-(4-Dibenzofuran-3-yl-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid



The title compound was prepared from 3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid (Example 175, Step B) and 4-Dibenzofuran-3-yl-phenol following the Standard Procedure J. MS (ES) for $C_{32}H_{30}O_7$ $[M+NH_4]^+$:544, $[M+Na]^+$: 549.

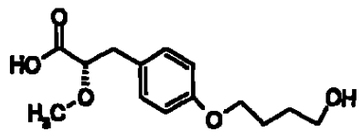
Example 183

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-butoxy]-phenyl}-2-methoxy-propionic acid



Step A

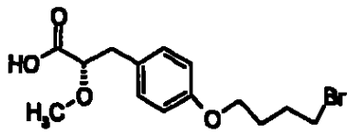
(2S)-3-[4-(4-Hydroxy-butoxy)-phenyl]-2-methoxy-propionic acid ethyl ester



A mixture of 3-(4-Hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester and 3-(tert-Butyl-dimethyl-silanyloxy)-butan-1-ol were treated under Mitsounobu coupling Standard conditions B using DIAD and THF. The product thus obtained was treated under Standard Procedure E for cleaveage protected alcohols to give the title product.

Step B

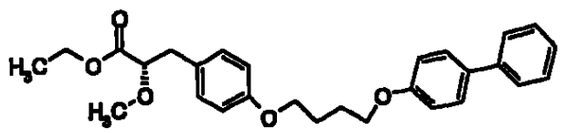
(2S)-3-[4-(4-Bromo-butoxy)-phenyl]-2-methoxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-[4-(4-Hydroxy-butoxy)-phenyl]-2-methoxy-propionic acid ethyl ester and following the procedure described in Example 132, Step D we obtained the title compound.

Step C

(2S)-3-{4-[4-(Biphenyl-4-yloxy)-butoxyl-phenyl}-2-methoxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-[4-(4-Bromo-butoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Step B) and 4-phenylphenol under the Standard Procedure I to give the product.

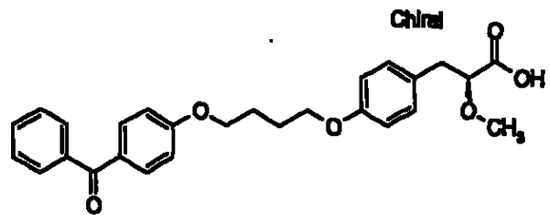
Step D

2S)-3-{4-[4-(Biphenyl-4-yloxy)-butoxyl-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-{4-[4-(Biphenyl-4-yloxy)-butoxy]-phenyl}-2-methoxy-propionic acid ethyl ester from Step C under the standard Hydrolysis procedure C. (LiOH). ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.57-7.49 (m, 4H); 7.45-7.37 (m, 2H); 7.32-7.11 (m, 3H); 6.97 (d, 2H, J= 8.9); 6.84 (d, 2H, J= 8.9); 4.11-3.93 (m, 5H); 3.40 (s, 3H); 3.10 (dd, 1H, J= 14.0, 4.3); 2.96 (dd, 1H, J= 14.5, 7.0); 1.99-1.97 (m, 4H) ppm.

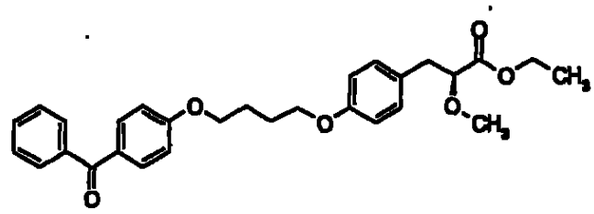
Example 184

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-butoxy]-phenyl}-2-methoxy-propionic acid



Step A

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-butoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-[4-(4-Bromo-butoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example183, Step B) and 4-hydroxybenzophenone under the Standard Procedure I to give the product.

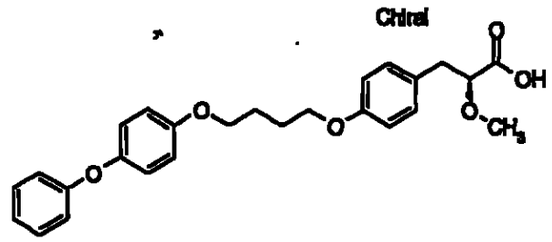
Step B

(2S)-3-{4-[4-(4-Benzoyl-phenoxy)-butoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-{4-[4-(4-Benzoyl-phenoxy)-butoxy]-phenyl}-2-methoxy-propionic acid ethyl ester from Step A under the Standard hydrolysis procedure C. (LiOH). ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.81 (d, 2H, J=8.9), 7.75 (dd, 2H, J=8.3, 1.4), 7.6-7.4 (m, 3H), 7.15 (d, 2H, J=8.6), 6.81 (d, 2H, J=8.3), 4.2-3.9 (m, 5H), 3.37 (s, 3H), 3.08 (dd, 1H, J=14.2, 4.3), 2.94 (dd, 1H, J=14.2, 7.5), 2.1-1.9 (m, 4H) ppm.

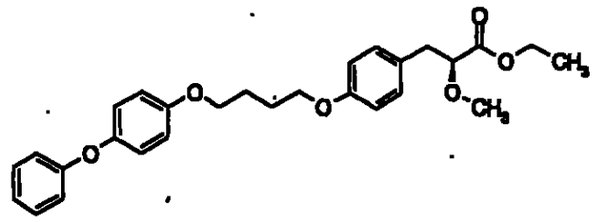
Example 185

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butoxy]-phenyl}-propionic acid



Step A

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butoxy]-phenyl}-propionic acid ethyl ester



The title compound was prepared from (2S)-3-[4-(4-Bromo-butoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 183, Step B) and 4-phenoxyphenol under the Standard Procedure I to give the product.

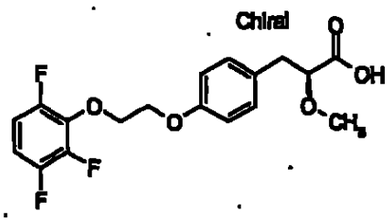
Step B

(2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butoxy]-phenyl}-propionic acid

The title compound was prepared from (2S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-butoxy]-phenyl}-propionic acid ethyl ester, from Step A under the Standard hydrolysis procedure C. (LiOH). ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.4-7.2 (m, 2H), 7.15 (d, 2H, J=8.6), 7.1-6.7 (m, 9H), 4.0-3.9 (m, 5H), 3.34 (s, 3H), 3.08 (dd, 1H, J=14.0, 4.0), 2.93 (dd, 1H, J=14.0, 7.8), 2.1-1.9 (m, 4H) ppm.

Example 186

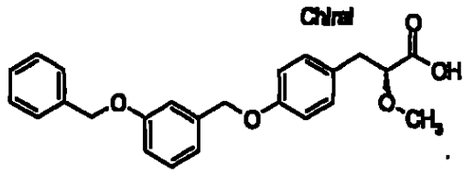
(2S)-2-Methoxy-3-{4-[2-(2,3,6-trifluoro-phenoxy)-ethoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-hydroxy-phenyl]-2-methoxypropionic acid linked to Wang's Resin (Example 94, Step C) via the Mitsoumobu coupling-cleveage (Standard Procedure G) with 2-(2,3,6-Trifluoro-phenoxy)-ethanol to give the desire product. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.15 (d, 2H, J=8.6), 6.9-6.8 (m, 4H), 4.51 (t, 2H, J=4.0), 4.27 (t, 2H, J=4.8), 3.97 (dd, 1H, J=7.2, 4.3), 3.39 (s, 3H), 3.09 (dd, 1H, J=14.5, 4.5), 2.95 (dd, 1H, J=14.5, 7.5) ppm.

Example 187

(2S)-3-[4-(3-Benzyloxy-benzyloxy)-phenyl]-2-methoxy-propionic acid

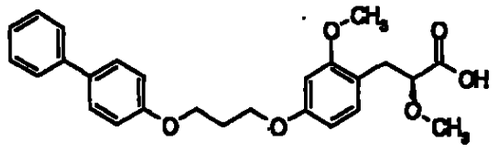


The title compound was prepared from (2S)-3-[4-(3-hydroxy-phenyl]-2-methoxypropionic acid linked to Wang's Resin (Example 94, Step C) via the Mitsoumobu coupling-cleveage (Standard Procedure G) with (3-Benzyloxy-phenyl)-methanol to give the desire product. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.5-7.2 (m,

5H), 7.2-6.8 (m, 8H), 5.07 (s, 2H), 5.01 (s, 2H), 3.99 (dd, 1H, J=7.0, 4.6), 3.40 (s, 3H), 3.10 (dd, 1H, J=14.2, 4.3), 2.96 (dd, 1H, J=14.5, 7.2) ppm.

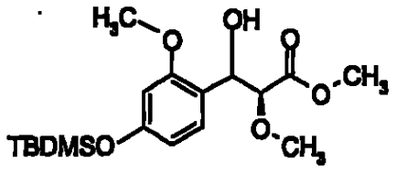
Example 188

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methoxy-phenyl}-2-methoxy-propionic aci



Step A

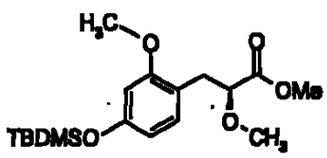
3-[4-(tert-Butyl-dimethyl-silanyloxy)-2-methoxy-phenyl]-3-hydroxy-2-methoxy-propionic acid methyl ester



A solution of 4-*tert*-butyldimethylsilanyloxy-2-methoxy benzaldehyde (1 eq) and methyl methoxyacetate (1.25 eq) in THF (10 mL) at -78°C was added dropwise to sodium bis(trimethylsilyl)amide (1.25 eq, 1N in THF) at -78°C. The reaction mixture was stirred for 3 h and quenched with 1N HCl (5 mL). The mixture was allowed to warm to room temperature, diluted with water (15 mL), and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column to obtain the title compound.

Step B

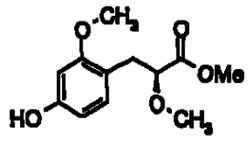
3-[4-(tert-Butyl-dimethyl-silanyloxy)-2-methoxy-phenyl]-2-methoxy-propionic acid methyl ester



A mixture of 3-[4-(tert-Butyl-dimethyl-silanyloxy)-2-methoxy-phenyl]-3-hydroxy-2-methoxy-propionic acid methyl ester (1 eq), Mesylchloride (1 eq) triethylamine (4 eq) and a catalytic amount of DMAP (0.1 eq) in dichloromethane was stirred at room temperature over night. The reaction mixture was diluted with ether and washed with HCl 1N. Dried and concentrated in vacuo to give a residue which was chromatographed in silicagel to yield a compound which was dissolved in methanol was treated with Mg (20 eq) and stirred until gas evolution was observed. Cooled to 0°C and stirred for 4 hours. The solvent was removed and the residue reconstituted in ether washed with HCl 1N and brine and concentrated to give the title product.

Step C

2-(4-Hydroxy-2-methoxy-benzyl)-butyric acid methyl ester



3-[4-(tert-Butyl-dimethyl-silanyloxy)-2-methoxy-phenyl]-2-methoxy-propionic acid methyl ester from Step B was treated under the Standard Procedure E to cleveage the protected silyl group and obtained the product.

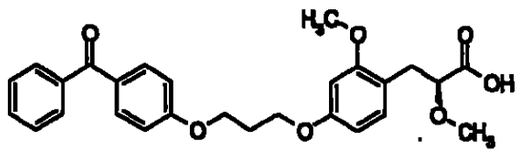
Step D

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-methoxy-phenyl}-2-methoxy-propionic acid

A mixture solution of 2-(4-hydroxy-2-methoxy-benzyl)-butyric acid methyl ester from Step C and 3-(biphenyl-4-yloxy)-propan-1-ol was reacted under the Standard Mitsounobu coupling conditions B (DIAD/toluene) to give the corresponding coupled product, which afforded the title compound via the Standard hydrolysis procedure C (NaOH). MS(ES) for $C_{25}H_{28}O_6$ $[M+NH_4]^+$: 454.

Example 189

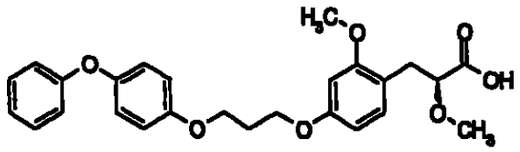
3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-methoxy-phenyl}-2-methoxy-propionic acid



A mixture solution of 2-(4-Hydroxy-2-methoxy-benzyl)-butyric acid ethyl ester from Example 188, Step C and [4-(3-Hydroxy-propoxy)-phenyl]-phenyl-methanone were allowed to react under the Standard Mitsounobu coupling conditions B (DIAD/toluene) to give the corresponding coupled product which by the Standard hydrolysis procedure C (NaOH) yield the title compound. MS (ES) for $C_{27}H_{28}O_7$ $[M+H]^+$: 465.

Example 190

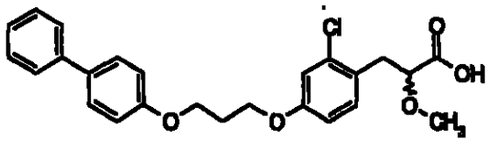
2-Methoxy-3-{2-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid



A mixture solution of 2-(4-Hydroxy-2-methoxy-benzyl)-butyric acid ethyl ester from Example 188, Step C and 3-(4-Phenoxy-phenoxy)-propan-1-ol were allowed to react under the Standard Mitsounobu coupling conditions B (DIAD/toluene) to give the corresponding coupled product which by the Standard hydrolysis procedure C (NaOH) yielded the title compound. MS (ES) for $C_{25}H_{28}O_7$ $[M+Na]^+$: 475.

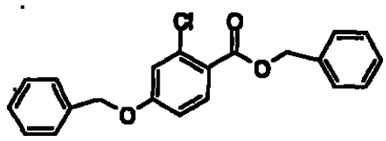
Example 191

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid



Step A

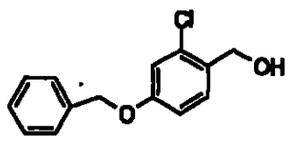
4-Benzyloxy-2-chloro-benzoic acid benzyl ester



A mixture solution of 2-chloro-4-hydroxybenzoic (1 eq) acid with benzyl bromide (2 eq) and K_2CO_3 (3 eq) in acetonitrile were heated at 85°C. Then filtered and concentrated to dryness to give after chromatography in silicagel the title compound.

Step B

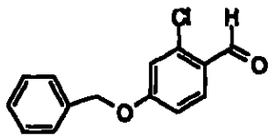
(4-Benzyloxy-2-chloro-phenyl)-methanol



A mixture of 4-Benzyloxy-2-chloro-benzoic acid benzyl ester from Step A with DIBAL-H 1M in toluene (2.2 eq)in THF were stirred at room temperature for 3 hours. The quenched with tartrate saturated solution and extracted with ethyl acetate. Concentrated to dryness and purified by chromatography to afford the title compound.

Step C

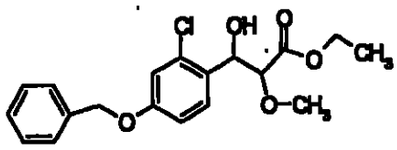
4-Benzyloxy-2-chloro-benzaldehyde



To a solution of (4-Benzyloxy-2-chloro-phenyl)-methanol in dichloromethane, MnO_2 (10 eq) were added and the mixture reaction stirred overnight. Filtered through a pad of celite and purified by chromatography in silicagel to give the title product.

Step D

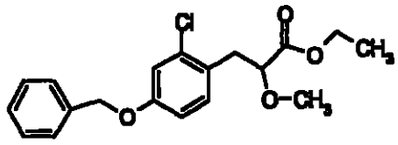
3-(4-Benzyloxy-2-chloro-phenyl)-3-hydroxy-2-methoxy-propionic acid ethyl ester



A solution of 4'-Benzyloxy-2-chloro-benzaldehyde (1 eq) and methyl methoxyacetate (1.25 eq) in THF (10 mL) at –78°C was added dropwise to sodium bis(trimethylsilyl)amide (1.25 eq, 1N in THF) at –78°C. The reaction mixture was stirred for 3 h and quenched with 1N HCl (5 mL). The mixture was allowed to warm to room temperature, diluted with water (15 mL), and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column to obtained the title compound.

Step E

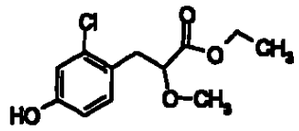
3-(4-Benzyloxy-2-chloro-phenyl)-2-methoxy-propionic acid ethyl ester



A mixture of 3-(4-Benzyloxy-2-chloro-phenyl)-3-hydroxy-2-methoxy-propionic acid ethyl ester (1 eq), Mesylchloride (1 eq) triethylamine (4 eq) and a catalytic amount of DMAP (0.1 eq) in dichloromethane was stirred at room temperature over night. The reaction mixture was diluted with ether and washed with HCl 1N. Dried and concentrated in vacuo to give a residue which was chromatographed in silicagel to yield a compound which was dissolved in methanol was treated with Mg (20 eq) and stirred until gas evolution was observed. Cooled to 0°C and stirred for 4 hours. The solvent was removed and the residue reconstituted in ether washed with HCl 1N and brine and concentrated to give the title product.

Step F

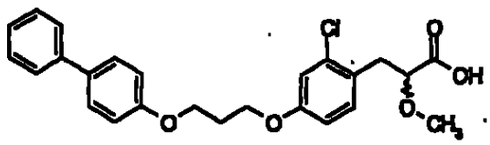
3-(2-Chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester



3-(4-Benzyloxy-2-chloro-phenyl)-2-methoxy-propionic acid ethyl ester in ethyl acetate was treated with Pd(C) and H_2 under balloon pressure. Then filtered through celite and concentrated to give the title compound.

Step G

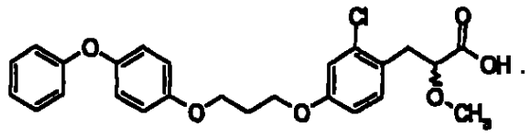
3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid



A mixture solution of 3-(2-Chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester from Step F and 3-(Biphenyl-4-yloxy)-propan-1-ol were allowed to react under the Standard Mitsounobu coupling conditions B (DIAD/toluene) to give the corresponding coupled product which by the Standard hydrolysis procedure C (NaOH) yield the title compound. MS (ES) for $C_{25}H_{25}ClO_5$ $[M+NH_4]^+$: 458.

Example 192

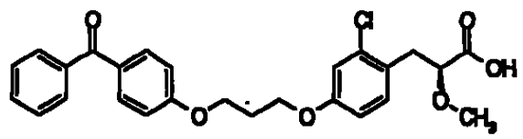
3-{2-Chloro-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



A mixture solution of 3-(2-Chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester from Example 191, Step F and 3-(4-Phenoxy-phenoxy)-propan-1-ol were allowed to react under the Standard Mitsounobu coupling conditions B (DIAD/toluene) to give the corresponding coupled product which by the Standard hydrolysis procedure C (NaOH) yield the title compound. MS (ES) for $C_{25}H_{25}ClO_6$ $[M+NH_4]^+$: 474.

Example 193

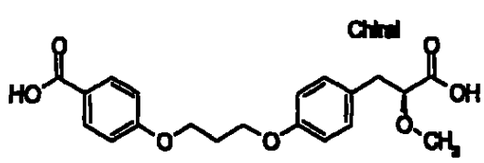
3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid



A mixture solution of 3-(2-Chloro-4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester from Example 132, Step F and [4-(3-Hydroxy-propoxy)-phenyl]-phenyl-methanone were allowed to react under the Standard Mitsounobu coupling conditions B (DIAD/toluene) to give the corresponding coupled product which by the Standard hydrolysis procedure C (NaOH) yield the title compound. MS (ES) for $C_{26}H_{25}ClO_6$ $[M+H]^+$: 469.

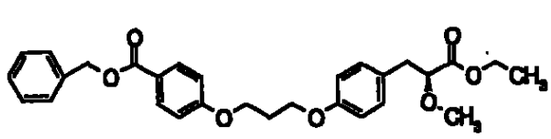
Example 194

(2S)-4-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid



Step A

(2S)-4-{3-[4-(2-Ethoxycarbonyl-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid benzyl ester



(2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from 0, Step B and 4-Hydroxy-benzoic acid benzyl ester were treated under Mitsounobu Standard coupling conditions B to give the title compound.

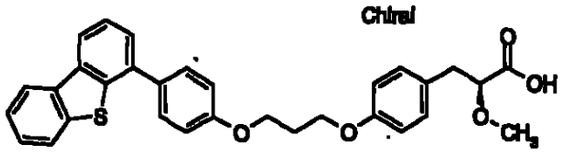
Step B

(2S)-4-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid

The title compound was prepared from (2S)-4-{3-[4-(2-Ethoxycarbonyl-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid benzyl ester (Step A) by Standard Hydrolysis procedure C (NaOH). MS (ES) for $C_{20}H_{22}O_7$ $[M+Na]^+$: 397.

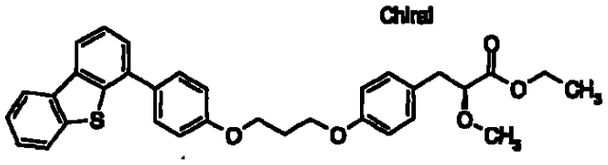
Example 195

(2S)-3-{4-[3-(4-Dibenzothiophen-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

(2S)-3-{4-[3-(4-Dibenzothiophen-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



(2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 171, Step B and 4-Dibenzothiophen-4-yl-phenol were treated under Mitsounobu Standard coupling conditions B to give the title compound.

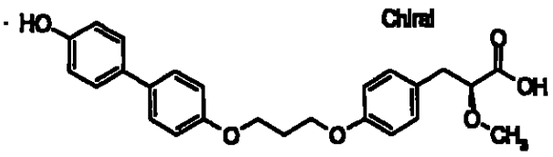
Step B

(2S)-3-{4-[3-(4-Dibenzothiophen-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-{4-[3-(4-Dibenzothiophen-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Step A) by Standard Hydrolysis procedure C (NaOH). MS (ES) for $C_{31}H_{33}O_5S$ $[M+NH_4]^+$: 530.

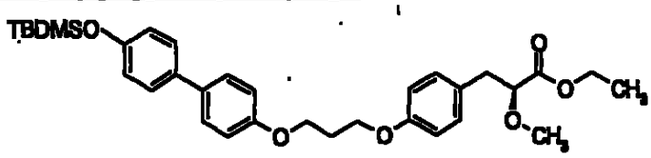
Example 196

(2S)-3-{4-[3-(4'-Hydroxy-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

(2S)-3-(4-{3-[4'-(tert-Butyl-dimethyl-silanyloxy)-biphenyl-4-yloxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A, and 4-(*tert*-Butyl-dimethyl-silanyloxy)-biphenyl-4-ol were treated with $CsCO_3$ (3 eq) in DMF and stirred at room temperature over night. Filtered and concentrated in vacuo to give the title compound.

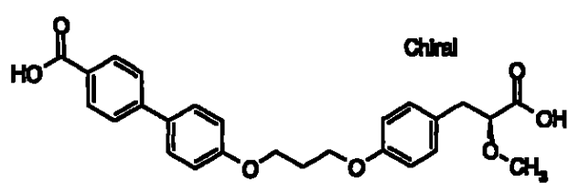
Step B

(2S)-3-{4-[3-(4'-Hydroxy-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-(4-{3-[4'-(tert-Butyl-dimethyl-silanyloxy)-biphenyl-4-yloxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester (Step A) by Standard Hydrolysis procedure C (NaOH). MS (ES) for $C_{25}H_{26}O_6$ $[M+Na]^+$: 445.

Example 197

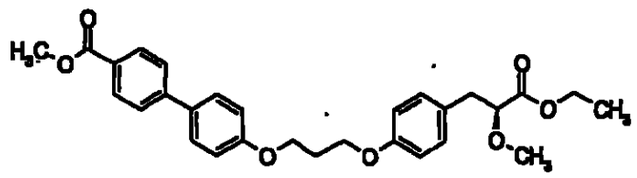
(2S)-4'-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid



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Step A

(2S)-4'-{3-[4-(2-Ethoxycarbonyl-2-methoxy-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid methyl ester



(2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 171, Step B and 4'-Hydroxy-biphenyl-4-carboxylic acid methyl ester were treated under Mitsounobu Standard coupling conditions B to give the title compound.

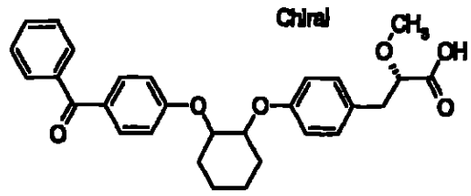
Step B

(2S)-4'-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid

The title compound was prepared from (2S)-4'-{3-[4-(2-Ethoxycarbonyl-2-methoxy-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid methyl ester (Step A) by Standard Hydrolysis procedure C (NaOH). MS (ES) for $C_{26}H_{26}O_7$ $[M+NH_4]^+$: 468, $[M+Na]^+$: 473.

Example 198

(2S)-3-{4-[2-(4-Benzoyl-phenoxy)-cyclohexyloxy]-phenyl}-2-methoxy-propionic acid



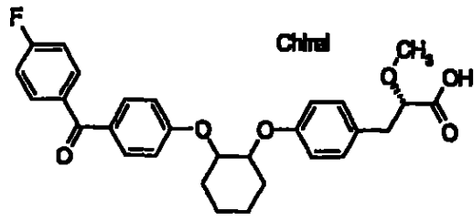
The title compound was prepared from (2S)-3-(4-hydroxyphenyl)-2-methoxy-propionic acid linked to Wang's resin (Example 94, Step C) via Mitsounobu coupling (Standard Procedure F) to give 3-[4-(2-Hydroxy-cyclohexyloxy)-phenyl]-2-methoxy-propionic acid linked to the resin. A second Mitsounobu coupling

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reaction with 4-hydroxybenzophenone via Standard Procedure G allow us to get the title compound. ^{1}H-NMR ($CDCl_3$, 200MHz): 7.75 (d, 4H, J= 8.6); 7.57-7.43 (m, 3H); 7.13 (d, 2H, J= 8.9); 6.89 (d, 2H, J= 9.1); 6.79 (d, 2H, J= 8.6); 4.53-4.36 (m, 2H); 4.04-3.99 (m, 1H); 3.43 (s, 3H); 3.08-2.94 (m, 2H); 1.38-1.29 (m, 8H) ppm.

Example 199

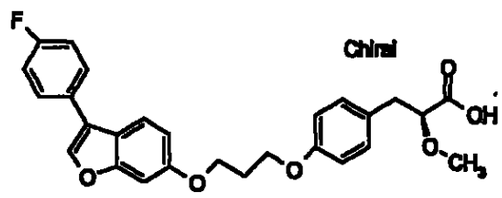
(2S)-3-(4-{2-[4-(4-Fluoro-benzoyl)-phenoxy]-cyclohexyloxy}-phenyl)-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-(4-hydroxyphenyl)-2-methoxy-propionic acid linked to Wang's resin (Example 94, Step C) via Mitsounobu coupling (Standard Procedure F) to give 3-[4-(2-Hydroxy-cyclohexyloxy)-phenyl]-2-methoxy-propionic acid linked to the resin. A second Mitsounobu coupling reaction with 4-fluoro-4'-hydroxybenzophenone via Standard Procedure G allows us to get the title compound. ^{1}H-NMR ($CDCl_3$, 200MHz): 7.83-7.69 (m, 4H); 7.19-7.11 (m, 4H); 6.89 (d, 2H, J= 8.9); 6.79 (d, 2H, J= 8.6); 4.53-4.33 (m, 2H); 4.02 (dd, 1H, J= 6.5, 4.8); 3.43 (s, 3H); 3.10 (dd, 1H, J= 14.4, 4.8), 2.98 (dd, 1H, J= 14.4, 6.5); 1.38-1.29 (m, 8H) ppm.

Example 200

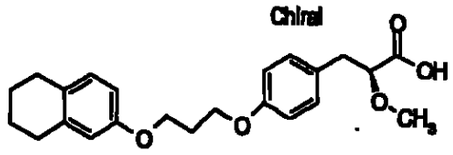
(2S)-3-(4-{3-[3-(4-Fluoro-phenyl)-benzofuran-6-yloxy]-propoxy}-phenyl)-2-methoxy-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 3-(4-Fluoro-phenyl)-benzofuran-6-ol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{25}FO_5$ $[M+NH_4]^+$: 482, $[M+Na]^+$: 487, $[M+H]^+$: 464.

Example 201

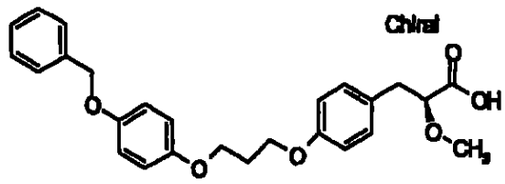
(2S)-2-Methoxy-3-{4-[3-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 5,6,7,8-Tetrahydro-naphthalen-2-ol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard Hydrolysis Procedure C (NaOH) to give the title compound. MS(ES) for $C_{23}H_{28}O_5$ $[M+Na]^+$: 407, $[M+H]^+$: 385.

Example 202

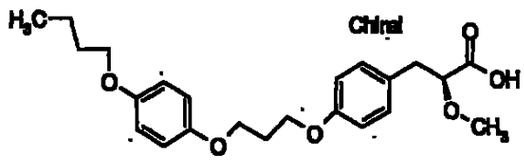
(2S)-3-{4-[3-(4-Benzyloxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-Benzyloxy-phenol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{26}H_{28}O_6$ $[M-H]^-$: 435.

Example 203

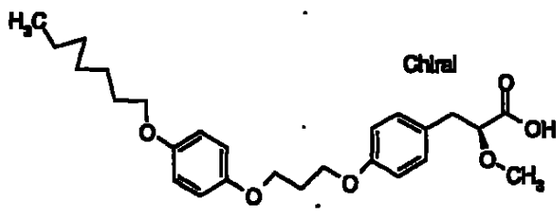
(2S)-3-{4-[3-(4-Butoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-Butoxy-phenol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{23}H_{30}O_6$ $[M+NH_4]^+$: 420, $[M+Na]^+$: 425, $[M+H]^+$: 403.

Example 204

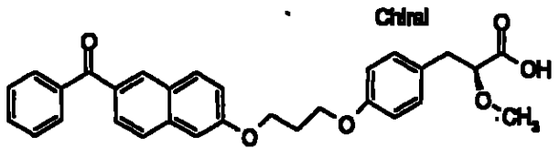
(2S)-3-{4-[3-(4-Heptyloxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-Heptyloxy-phenol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{26}H_{36}O_6$ $[M+Na]^+$: 467, $[M+H]^+$: 445.

Example 205

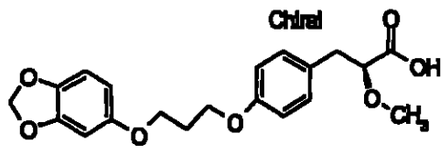
(2S)-3-{4-[3-(6-Benzoyl-naphthalen-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with (6-Hydroxy-naphthalen-2-yl)-phenyl-methanone under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{30}H_{28}O_5$ $[M+Na]^+$: 507, $[M+H]^+$: 485.

Example 206

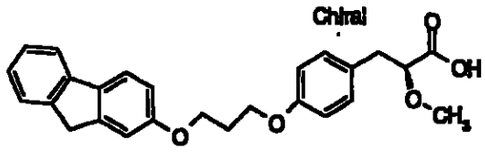
(2S)-3-{4-[3-(Benzo[1,3]dioxol-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with Benzo[1,3]dioxol-5-ol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{20}H_{22}O_7$ $[M+Na]^+$: 397, $[M+H]^+$: 375.

Example 207

(2S)-3-{4-[3-(9H-Fluoren-2-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

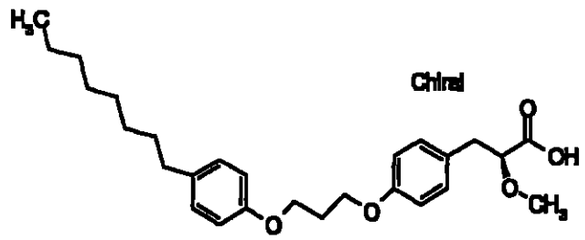


(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 9H-Fluoren-2-ol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard

hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{26}H_{26}O_5$ $[M+Na]^+$: 441.

Example 208

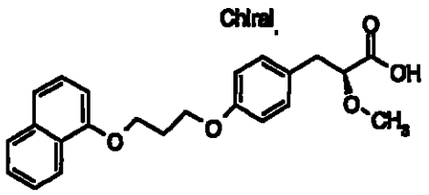
(2S)-2-Methoxy-3-{4-[3-(4-octyl-phenoxy)-propoxy]-phenyl}-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-Octyl-phenol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{38}O_5$ $[M+Na]^+$: 466.

Example 209

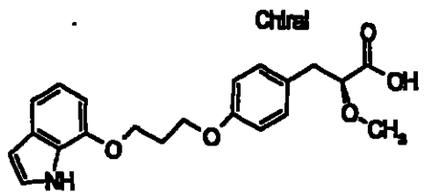
(2S)-2-Methoxy-3-{4-[3-(naphthalen-1-yloxy)-propoxy]-phenyl}-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with Naphthalen-1-ol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{23}H_{24}O_5$ $[M+Na]^+$: 403, $[M+H]^+$: 381.

Example 210

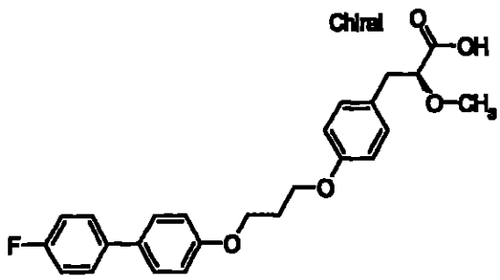
(2S)-3-{4-[3-(1H-Indol-7-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 1H-Indol-7-ol under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{21}H_{23}NO_5$ $[M+Na]^+$: 392, $[M+H]^+$: 370.

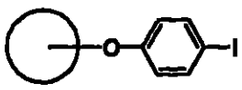
Example 211

(2S)-3-{4-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

Preparation of p-Iodophenol linked to the Wang's resin

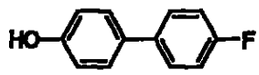


Wang' resin, (1 eq), *p*-iodophenol (4.5 eq) and PPh_3 (5-8 eq) were suspended in a vial and cooled to 0°C then DIAD was added (5 eq). The mixture reaction was allowed to get room temperature and stirred overnight. Filtered of and washed with MeOH-CH_2Cl_2-THF-HClaq and CH_2Cl_2 to give the product.

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Step B

4'-Fluoro-biphenyl-4-ol



A mixture of *p*-Iodophenol linked to the Wang's resin from Step A (1 eq), 4-fluorobenzene boronic acid (6 eq), K_2CO_3 (12 eq) and $Pd(OAc)_2$ (0.5 eq) were suspended in a mixture of dioxane/water (6/1) and the mixture was heated at 100°C and stirring for 36 hours. The resin was washed with DMF/H_2O and MeOH/THF/HCl diluted and MeOH/CH_2Cl_2. After it was dried, was suspended in dichloromethane, and TFA 95% was added. The mixture was stirred at room temperature for 30 min then filtered and washed with MeOH and dichloromethane. The solvents were concentrated to dryness to give the title product

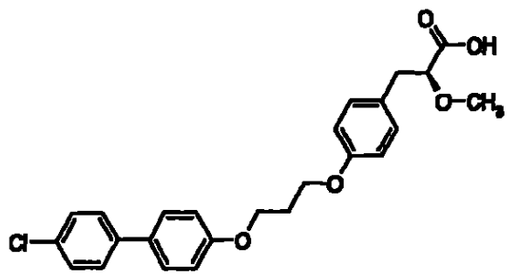
Step C

(2S)-3-{4-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4'-Fluoro-biphenyl-4-ol from Step B under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{25}FO_5$ $[M+NH_4]^+$: 442, $[M+Na]^+$: 447.

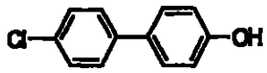
Example 212

(2S)-3-{4-[3-(4'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

4-chlorobiphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 4-chlorophenyl boronic acid.

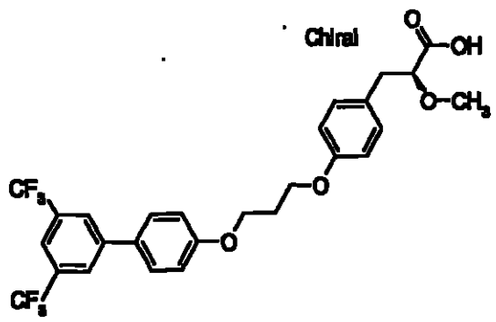
Step B

(2S)-3-{4-[3-(4'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with chloro-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{25}ClO_5$ $[M+Na]^+$: 463, $[M+H]^+$: 441.

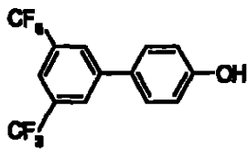
Example 213

(2S)-3-{4-[3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

3',5'-Bis-trifluoromethyl-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 3,5-bis(trifluoromethyl)phenyl boronic acid.

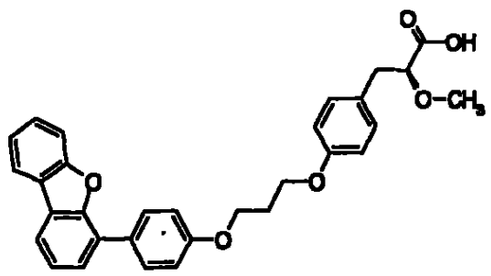
Step B

(2S)-3-{4-[3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 3',5'-Bis-trifluoromethyl-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{24}F_6O_5$ $[M+Na]^+$: 565, $[M+H]^+$: 543.

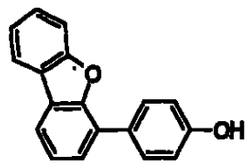
Example 214

(2S)-3-{4-[3-(4-Dibenzofuran-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

4-Dibenzofuran-4-yl-phenol



The title compound was prepared following the procedure described in Example 211, Step B with 4-dibenzofurane boronic acid.

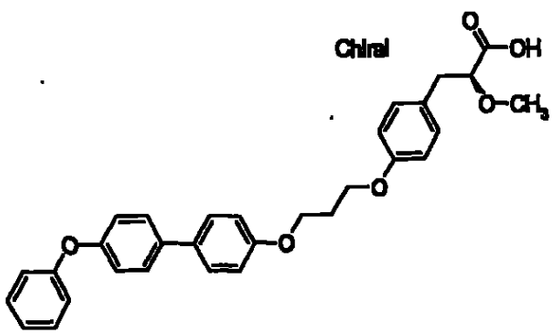
Step B

(2S)-3-{4-[3-(4-Dibenzofuran-4-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from 0, Step A was treated with 4-Dibenzofuran-4-yl-phenol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{31}H_{30}O_6$ $[M+Na]^+$: 519.

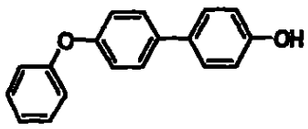
Example 215

(2S)-2-Methoxy-3-{4-[3-(4'-phenoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid



Step A

4'-Phenoxy-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 4-phenoxyphenyl boronic acid.

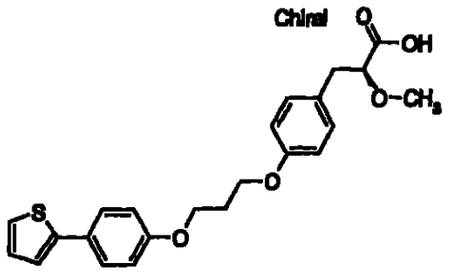
Step B

(2S)-2-Methoxy-3-{4-[3-(4'-phenoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4'-Phenoxy-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{31}H_{30}O_6$ $[M+NH_4]^+$: 516, $[M+Na]^+$: 521.

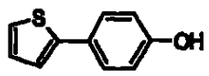
Example 216

(2S)-2-Methoxy-3-{4-[3-(4-thiophen-2-yl-phenoxy)-propoxy]-phenyl}-propionic acid



Step A

4-Thiophen-2-yl-phenol



The title compound was prepared following the procedure described in Example 211, Step B with tiophene-2-boronic acid.

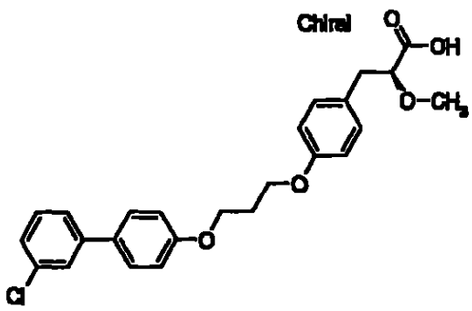
Step B

(2S)-2-Methoxy-3-{4-[3-(4-thiophen-2-yl-phenoxy)-propoxy]-phenyl}-propionic acid

2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-Thiophen-2-yl-phenol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{23}H_{24}O_5S$ $[M+NH_4]^+$: 430, $[M+Na]^+$: 435.

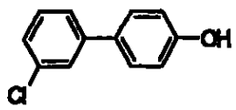
Example 217

(2S)-3-{4-[3-(3'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

3'-Chloro-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 3-chlorophenyl boronic acid.

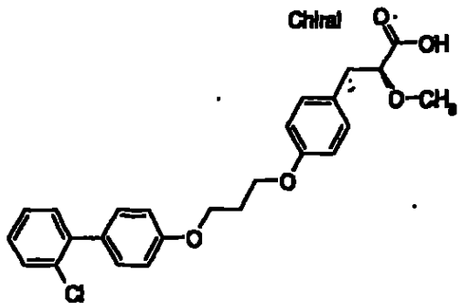
Step B

(2S)-3-{4-[3-(3'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from 0, Step A was treated with 3'-Chloro-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{25}ClO_5$ $[M+NH_4]^+$: 458, $[M+Na]^+$: 463.

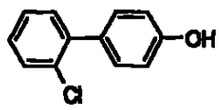
Example 218

(2*S*)-3-{4-[3-(2'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

2'-Chloro-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 2-chlorophenyl boronic acid

Step B

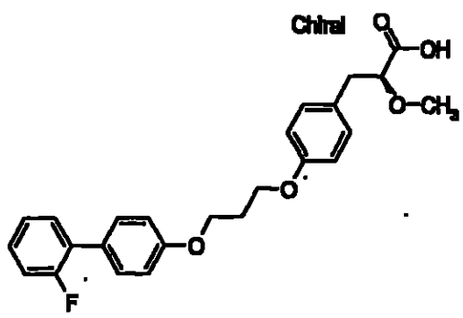
(2*S*)-3-{4-[3-(2'-Chloro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 2-Chloro-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under

Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{25}ClO_5$ $[M+NH_4]^+$: 458, $[M+Na]^+$: 463.

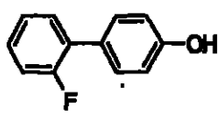
Example 219

(2S)-3-{4-[3-(2'-Fluoro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

2'-Fluoro-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 2-fluorophenyl boronic acid

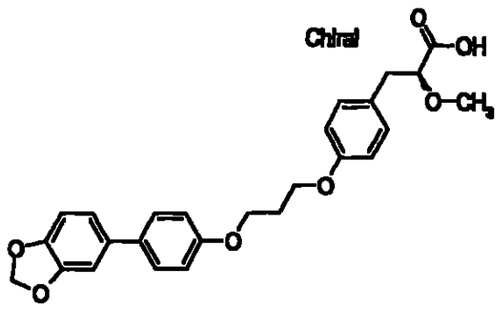
Step B

(2S)-3-{4-[3-(2'-Fluoro-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 2-fluoro-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{25}FO_5$ $[M+NH_4]^+$: 442, $[M+Na]^+$: 447.

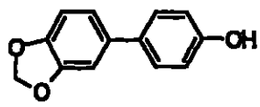
Example 220

(2S)-3-{4-[3-(4-Benzo[1,3]dioxol-5-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

4-Benzo[1,3]dioxol-5-yl-phenol



The title compound was prepared following the procedure described in Example211, Step B with 3,4-methylenedioxophenyl boronic acid

Step B

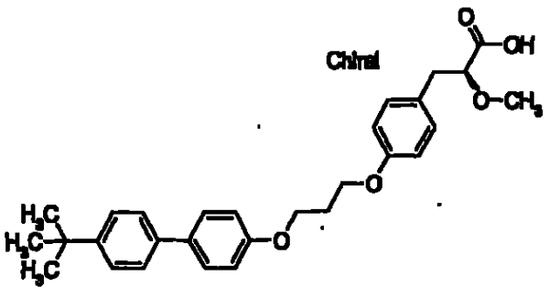
(2S)-3-{4-[3-(4-Benzo[1,3]dioxol-5-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-Benzo[1,3]dioxol-5-yl-phenol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{26}H_{26}O_7$ $[M+NH_4]^+$: 468, $[M+Na]^+$: 473.

Example 221

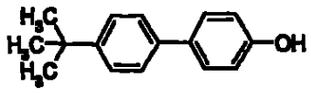
(2S)-3-{4-[3-(4'-tert-Butyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

320



Step A

4'-tert-Butyl-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 4-*tert*-butylphenyl boronic acid

Step B

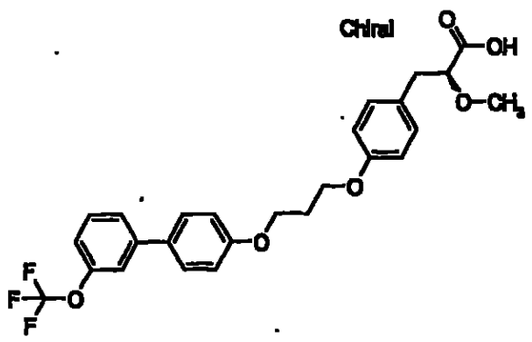
(2*S*)-3-{4-[3-(4'-tert-Butyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4'-*tert*-Butyl-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{29}H_{34}O_5$ $[M+NH_4]^+$: 480, $[M+Na]^+$: 485.

Example 222

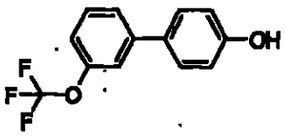
(2*S*)-2-Methoxy-3-{4-[3-(3'-trifluoromethoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid

321 300



Step A

3'-Trifluoromethoxy-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 3-trifluoromethoxybenzebe boronic acid

Step B

(2S)-2-Methoxy-3-{4-[3-(3'-trifluoromethoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid

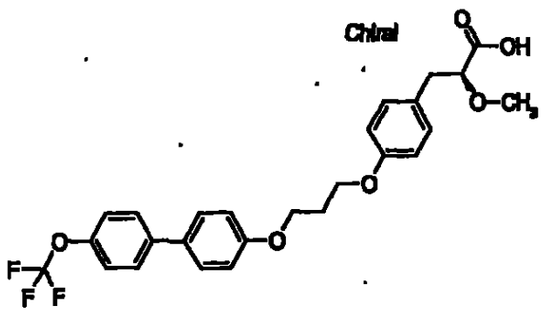
(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 3'-Trifluoromethoxy-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound.

MS(ES) for $C_{25}H_{25}F_3O_6$ $[M+Na]^+$: 513, $[M+H]^+$: 491.

Example 223

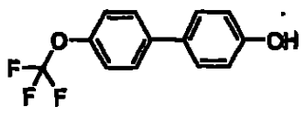
(2S)-2-Methoxy-3-{4-[3-(4'-trifluoromethoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid

322



Step A

4'-Trifluoromethoxy-biphenyl-4-ol



The title compound was prepared following the procedure described in Example 211, Step B with 4-trifluoromethoxybenzene boronic acid

Step B

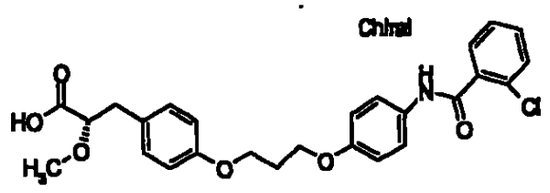
(2*S*)-2-Methoxy-3-{4-[3-(4'-trifluoromethoxy-biphenyl-4-yloxy)-propoxy]-phenyl}-propionic acid

2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4'-Trifluoromethoxy-biphenyl-4-ol from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound.

MS(ES) for $C_{26}H_{25}F_3O_6$ $[M+NH_4]^+$: 508, $[M+Na]^+$: 513.

Example 224

(2*S*)-3-(4-{3-[4-(2-Chloro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



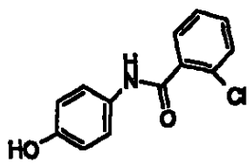
Step A

p-Aminophenol linked to Wang's resin

A suspension of Wang's resin in THF/CH_2Cl_2 was treated with DIAD (5 eq), Ph3P (5 eq) and p-nitrophenol(5 eq). The mixture was stirred overnight and then the resin was filtered through and washed with MeOH/CH_2Cl_2 several times. After dried the resin was suspended in DMF and treated with SnCl2 (10 eq) and stirred again overnight. Filtered and washed with MeOH/CH_2Cl_2 several times and dried to give th product.

Step B

2-Chloro-N-(4-hydroxy-phenyl)-benzamide



A suspension of p-aminophenol linked to the Wang's resin from Step A (1 eq) in dichloromethane was treated with triethylamine (2ml/mmol) and 2-chloro-benzoyl chloride (10 eq). The mixture reaction was stirred for 1 hour and then the resin was filtered, washed with MeOH/CH_2Cl_2 several times and dried. The resin was then treated with TFA 95%/H_2O 5% and stirred at room temperature for 30 minutes. Filtered and washed with dichloromethane/methanol and concentrated to dryness to afford the title compound.

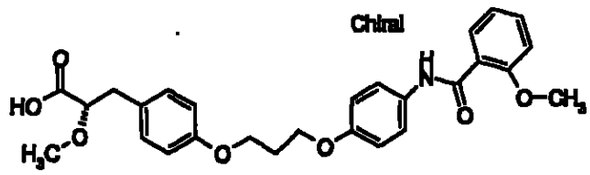
Step C

(2S)-3-{4-{3-[4-(2-Chloro-benzoylamino)-phenoxy]-propoxy}-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 2-Chloro-N-(4-hydroxy-phenyl)-benzamide from Step B under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{26}H_{26}ClNO_6$ $[M+H]^+$: 484.

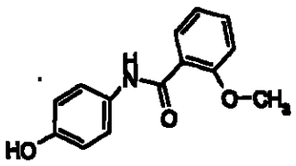
Example 225

(2*S*)-2-Methoxy-3-(4-{3-[4-(2-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

N-(4-Hydroxy-phenyl)-2-methoxy-benzamide



The title compound was prepared following the procedure described in 0, Step B with 2-methoxy-benzoyl chloride.

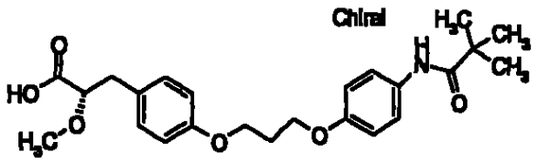
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4-(2-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with N-(4-Hydroxy-phenyl)-2-methoxy-benzamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{29}NO_7$ $[M+H]^+$: 480.

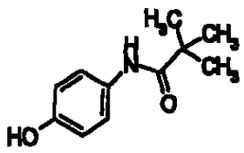
Example 226

(2*S*)-3-(4-{3-[4-(2,2-Dimethyl-propionylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

N-(4-Hydroxy-phenyl)-2,2-dimethyl-propionamide



The title compound was prepared following the procedure described in Example 224, Step B with 2,2-Dimethyl-propionyl chloride.

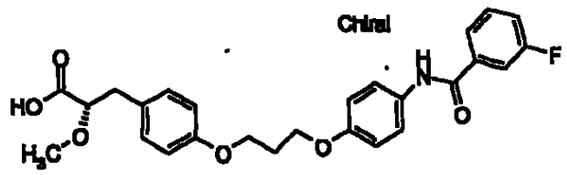
Step B

(2*S*)-3-(4-{3-[4-(2,2-Dimethyl-propionylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with N-(4-Hydroxy-phenyl)-2,2-dimethyl-propionamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{24}H_{31}NO_6$ $[M+H]^+$: 430.

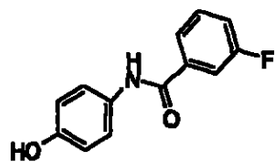
Example 227

(2*S*)-3-(4-{3-[4-(3-Fluoro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

3-Fluoro-N-(4-hydroxy-phenyl)-benzamide



The title compound was prepared following the procedure described in Example 224, Step B with 3-Fluoro-benzoyl chloride.

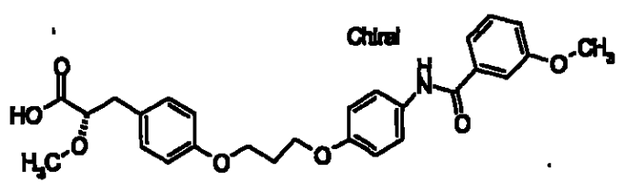
Step B

(2*S*)-3-(4-{3-[4-(3-Fluoro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 3-Fluoro-N-(4-hydroxy-phenyl)-benzamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{26}H_{26}FNO_6$ $[M+H]^+$: 468.

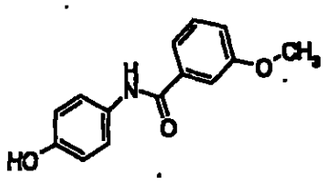
Example 228

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

N-(4-Hydroxy-phenyl)-3-methoxy-benzamide



The title compound was prepared following the procedure described in Example 224, Step B with 3-methoxy-benzoyl chloride.

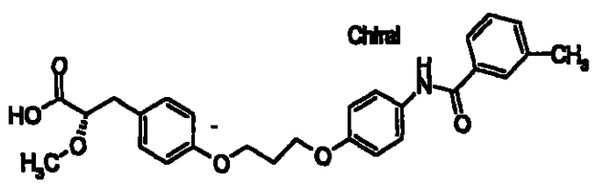
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methoxy-benzoylamino)-phenoxyl-propoxy}-phenyl)-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with N-(4-Hydroxy-phenyl)-3-methoxy-benzamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{29}NO_7$ $[M+H]^+$: 480.

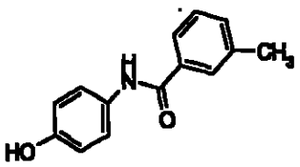
Example 229

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methyl-benzoylamino)-phenoxyl-propoxy}-phenyl)-propionic acid



Step A

N-(4-Hydroxy-phenyl)-3-methyl-benzamide



The title compound was prepared following the procedure described in Example 224, Step B with 3-methyl-benzoyl chloride.

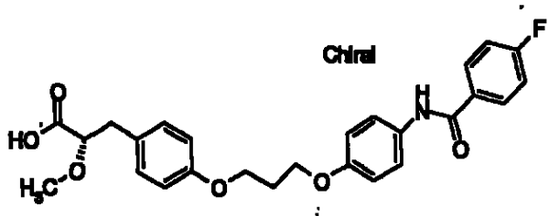
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methyl-benzoylamino)-phenoxyl-propoxy}-phenyl)-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with N-(4-Hydroxy-phenyl)-3-methyl-benzamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{29}NO_6$ $[M+H]^+$: 464.

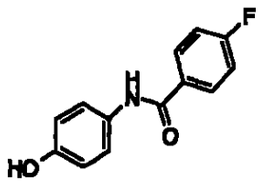
Example 230

(2*S*)-3-{4-{3-[4-(4-Fluoro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

4-Fluoro-N-(4-hydroxy-phenyl)-benzamide



The title compound was prepared following the procedure described in Example 224, Step B with 4-Fluoro-benzoyl chloride.

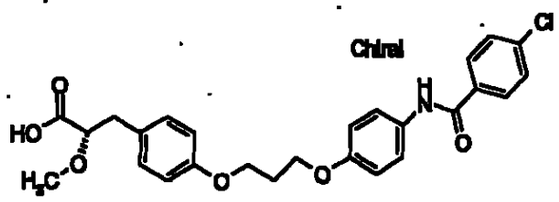
Step B

(2S)-3-{4-{3-[4-(4-Fluoro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-Fluoro-N-(4-hydroxy-phenyl)-benzamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{26}H_{26}FNO_6$ $[M+H]^+$: 468.

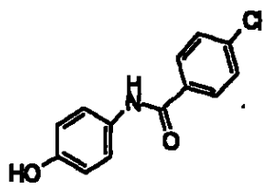
Example 231

(2*S*)-3-(4-{3-[4-(4-Chloro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

4-Chloro-N-(4-hydroxy-phenyl)-benzamide



The title compound was prepared following the procedure described in Example 224, Step B with 4-chloro-benzoyl chloride.

Step B

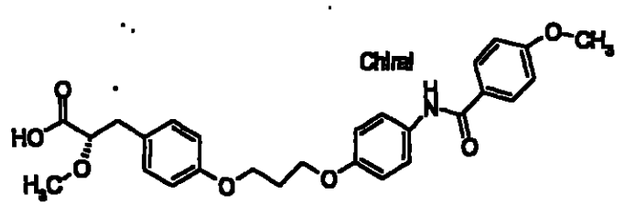
(2*S*)-3-(4-{3-[4-(4-Chloro-benzoylamino)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-chloro-N-(4-hydroxy-phenyl)-benzamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{24}ClNO_6$ $[M+H]^+$: 484.

Example 232

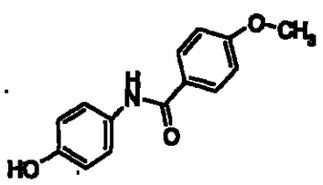
(2*S*)-2-Methoxy-3-(4-{3-[4-(4-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid

330



Step A

N-(4-Hydroxy-phenyl)-4-methoxy-benzamide



The title compound was prepared following the procedure described in Example 224, Step B with 4-methoxy-benzoyl chloride.

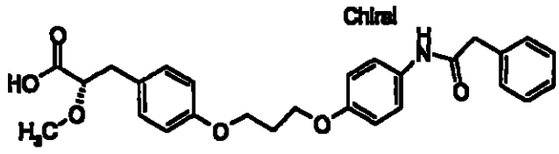
Step B

(2*S*)-2-Methoxy-3-{4-[3-[4-(4-methoxy-benzoylamino)-phenoxy]-propoxy}-phenyl)-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 4-methoxy-N-(4-hydroxy-phenyl)-benzamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{29}NO_7$ $[M+H]^+$: 480.

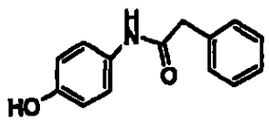
Example 233

(2*S*)-2-Methoxy-3-{4-[3-(4-phenylacetylamino-phenoxy)-propoxy]-phenyl}-propionic acid



Step A

N-(4-Hydroxy-phenyl)-2-phenyl-acetamide



The title compound was prepared following the procedure described in Example 224, Step B with Phenyl-acetyl chloride.

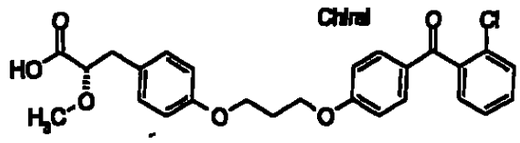
Step B

(2*S*)-2-Methoxy-3-{4-[3-(4-phenylacetylamino-phenoxy)-propoxy]-phenyl}-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with N-(4-Hydroxy-phenyl)-2-phenyl-acetamide from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{29}NO_6$ $[M+H]^+$: 484.

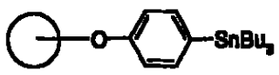
Example 234

(2*S*)-3-(4-{3-[4-(2-Chloro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

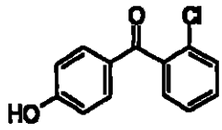
4-Tributylstannanyl-phenol linked to Wang's resin



p-Iodophenol linked to Wang's resin from Example 211, Step A, was suspended in toluene and bis-tributyltin was added (5 eq). The mixture reaction was stirred at 100°C overnight. Then filtered through and the resin was washed with CH_2Cl_2/MeOH/Hexane/MeOH/CH_2Cl_2 to give the compound.

Step B

(2-Chloro-phenyl)-(4-hydroxy-phenyl)-methanone



4-Tributylstannanyl-phenol linked to Wang's resin from Step A (1 eq), $Pd_2(dba)_3$ (0.3 eq) and K_2CO_3 (70 mg) were suspended in THF/Diisopropilmethylamine. To this mixture 2-chloro-benzoyl chloride was added and stirred for 2 hours. The suspension was filtered and the resin washed with MeOH/CH_2Cl_2/DMF, then HCl diluted/dioxane and Na_2CO_3 5%(dioxane) and DMF/MeOH/CH_2Cl_2. Once the resin was dried TFA 95% and CH_2Cl_2 were added and the mixture stirred at room temperature for 30 min. The resin was filtered and washed with MeOH/CH_2Cl_2. The solvents were collected and concentrated to dryness to give the title product.

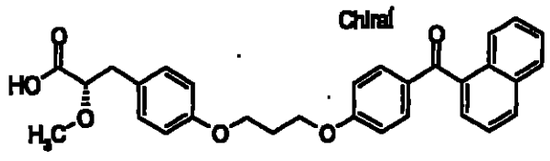
Step C

(2*S*)-3-(4-{3-[4-(2-Chloro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with (2-Chloro-phenyl)-(4-hydroxy-phenyl)-methanone from Step B under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{25}ClO_6$ $[M+NH_4]^+$: 491,$[M+H]^+$: 469.

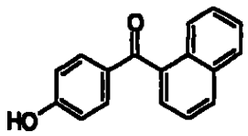
Example 235

(2*S*)-2-Methoxy-3-(4-{3-[4-(naphthalene-1-carbonyl)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

(4-Hydroxy-phenyl)-naphthalen-1-yl-methanone



The title compound was prepared following the procedure described in Example 234, Step B with naphthalene-1-carbonyl chloride.

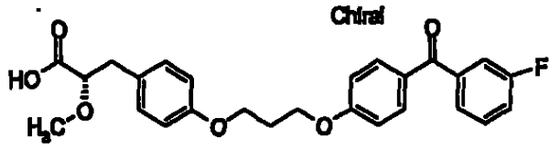
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4-(naphthalene-1-carbonyl)-phenoxy]-propoxy}-phenyl)-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with (4-Hydroxy-phenyl)-naphthalen-1-yl-methanone from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{30}H_{28}O_6$ $[M+NH_4]^+$: 507,$[M+H]^+$: 485.

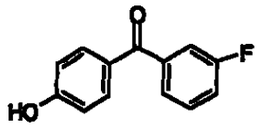
Example 236

(2*S*)-3-(4-{3-[4-(3-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

(3-Fluoro-phenyl)-(4-hydroxy-phenyl)-methanone



The title compound was prepared following the procedure described in Example 234, Step B with 3-Fluoro-benzoyl chloride.

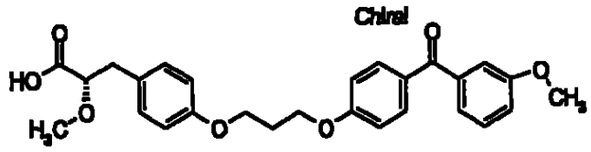
Step B

(2*S*)-3-(4-{3-[4-(3-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with (3-Fluoro-phenyl)-(4-hydroxy-phenyl)-methanone from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{25}FO_5$ $[M+H]^+$: 453.5.

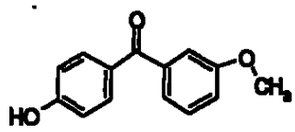
Example 237

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methoxy-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

(4-Hydroxy-phenyl)-(3-methoxy-phenyl)-methanone



The title compound was prepared following the procedure described in Example 234, Step B with 3-methoxy-benzoyl chloride.

Step B

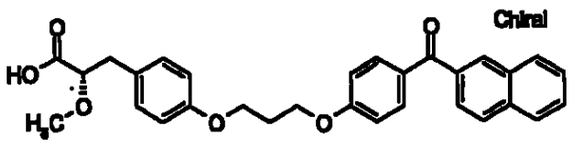
(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methoxy-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with (4-Hydroxy-phenyl)-(3-methoxy-phenyl)-methanone from Step A under the Standard Procedure J. The compound thus

obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{28}O_7$ $[M+H]^+$: 465.

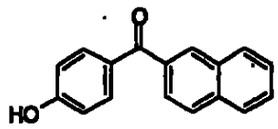
Example 238

(2*S*)-2-Methoxy-3-(4-{3-[4-(naphthalene-2-carbonyl)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

(4-Hydroxy-phenyl)-naphthalen-2-yl-methanone



The title compound was prepared following the procedure described in Example 234, Step B with naphthalene-2-carbonyl chloride.

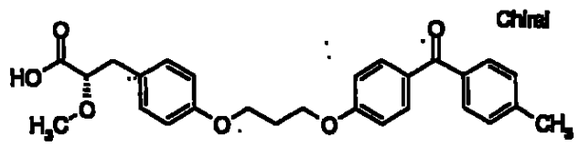
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4-(naphthalene-2-carbonyl)-phenoxy]-propoxy}-phenyl)-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with (4-Hydroxy-phenyl)-naphthalen-2-yl-methanone from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{30}H_{28}O_6$ $[M+H]^+$: 485.

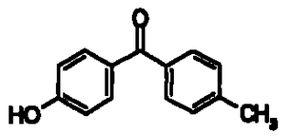
Example 239

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-methyl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

(4-Hydroxy-phenyl)-p-tolyl-methanone



The title compound was prepared following the procedure described in Example 234, Step B with 4-methyl-benzoyl chloride.

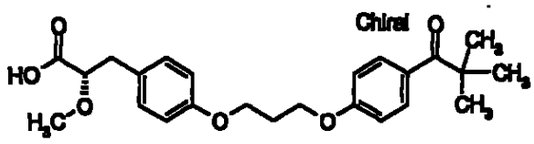
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4-(4-methyl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with (4-Hydroxy-phenyl)-p-tolyl-methanone from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{27}H_{28}O_6$ $[M+NH_4]^+$: 471 $[M+H]^+$: 449.

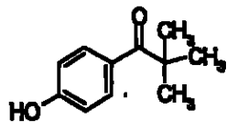
Example 240

(2*S*)-3-(4-{3-[4-(2,2-Dimethyl-propionyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

1-(4-Hydroxy-phenyl)-2,2-dimethyl-propan-1-one



The title compound was prepared following the procedure described in Example 234, Step B with 2,2-Dimethyl-propionyl chloride.

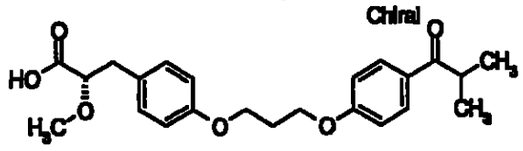
Step B

(2S)-3-{4-{3-[4-(2,2-Dimethyl-propionyl)-phenoxy]-propoxy}-phenyl}-2-methoxy-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 1-(4-Hydroxy-phenyl)-2,2-dimethyl-propan-1-one from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{24}H_{30}O_6$ $[M+NH_4]^+$: 437 $[M+H]^+$: 415.

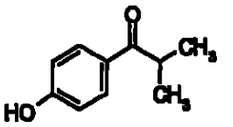
Example 241

(2S)-3-{4-[3-(4-Isobutyryl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

1-(4-Hydroxy-phenyl)-2-methyl-propan-1-one



The title compound was prepared following the procedure described in Example 234, Step B with Isobutyryl chloride.

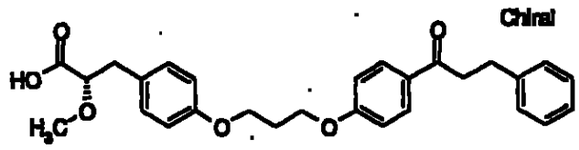
Step B

(2*S*)-3-{4-[3-(4-Isobutyryl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 1-(4-Hydroxy-phenyl)-2-methyl-propan-1-one from Step A under the Standard Procedure J. The compound thus obtained was allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{25}H_{28}O_6$ $[M+NH_4]^+$: 423 $[M+H]^+$: 401.

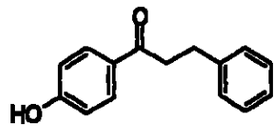
Example 242

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-phenyl-propionyl)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

1-(4-Hydroxy-phenyl)-3-phenyl-propan-1-one



The title compound was prepared following the procedure described in Example 234, Step B with 3-Phenyl-propionyl chloride.

Step B

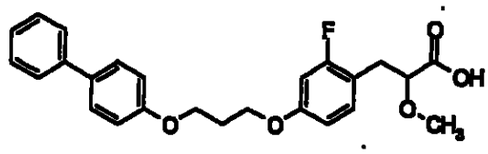
(2*S*)-2-Methoxy-3-(4-{3-[4-(3-phenyl-propionyl)-phenoxy]-propoxy}-phenyl)-propionic acid

(2S)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester from Example 173, Step A was treated with 1-(4-Hydroxy-phenyl)-3-phenyl-propan-1-one from Step A under the Standard Procedure J. The compound thus obtained was

allowed to react under Standard hydrolysis procedure C (NaOH) to give the title compound. MS(ES) for $C_{28}H_{30}O_6$ $[M+NH_4]^+$: 485 $[M+H]^+$: 463.

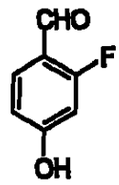
Example 243

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-propionic acid



Step A

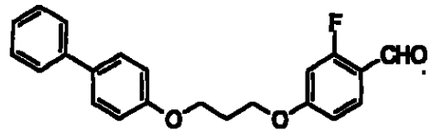
2-Fluoro-4-hydroxy-benzaldehyde



2-Fluoro-4-methoxy-benzaldehyde (1 g, 6.49 mmol) was added to a suspension of anhydrous potassium iodide (2.15 g, 13 mmol) and aluminum trichloride (1.04 g, 7.8 mmol) in anhydrous toluene (10 mL), and the mixture was stirred at 40°C for 3 hours. Aluminum trichloride (2.15 g, 13 mmol) and anhydrous potassium iodide (0.86 g, 6.49 mmol) were added, and the mixture was stirred for 3 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 X 20 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 4:1) to give 2-fluoro-4-hydroxy-benzaldehyde as a white solid (260 mg, 29%). ^{1}H NMR (200 MHz, Acetone-d_6): δ 10.08 (s, 1H), 9.77 (b, 1H), 7.69 (t, 1H, J=8.4), 6.78 (dd, 1H, *J*=8.8, 2.6), 6.65 (dd, 1H, *J*=12.5, 2.2)ppm.

Step B

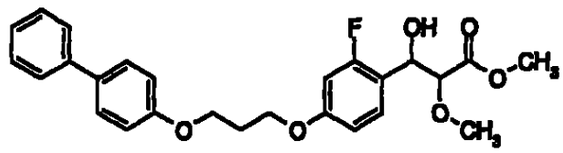
4-[3-(Biphenyl-4-yloxy)-propoxy]-2-fluoro-benzaldehyde



Potassium *tert*-butoxide (0.217 g, 1.93 mmol) was added to a solution of 2-fluoro-4-hydroxy-benzaldehyde (0.246 g, 1.76 mmol) in anhydrous DMF (5 mL) at 0°C, and the mixture was stirred for 30 min. 4-(3-Bromo-propoxy)-biphenyl (0.564 g, 1.93 mmol, Example 132, Step D) was added, and the mixture stirred at room temperature for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc (5 X 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 4:1) to give 4-[3-(biphenyl-4-yloxy)-propoxy]-2-fluoro-benzaldehyde as a white solid (540 mg, 88%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.19 (s, 1H), 7.80 (t, 1H, *J*=8.4); 7.55-7.48 (m, 4H); 7.42-7.27 (m, 3H); 6.99-6.93 (m, 2H); 6.78 (dd, 1H, *J*=8.8, 2.6); 6.64 (dd, 1H, *J*=12.4, 2.2); 4.27-4.15 (m, 4H); 2.30 (qn, 2H, *J*=5.9)ppm.

Step C

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-3-hydroxy-2-methoxy-propionic acid methyl ester

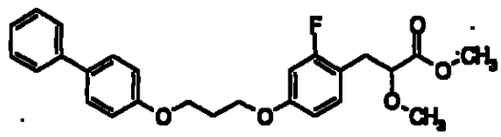


A solution of 4-[3-(biphenyl-4-yloxy)-propoxy]-2-fluoro-benzaldehyde (0.320 g, 0.91 mmol) and methyl methoxyacetate (0.099 mL, 1 mmol) in THF (10 mL) at -78°C was added dropwise to sodium bis(trimethylsilyl)amide (1 mL, 1 mmol, 1N in THF) at -78°C. The reaction mixture was stirred for 3 hours, quenched with 1N HCl (1 mL), and allowed to warm to room temperature. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 2:1) to

give a 1:1 diastereomeric mixture of 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-3-hydroxy-2-methoxy-propionic acid methyl ester as a white solid (250 mg, 60%). ^{1}H NMR (200 MHz, $CDCl_3$): 7.55-7.47 (m, 4H), 7.42-7.23 (m, 4H), 6.95 (d, 2H, *J*=8.4), 6.73-6.66 (m, 1H), 6.59 (dd, 1H, *J*=12.4, 2.6), 5.19 (dd, 1H, *J*=15.4, 4.8), 4.18-4.04 (m, 4H), 3.93 (d, 1H, *J*=5.1), 3.68 and 3.63 (2 s, 3H), 3.39 and 3.37 (2 s, 3H), 3.12 (b, 1H), 2.24 (qn, 2H, *J*=6.2)ppm.

Step D

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-propionic acid methyl ester



Trifluoroacetic anhydride (0.043 mL, 0.37 mmol) and pyridine (0.074 mL, 0.93 mmol) were added to a solution of 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-3-hydroxy-2-methoxy-propionic acid methyl ester (0.142 g, 0.31 mmol) in methylene chloride (1 mL) at 0°C. The resulting mixture was stirred for 4 hours at room temperature and was concentrated under vacuum. The residue was dissolved in ethyl acetate (50 mL) and 10% palladium on carbon (0.064 g) was added to the solution. The mixture was stirred under hydrogen pressure (5 atm) for 16 hours. The mixture was filtered through celite and concentrated under vacuum. The residue was purified by silica gel chromatography (silica gel, hexanes/ethyl acetate 4:1) to give 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-propionic acid methyl ester as a white solid (30 mg, 22 %). ^{1}H NMR (200 MHz, $CDCl_3$): 7.60-7.50 (m, 4H); 7.46-7.27 (m, 3H); 7.18-7.09 (m, 1H); 7.03-6.96 (m, 2H); 6.70-6.61 (m, 2H); 4.17 (dt, 4H, *J*=9.1, 6.2); 4.00 (dd, 1H, *J*=7.3, 5.9); 3.74 (s, 3H); 3.37 (s, 3H); 3.13-2.93 (m, 2H); 2.28 (qn, 2H, *J*=6.2).

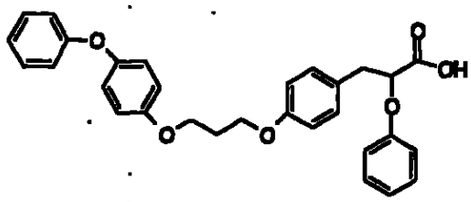
Step E

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-propionic acid

1N aqueous lithium hydroxide solution (1.37 mL) was added to a solution of 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-propionic acid methyl ester (0.075 g, 0.17 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred overnight, diluted with water (10 mL), and extracted with diethyl ether (3 X 20 mL). The aqueous layer was acidified with 1N HCl to pH 1 and extracted with ethyl acetate (3 X 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-propionic acid as a white solid (60mg, 83%). ^1H NMR (200 MHz, $CDCl_3$): 7.56-7.29 (m, 7H), 7.18-7.09 (m, 1H), 6.98 (d, 2H, *J*=8.6), 6.66-6.60 (m, 2H), 4.17 (dt, 4H, *J*=8.9, 5.9), 4.03 (dd, 1H, *J*=6.7, 4.8), 3.40 (s, 3H), 3.23-3.14 (m, 1H), 2.97 (dd, 1H, *J*=14.0, 6.7), 2.26 (q, 2H, *J*=5.9)ppm.

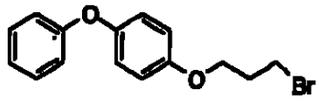
Example 244

2-phenoxy-3-[4-(4-phenoxy-phenoxy)propoxyphenyl]propanoic acid



Step A

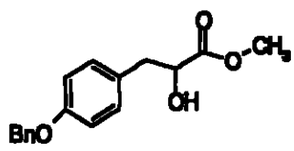
1-(3-bromopropoxy)-4-phenoxybenzene



The title compound was prepared from 4-phenoxyphenol following the same procedure as in Example 132, Step D. ^1H-NMR (200.15 MHz, $CDCl_3$): δ 7.35-7.25 (m, 2H), 7.09-6.87 (m, 7H), 4.10 (t, 2H, J=5.9), 3.62 (t, 2H, J=6.1), 2.55-2.21 (m, 2H)ppm.

Step B

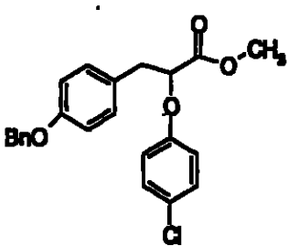
4-Benzyloxyphenyl-2-hydroxypropanoic acid methyl ester



A solution of DL-4-hydroxyphenyllactic acid (0.5 g, 2.74mmol) was stirred over night in MeOH/HCl saturated solution. The reaction was concentrated to dryness and the crude product (0.545 g, 2.7 mmol) was treated with K_2CO_3 (3 eq.) and benzyl bromide (0.507 g, 2.97 mmol) in acetonitrile (20 ml) and refluxed overnight. The crude reaction was filtered off and concentrated to produce a crude product. The residue was purified by chromatography (silca-gel, hexanes/Ethyl acetate (3:1) to give a white oil (97%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.43-7.35 (m, 5H), 7.14 (d, 2H, J=8.59), 6.92 (d, 2H, J=8.59), 5.04 (s, 2H), 4.42 (dd, 1H, J=10.7, 6.1), 2.97 (ddd, 2H, J=4.5, 13.9, 31.1)2.73 (d, 1H, J=6.1).

Step C

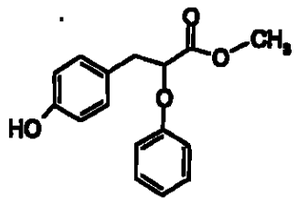
4-Benzyloxyphenyl-2-(4-chlorophenoxy)propanoic acid methyl ester



A solution of triphenylphosphine (0.1 g, 0,38 mmol) in 5 ml of dry THF was treated at 0°C with DEAD (0.066 g, 0.38 mmol) and stirred over 30 min. Then a solution of 4-Benzyloxyphenyl-2-hydroxypropanoic acid methyl ester (0.1 g, 0.35 mmol) and p-chlorophenol (0.048 g, 0.38 mmol) in 2 ml of THF was added to the solution and the mixture reaction was stirred at room temperature overnight. The mixture was concentrated to dryness and chromatographed in silicagel (hexanes/Ethyl acetate 3:1) to give 0.082 g of product (60%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.46-7.31 (m, 5H), 7.28-7.13 (m, 4H), 6.93 (d, 2H, J=8.8), 6.75 (d, 2H, J=8.8), 5.04 (s, 2H), 4.73(t, 1H, J=6.1), 3.71 s (s, 3H), 3.18 (d, 2H, J=6.4).

Step D

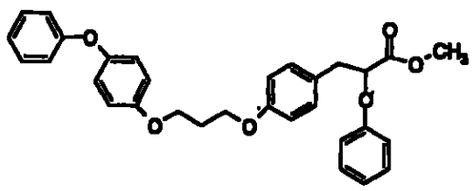
4-Hydroxyphenyl-2-phenoxypropanoic acid methyl ester



A solution of 4-Benzyloxyphenyl-2-(4-chlorophenoxy) propanoic acid methyl ester in ethanol with 10% Pd/C (5 wt%) was stirred under hydrogen atmosphere (1tm) over 2 hours. The catalyst was removed via filtration through a pad of celite and the filtrated concentrated in vacuo to produce the title compound (90%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.25-7.14 (m, 4H), 7.94-7.73 (m, 4H), 4.81-4.69 (m, 1H), 3.70 (s, 3H), 3.16 (d, 2H, *J*=4.1).

Step E

2-phenoxy-3-[4-(4-phenoxy phenoxy)propoxyphenyl] propanoic acid methyl ester



A mixture of 3-(4-hydroxyphenyl)-2-phenoxypropanoic acid methyl ester (0.055 g, 0.18 mmol) with 1-(3-bromopropoxy)-4-phenoxybenzene (Step A)(0.055 g, 0.18 mmol) and potassium tert-butoxide (0.020 g, 0.18 mmol) were stirred in DMF (5 mL) overnight. The mixture reaction concentrated in vacuo with toluene (2 times), reconstituted in Ethyl acetate and washed with water (3 times) and brine, dryed (Na_2SO_4) and concentrated to afford a crude product that was purified by chromatographied in silicagel (hexanes/ Ethyl acetate, 3:1) to give 0.022 g of the title compound (23%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.34-7.15 (m, 6H), 7.07-6.71 (m, 12H), 4.80-4.68 (m, 1H), 4.13 (t, 4H, J=15.1), 3.71 (s, 3H), 3.20-3.15 (m, 2H), 2.30-2.18 (q, 2H).

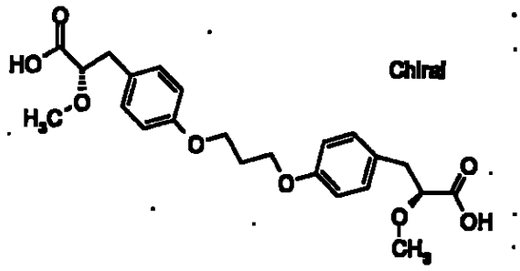
Step F

2-phenoxy-3-[4-(4phenoxy phenoxy)propoxyphenyl] propanoic acid

The title compound was prepared from 2- phenoxy-3-[4-(4phenoxy phenoxy)propoxyphenyl] propanoic acid methyl ester (0.022 g, 0.04 mmol) That was stirred with an excess of LiOH 3N (5 eq.)in THF (3 ml) overnight. The solution was acidulate with HCl 1N (to pH 1-2) and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated under vacuum to produce an oily solid (80%). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.33-7.16 (m, 6H), 7.03-6.70 (m, 12H), 4.84-4.71 (m, 1H), 4.13 (t, 4H, J= 6.1), 3.24-3.19 (m, 2H)ppm.

Example 245

(2S,2'S)-3-(4-{3-[4-(2'-Carboxy-2'-methoxy-ethyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

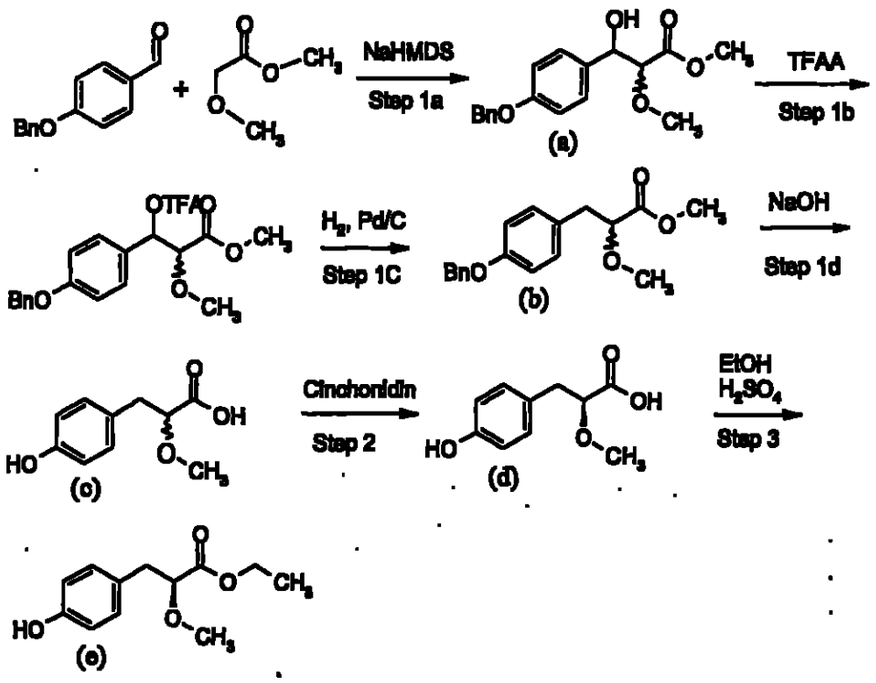


A mixture of (2S)-3-[4-(3-hydroxy-phenyl]-2-methoxypropionic acid ethyl ester (2 eq), and propylene glycol (1.3 eq) were allowed to react under the Standard Mitsonobu coupling conditions B (DIAD/Tohuene), and the resulting product of this reaction was treated following the Standard hydrolysis conditions C to give the title compound. MS(ES) for $C_{23}H_{28}O_8$ $[M+NH_4]^+$: 450, $[M+H]^+$: 433.

Example 246

Synthesis of α-Methoxycinnamate Intermediate, ethyl 2S-2-methoxy-3-(4-hydoxyphenyl) propanoate (e)

Scheme



Step 1a: methyl 3-hydroxy-2-methoxy-3-[4-(phenylmethoxy)phenyl]propanoate (a)

Sodium bis-(trimethylsilyl)amide (440 ml, 0.44 mol, 1.0 M in THF) was cooled to -70°C under a nitrogen atmosphere. A solution of 4-benzyloxybenzaldehyde (85 g, 0.4mol) and methyl methoxyacetate (52 g, 0.5mol) in THF (0.5 L) was added dropwise at -70°C over 2 hours, and the mixture was stirred for an hour. A solution of concentrated HCl (85 mL) and water (85 mL) was added at -70°C. The resulting solution was allowed to warm to ambient temperature and was extracted with MTBE (2 x 0.5 L). The combined extracts were washed with brine (0.5 L), dried ($MgSO_4$), filtered, and concentrated under to give 133g of a red oil.

Step 1b and Step 1c: methyl 3-(4-hydroxyphenyl)-2-methoxypropanoate (b)

Methyl 3-hydroxy-2-methoxy-3-[4-(phenylmethoxy)phenyl]propanoate (133 g, crude from above) was dissolved in CH_2Cl_2 (700 mL), and pyridine (129 mL, 1.6 mol) was added. The resulting solution was cooled in a water bath and trifluoroacetic anhydride (85 mL, 0.6 mol) was added dropwise under nitrogen. The

bath was removed, and the mixture was stirred at ambient temperature for 16 hours. The solution was cooled to 0°C and concentrated HCl (150 mL) in water (1 L) was added dropwise. The organic layer was separated and concentrated, and ethyl acetate (0.5 L) was added. The resulting solution was treated with hydrogen gas under 50 psi in the presence of 5% Pd-C (80 g, 50% water wet) at ambient temperature for 16 hours. The catalyst was filtered, and the filtrate was concentrated under vacuum to give 122 g oil. ^{1}H-NMR ($CDCl_3$): 7.1 (2H, d); 6.7 (d, 2H); 5.4 (s, 1H); 4.0 (m, 1H); 3.7 (s, 3H); 3.4 (s, 3H); 3.0 (m, 1H). MS (ES)=209.2 (M-1).

Step 1d: 3-(4-hydroxyphenyl)-2-methoxypropanoic acid (c)

Methyl 3-(4-hydroxyphenyl)-2-methoxypropanoate (132 g, 0.631 mol) was dissolved in methanol (700 mL) and 5N sodium hydroxide (631 mL, 3.16 mol) was added dropwise at ambient temperature. The solution was stirred for 16 hours at ambient temperature. The methanol was removed under vacuum, and water (500 mL) was added. The mixture was extracted with MTBE (2 x 500 mL). The aqueous solution was brought to pH=1 with concentrated HCl and then extracted with MTBE (2 x 500 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum to give the racemic acid as an oil (110 g) which was crystallized upon standing. ^{1}H-NMR (DMSO): 7.0 (d, 2H); 6.6 (d, 2H); 4.0 (m, 1H); 2.8 (m, 2H). MS (ES)= 195.1 (M-1).

Step 2: (2S)-3-(4-hydroxyphenyl)-2-methoxypropanoic acid (d)

Cinchonidine salt of (2S)-3-(4-hydroxyphenyl)-2-methoxypropanoic acid.

A slurry consisting of 3-(4-hydroxyphenyl)-2-methoxypropanoic acid (21.21 g, 0.1081 mol), (-)-cinchonidine (31.83 g, 0.1081 mol), and THF (424 mL) was heated briefly at reflux to give a red-brown solution. The mixture was cooled to ambient temperature and stirred for 3 days. The resulting slurry was cooled to 0°C for 4 hours and filtered to give about 17.06 g of the cinchonidine salt (71.2% ee by chiral HPLC). The cinchonidine salt was slurried in THF, heated to reflux for 1 hour, and cooled to ambient temperature overnight. The mixture was cooled to 0°C for 2

hours and filtered to give about 14.87 g of the cinchonidine salt (83.0% ee by chiral HPLC). The cinchonidine salt was slurried again in THF, and heated to reflux for 1 hour, and cooled to ambient temperature. The mixture was cooled to 0 °C for 2 hours and filtered to give about 12.87 g (24%) of the cinchonidine salt of (2S)-3-(4-hydroxyphenyl)-2-methoxypropanoic acid (91.4% ee by chiral HPLC).

(2S)-3-(4-hydroxyphenyl)-2-methoxypropanoic acid

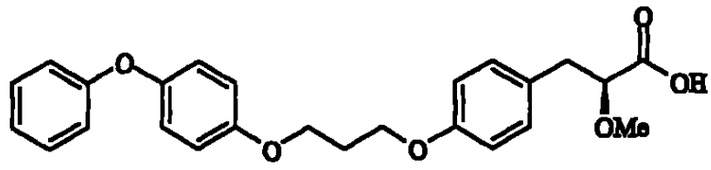
The cinchonidine salt of (2S)-3-(4-hydroxyphenyl)-2-methoxypropanoic acid (73.59 g, 0.15 mol) (98.1% ee by chiral HPLC) was suspended in 1N HCl solution (750 mL) and extracted with methyl tert butyl ether (3 x 200 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give about 24.12 g (82%) of (2S)-3-(4-hydroxyphenyl)-2-methoxypropanoic acid (96.7% ee by chiral HPLC). ^{1}H NMR (DMSO-d_6): δ 2.72-2.89 (m, 2H), 3.21 (s, 3H), 3.8-3.87 (m, 1H), 6.64-6.67 (d, 2H), 6.97-7.02 (d, 2H), 9.15 (s, broad, 1H), 12.62 (s, broad, 1H). MS (ES$^+$) m/z 219.0 ([M+Na]$^+$). MS (ES$^-$) m/z 195.1 ([M-H]$^-$). $[\alpha]_D$ = -2.2° (c = 1, MeOH).

Step 3: ethyl 2S-2-methoxy-3-(4-hydoxyphenyl) propanoate (e)

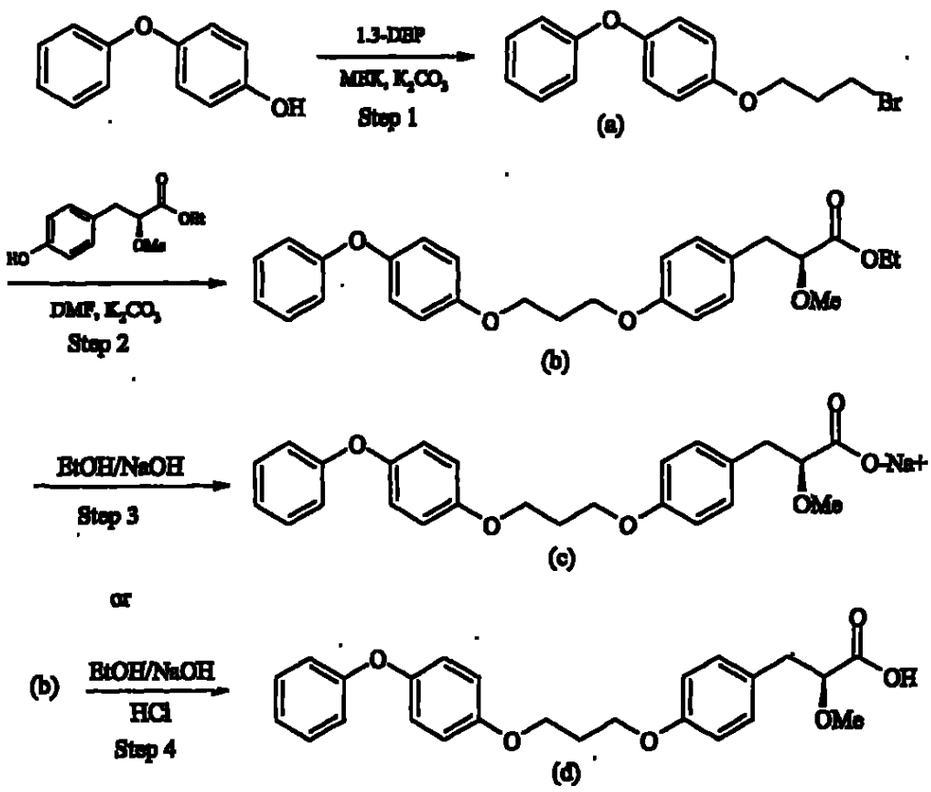
A solution of (2S)-3-(4-hydroxyphenyl)-2-methoxypropanoic acid (35 g) in 140 ml of ethanol was mixed with 5.66 ml of concentrated sulfuric acid and stirred at room temperature until complete as indicated by HPLC. The ethanol was removed via vacuum distillation (55°C/28"Hg) and 110 ml of water was added. The pH was adjusted to about 7 to 8 with sodium bicarbonate, and the mixture was extracted with add 50 ml ethyl acetate (3 x 50 ml). The organic layers were combined, washed with 50 ml 20% NaCl solution, dried with 15 g of magnesium sulfate, and concentrate product to afford ethyl 2S-2-methoxy-3-(4-hydoxyphenyl) propanoate as an oil. ^{1}H-NMR ($CDCl_3$): 7.1(d, 2H); 6.7(d, 2H); 4.2(m, 2H); 3.9(m, 1H); 3.6(s, 3H); 2.95(m, 2H); 1.25(t, 3H). MS (ES): 223.2 (M-1).

Example 247

Synthesis of 2S-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid



Scheme



Step 1: 1-bromo-3-(4-phenoxyphenyl)propane (a)

To a 22 L flask was added 4-phenoxyphenol (900 g), 1,3-dibrompropane (5858 g), powered potassium carbonate (1335 g), and methyl ethyl ketone (9 L). The mixture was stirred for 30 minutes at 22°C. The off white slurry was heated to a gentle reflux (~83°C) and held at that temperature for 16 hours. The off white slurry was cooled to 25°C and vacuum filtered, washing the cake of inorganic salts with methyl ethyl ketone (4 L). The filtrate was concentrated on a rotary evaporator while

increasing the temperature to 90°C under house vacuum. After the condensation had stopped, the oil was held at 90°C under vacuum for an additional two hours to ensure the remaining 1,3-dibrompropane below 8% by GC analysis. The residue was dissolved in 3L of methyl alcohol, and the white slurry was cooled slowly to about 0-5°C and held at that temperature overnight. The product was filtered, washed with cold methyl alcohol (6 L), and dried at 30°C for about 20 hours to afford about 1234 g of compound (a) in 84 % yield (99.4 % pure by GC). ^{1}H-NMR ($CDCl_3$): 7.3(2H, m), 7.1(2H, m), 7.0(2H, m), 6.9(2H, m), 4.1(2H, m); 3.6(2H, m); 2.3(2H, m).

Step 2: ethyl 2*S*-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoate(b)

1-Bromo-3-(4-phenoxyphenyl)propane (1337 g), ethyl 2*S*-2-methoxy-3-(4-hydoxyphenyl)propanoate (957 g) and dimethylformamide (5 L) were charged to a 22 L flask. After a solution was obtained, powered potassium carbonate (1770 g) was added. The mixture was stirred for 16 hours at ambient temperature and then quenched by adding water (6.5 L) while maintaining temperature at 20 to 30°C. The aqueous layer was extracted three times with ethyl acetate (5 L each). The combined organic layers were washed with water (3 x 4 L) and brine (4 L). The organic layer was then dried with sodium sulfate (1000 g), filtered, and washed with ethyl acetate. The filtrate was concentrated to afford about 1974 g of crude (b). ^{1}H-NMR ($CDCl_3$): 7.3(m, 2H); 7.2(d, 2H); 7.0(m, 1H); 6.95(m,4H); 6.9(d, 2H); 6.85(d, 2H); 4.2(m, 2H); 4.15(m, 4H); 3.9(t, 1H); 3.39(s, 3H); 2.99(m, 2H); 2.25(m, 2H); 1.25(m, 3H). MS (ES)= 468.2 ($M+NH_4$).

Step 3: 2*S*-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid, sodium salt (c)

To a 22L flask, a solution of compound (b) (987 g) in ethanol (10 L) was added and stirred, followed by adding 5 N NaOH (4.4 L) for over 60 minutes at a temperature at 20 to 30°C. The slurry was stirred for about an hour at ambient temperature and then cooled to 10-15°C where the mixture was held at that temperature for 1 hour

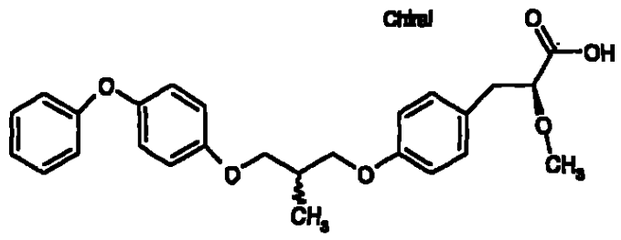
and filtered. The solid was washed with alcohol (8 L) and MTBE (50 L) to afford the compound (c), which can be further purified by recrystallizing from ethyl acetate: ^{1}H-NMR (DMSO): 7.35(m, 2H); 7.1(m, 3H); 7.0(m, 4H); 6.9(d, 2H); 6.8(d, 2H); 4.1(m, 4H); 3.4(t, 1H); 3.1(s, 3H); 2.8(dd, 1H); 2.6(m, 1H); 2.15(m, 2H). MS (ES): 421.2 (M-1).

Step 4: 2*S*-2-methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]phenyl}propanoic acid (d)

2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester (b) (12.15 g, 27 mmol) was dissolved in ethanol (250ml) at ambient temperature, and 5N NaOH (54 ml, 270 mmol) was added dropwise. The slurry was stirred at ambient temperature for 2 hours. The mixture was diluted with water (250 ml), and conc. HCl (33ml) was added dropwise. The resulting slurry was stirred at ambient temperature for about 2 hours. The white solid was filtered and dried under vacuum at 70°C for 16 hours to afford about 10.5 g of the compound (d). ^{1}H-NMR ($CDCl_3$): 7.3 (m, 2H), 7.18 (d, 2H), 7.07 (t, 1H), 6.9 (m, 8H), 4.19 (m, 4H), 4.0 (m, 1H), 3.4 (s, 3H), 3.0 (m, 2H), 2.25 (m 2H). MS (ES): 421.2 (M-1).

Example 248

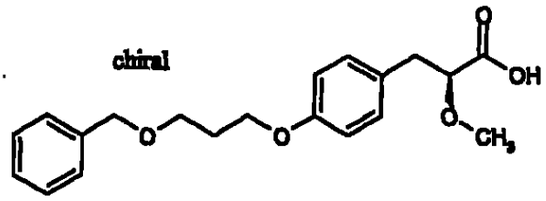
(2*S*)-(2'*R,S*)-2-Methoxy-{4-[2'-methyl-3-(4-phenoxy-phenoxy)-propoxyl-phenyl}-propionic acid



A solution of (2*S*)-2-Methoxy-3-{4-[2-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid {4-[2-methylen-3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid from Example 74, in ethanol was treated with Pd/C and H_2 for over 2 hours at 1 atm. The mixture was filtered through celite and concentrated to dryness to afford the title compound as a mixture of isomers. MS (ES) for $C_{25}H_{28}O_5$ $[M+NH_4]^+$: 454.2, $[M-H]^-$: 435.2.

Example 249

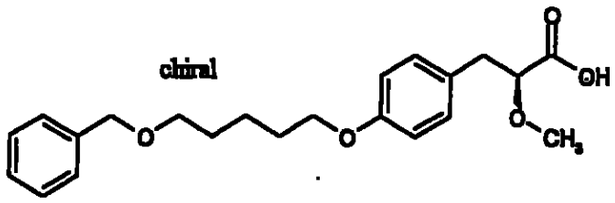
2(S)-3-[4-(3-Benzyloxy-propoxy)-phenyl]-2-methoxypropionic acid



The title compound was prepared from (2S)-3-[4-(3-hydroxy-phenyl]-2-methoxypropionic acid linked to Wang's Resin (Example 94, Step C) via the Mitsunobu reaction-cleavage (Standard Procedure G). ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.4-7.2 (m, 5H), 7.14 (d, 2H, *J*=8.6), 6.82 (d, 2H, *J*=8.6), 4.52 (s, 2H), 4.06 (t, 2H, *J*=6.2), 3.97 (dd, 1H, *J*=7.2, 4.6), 3.65 (t, 2H, *J*=6.2), 3.39 (s, 3H), 3.09 (dd, 1H, *J*=14.4, 4.4), 2.95 (dd, 1E, *J*=14.4, 7.2), 2.07 (qn, 2H, *J*=6.2).

Example 250

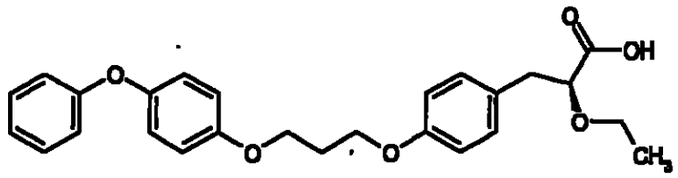
(2S)-3-[4-(5-Benzyloxy-pentyloxy)-phenyl]-2-methoxypropionic acid



The title compound was prepared from (2S)-3-[4-(3-hydroxy-phenyl]-2-methoxy-propionic acid linked to Wang's Resin (Example 94, Step C) via the Mitsunobu reaction-cleavage (Standard Procedure G) with 5-benzyloxy-pentan-1-ol. ^{1}H-NMR (200.15 MHz, $CDCl_3$): 7.4-7.3 (m, 5H), 7.14 (d, 2H, *J*=8.6), 6.81 (d, 2H, *J*=8.6), 4.51 (s, 2H), 4.0-3.9 (m, 3H), 3.50 (t, 2H, *J*=6.2), 3.39 (s, 3H), 3.08 (dd, 1H, *J*=14.2, 4.3), 2.95 (dd, 1H, *J*=14.2, 7.5), 1.9-1.5 (m, 6H).

Example 251

(2S)-2-ethoxy-{4-[3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid



Step A

(2S)-2-Hydroxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester

A solution of (2S)-2-hydroxy-3-(4-hydroxy-phenyl)-propionic acid in ethanol and H_2SO_4 (catalytic) was stirred overnight. The mixture was concentrated to dryness and reconstituted in ethyl acetate. The organic layer was washed with $NaHCO_3$, dried over $MgSO_4$ and concentrated to dryness to give the title product. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.03 (d, 2H, *J* = 8.6), 7.00 (d, 2H, *J* = 8.7), 6.72-6.77 (m, 1H), 4.44-4.30 (m, 1H), 4.22 (q, 2H, *J* = 7.9), 3.13-2-77 (m, 2H), 1.24 (t, 3H, *J* = 7.9).

Step B

(2S)-2-Hydroxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester

To a solution of compound (Step A) in DMF, $CsCO_3$ (1.0 eq) and 4-(3-bromopropoxy)-1-phenoxybenzene (1.1 eq) (Example 244, Step A) were added. The mixture was stirred at room temperature overnight. The solvent was concentrated in vacuum and ethyl acetate was added. The organic layer was washed with water and concentrated to affrod, after chromatography on silica gel, the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.28 (dd, 2H, J = 8.3, 0.8), 7.17-6.84 (m, 11H), 4.44-4.36 (m, 1H), 4.28-4.12 (m, 6H), 3.13-2.87 (m, 2H), 2.79-2.76 (m, 1H), 2.32-2.19 (m, 2H), 1.29 (t, 3H, J = 7.9).

Step C

2-Ethoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester

A solution of (2S)-2-hydroxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester, AgO_2 (1.5 eq) and ethyl iodide (excess) in dichloromethane was stirred over 10 days. The crude mixture was filtered through celite and concentrated to dryness. The compound was purified by chromatography to give the title product. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.34-7.26 (m, 2H), 7.18-6.82 (m, 11H), 4.18-4.17 (m, 6H), 4.01-3.94 (m, 1H), 3.68-3.53 (m, 1H), 3.43-3.28 (m, 1H), 2.96 (d, 2H, J = 6.5), 2.25 (qn, 2H, J = 6.2), 1.20 (dt, 6H, J = 12.6, 7.3).

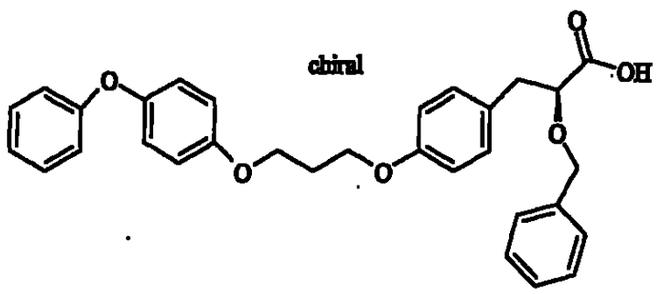
Step D

(2S)-2-ethoxy-{4-[3-(4-phenoxy-phenoxy)-propoxyl]-phenyl}-propionic acid

The title compound was prepared from 2-ethoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester (Step C) by standard hydrolysis procedure C (LiOH). MS (ES) for $C_{26}H_{28}O_6$ $[M+NH_4]^+$: 454.2, $[M-H]^-$:435.2.

Example 252

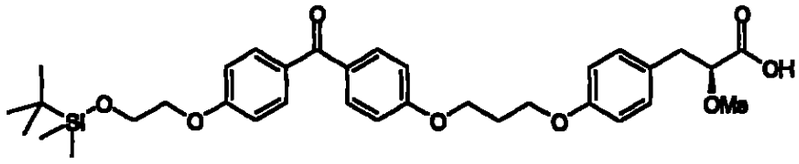
(2S)-2-Benzyloxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared as in Example 251 using benzyl bromide as alkylating agent. Hydrolysis under the Standard Procedure C of the corresponding ethyl ester derivative gave us the title compound. MS(ES) for $C_{31}H_{30}O_6$ $[M+NH_4]^+$: 516.2, $[M-H]^-$: 497.2.

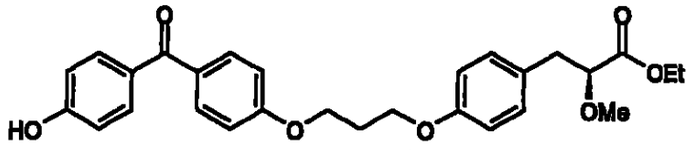
Example 253

(2S)-3-{4-[3-(4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzoyl}-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

(2S)-3-(4-{3-[4-(4-hydroxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester

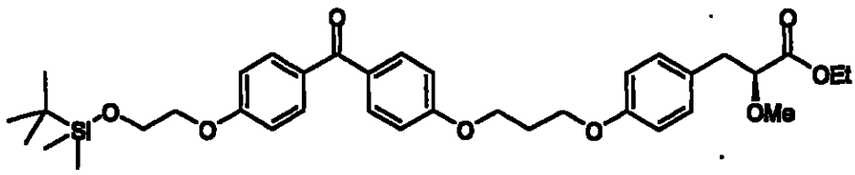


Concentrated sulfuric acid (0.05 mL) was added to a solution of (2S)-3-(4-{3-[4-(4-hydroxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid (0.18 mmol, 80 mg) (Example 170) in ethanol (20 mL) at room temperature. The mixture was stirred at room temperature for three days, and the solvent was concentrated under vacuum. After addition of water, the mixture was neutralized with solid $NaHCO_3$ and extracted with ethyl acetate (3 x 15 mL). The combined organic layers

were dried over $MgSO_4$, filtered and concentrated under vacuum to afford the title compound. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J*=8.6), 7.71 (d, 2H, *J*=8.8), 7.13 (d, 2H, *J*=8.6), 6.97-6.80 (m, 6H), 6.37 (br s, 1H), 4.25-4.10 (m, 6H), 3.93 (dd, 1H, *J*=7.0, 5.6), 3.35 (s, 3H), 2.95 (m, 2H), 2.27 (qn, 2H, *J*=5.9), 1.23 (t, 3H, *J*=7.1).

Step B

(2S)-3-{4-[3-(4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzoyl}-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



Diisopropyl azodicarboxilate (0.2 mmol, 0.04 mL) was added dropwise to a solution of 2-(tert-butyl-dimethyl-silanyloxy)-ethanol (0.26 mmol, 46 mg) (Example 122, Step A), (2S)-3-(4-{3-[4-(4-hydroxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester (0.13 mmol, 65 mg) and triphenylphosphine(0.2 mmol, 38 mg)in anhydrous toluene(2 mL) at 0°C under nitrogen. The mixture was stirred overnight at room temperature, quenched with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude mixture was chromatographed on silica gel using a 4/1 hexane/EtOAc mixture as eluent to afford the title product. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.76 (d, 4H, *J*=8.9), 7.13 (d, 2H, *J*=8.6), 6.96 (d, 4H, *J*=8.6), 6.83 (d, 2H, *J*=8.6), 4.26-4.09 (m, 8H), 4.02-3.87 (m, 3H), 3.35 (s, 3H), 2.97 (m, 2H), 2.28 (qn, 2H, *J*=5.9), 1.23 (t, 3H, *J*=7.1), 0.91 (s, 9H), 0.11 (s, 6H).

Step C

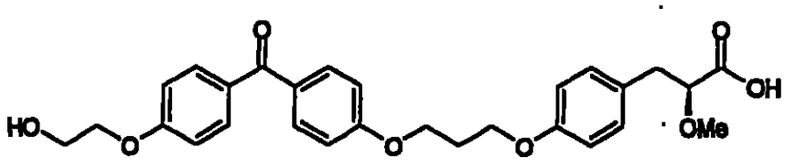
(2S)-3-{4-[3-(4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzoyl}-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2S)-3-{4-[3-(4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-benzoyl}-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic

acid ethyl ester by the standard hydrolysis procedure C (LiOH). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.76 (dd, 4H, *J*=8.6, 1.6), 7.15 (d, 2H, *J*=8.6), 6.95 (dd, 4H, *J*=8.8, 1.6), 6.83 (d, 2H, *J*=8.6), 4.24 (t, 2H, *J*=6.0), 4,17-4.09 (m, 5H), 4.02-3.94 (m, 3H), 3.39 (s, 3H), 3.12-2.90 (m, 2H), 2.27 (qn, 2H, *J*=6.0), 0.91 (s, 9H), 0.11 (s, 6H).

Example 254

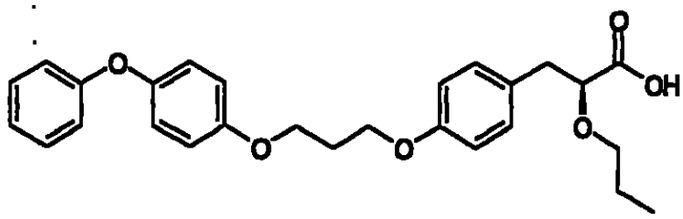
(2S)- 3-[4-(3-{4-[4-(2-Hydroxy-ethoxy)-benzoyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionic acid



The compound of (2S)-3-{4-[3-(4-{4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-benzoyl}-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Example 253, Step C) (0.05 mmol, 30 mg) was dissolved in 5 mL of a mixture of acetic acid, THF and H_2O (3:1:1) and stirred at room temperature for 2 hours. The mixture was diluted with H_2O and extracted with ethyl acetate (4 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to afford the title compound. MS(ES) for $C_{28}H_{30}O_8$ $[M+H]^+$: 495.1

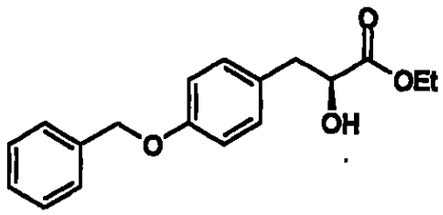
Example 255

(2S)-3-{4-[3-(4-Phenoxy-phenoxy)-propoxy]-phenyl}-2-propoxy-propionic acid



Step A

3-(4-Benzyloxy-phenyl)-2-hydroxy-propionic acid ethyl ester

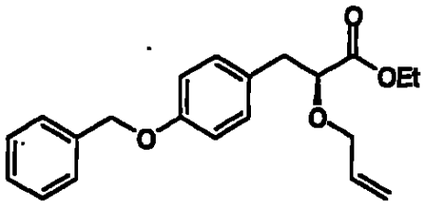


A mixture of 2-hydroxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (Example 251, Step A) (5.2 mmol, 1.1 g), benzyl bromide (5.2 mmol, 0.62 mL) and potassium carbonate (15.7 mmol, 2.2 g) in acetonitrile (20 mL) was refluxed overnight. The mixture was cooled down to room temperature and concentrated to dryness to give a crude, which was purified by column chromatography on silica gel to afford the title product.

MS (ES) for $C_{18}H_{20}O_4$ $[M+NH_4]^+$: 318.3

Step B

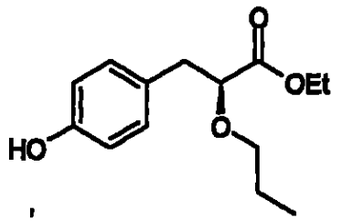
(2S)-2-Allyloxy-3-(4-benzyloxy-phenyl)-propionic acid ethyl ester



Silver (I) oxide (5.7 mmol, 1.3 g) was added to a mixture of (S)-3-(4-benzyloxy-phenyl)-2-hydroxy-propionic acid ethyl ester (3.8 mmol, 1.2 g) and allyl bromide (19 mmol, 1.6 mL) in DMF (10 mL) at room temperature, and the reaction mixture was heated at 50°C for 20 hours. After cooling to room temperature, the mixture was diluted with H_2O and extracted with ethyl acetate (5 x 25 mL). The combined organic layers were washed with water (4 x 20 mL) and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude mixture was chromatographed on silica gel using a 4/1 hexane/ethyl acetate mixture as eluent to afford the title product. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.46-7.32 (m, 5H), 7.18 (d, 2H, *J*=8.9), 6.91 (d, 2H, *J*=8.9), 5.91-5.72 (m, 1H), 5.25-5.12 (m, 2H), 5.05 (s, 2H), 4.11-4.03 (4H, m), 3.94-3.84 (m, 1H), 2.99 (d, 2H, *J*=7.0), 1.23 (t, 3H, *J*=7.0).

Step C

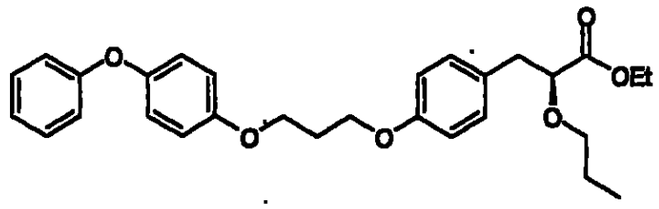
(2S)-3-(4-Hydroxy-phenyl)-2-propoxy-propionic acid ethyl ester



A mixture of (S)-2-allyloxy-3-(4-benzyloxy-phenyl)-propionic acid ethyl ester (1.33 mmol, 450 mg) and 10% Pd/C (45 mg) in EtOH (15 mL) were stirred under hydrogen atmosphere (1 atm) for 18 hours. The mixture was filtered through celite and concentrated under vacuum to afford the title product. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.10 (d, 4H, *J*=8.6), 6.73 (d, 2H, *J*=8.4), 5.90 (br s, 1H), 4.16 (q, 2H, *J*=7.3), 3.94 (t,1H, *J*=6.7), 3.53-3.45 (m, 1H), 3.27-3.16 (m, 1H), 2.93 (d, 2H, *J*=6.5), 1.54 (m, 2H), 1.22 (t, 3H, *J*=7.3), 0.84 (t, 3H, *J*=7.5).

Step D

(2S)-3-{4-[3-(4-Phenoxy-phenoxy)-propoxy]-phenyl}-2-propoxy-propionic acid ethyl ester



The title compound was prepared from (S)-3-(4-hydroxy-phenyl)-2-propoxy-propionic acid ethyl ester and 3-(4-phenoxy-phenoxy)-propyl bromide (Example 244) using the Standard Procedure I. The product was purified by column chromatography on silica gel using a 9/1 Hexane/Ethyl acetate mixture as eluent to afford the title product. MS(ES) for $C_{29}H_{34}O_6$ $[M+NH_4]^+$: 496.3

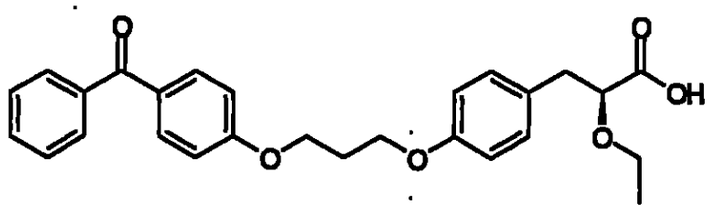
Step E

(2S)-3-{4-[3-(4-Phenoxy-phenoxy)-propoxy]-phenyl}-2-propoxy-propionic acid

The title compound was prepared from (S)-3-{4-[3-(4-Phenoxy-phenoxy)-propoxy]-phenyl}-2-propoxy-propionic acid ethyl ester by the standard hydrolysis procedure C (LiOH). MS(ES) for $C_{27}H_{30}O_6$ [M-H]: 449.2

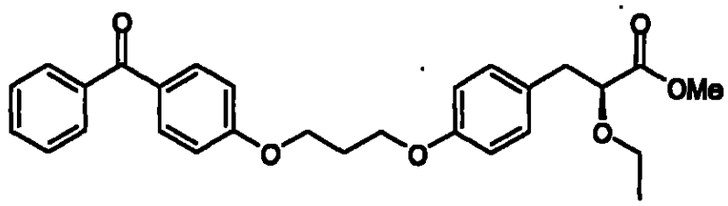
Example 256

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid



Step A

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid methyl ester



The title compound was prepared from 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid methyl ester and [4-(3-bromo-propoxy)-phenyl]-phenyl-methanone (prepared from 4-hydroxybenzophenone following the same procedure as in (Example 132, Steps B to D) using the Standard Procedure I. The product was purified by column chromatography on silica gel using a hexane/ethyl acetate mixture (4/1) as eluent to give the racemic product. This racemic mixture was subjected to chiral HPLC separation to give the pure enantiomer. ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.83-7.72 (m, 4H), 7.57-7.42 (m, 3H), 7.14 (d, 2H, *J*=8.8), 6.96 (d, 2H, *J*=8.8), 6.83 (d, 2H, *J*=8.6), 4.25 (t, 2H, *J*=6.1), 4,15 (t, 2H, *J*=6.2), 3.98 (dd, 1H, *J*=7.1, 6.0), 3.70 (s, 3H), 3.58 (dd, 1H, *J*=9.1, 7.0), 3.33 (dd, 1H, *J*=9.1, 7.0), 2.94 (m, 2H), 2.28 (qn, 2H,

J=6.2), 1.25 (t, 3H, J=7.3).

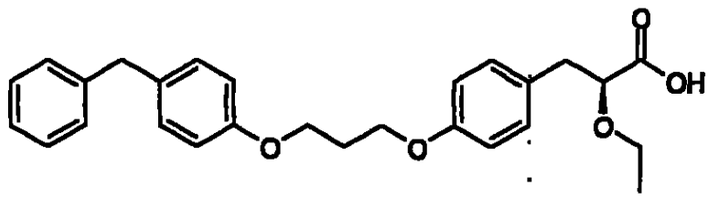
Step B

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid

The title compound was prepared from (S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid methyl ester by the standard hydrolysis procedure C (LiOH). MS(ES) for $C_{27}H_{28}O_6$ [M-H]$^-$: 447.1

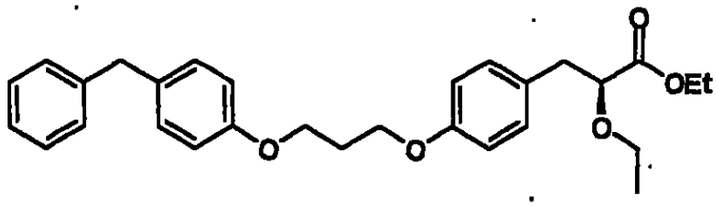
Example 257

(2S)- 3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid



Step A

(2S)- 3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester



The title compound was prepared from (S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester and 3-(4-benzyl-phenoxy)-propyl bromide (prepared from 4-benzylphenol following the same procedure as in (Example 132, Steps B to D) using the Standard Procedure I. The product was purified by column chromatography on silica gel using a hexane/ethyl acetate mixture (4/1) as eluent to give the title product. MS(ES) for $C_{28}H_{34}O_5$ [M+NH_4]$^+$: 480.2

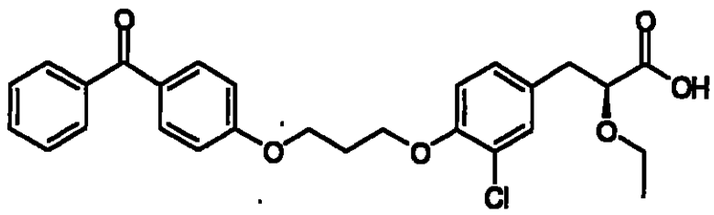
Step B

(2S)- 3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid

The title compound was prepared from (S)-3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester by the standard hydrolysis procedure C (LiOH). MS(ES) for $C_{27}H_{30}O_5$ [M-H]$^-$: 433.1

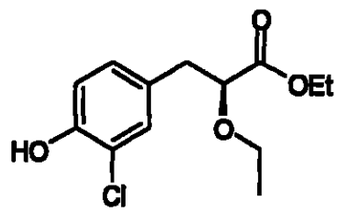
Example 258

(2S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-ethoxy-propionic acid



Step A

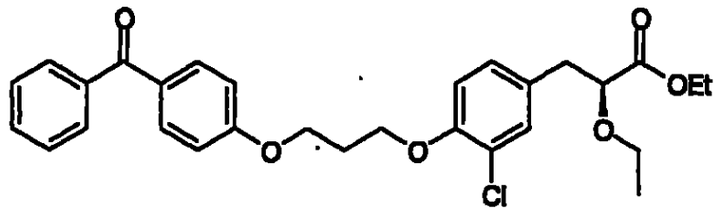
(2S)-3-(3-Chloro-4-hydroxy-phenyl)-2-ethoxy-propionic acid ethyl ester



N-Chlorosuccinimide (2.1 mmol) was added to a solution of (S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (2.1 mmol) in acetonitrile (12 mL) at room temperature, and the mixture was stirred at the same temperature for 5 days. Solvent was evaporated under vacuum, and the residue was washed with CCl_4. The resulting suspension was filtered, and the filtrate was concentrated under vacuum and chromatographed on silica gel using a 9/1 hexane/EtOAc mixture as eluent to afford title product. MS(ES) for $C_{13}H_{17}ClO_4$ [M-H]$^-$: 271.0

Step B

(2S)-3-{4-[3-(4-benzoyl-phenoxy)-propoxyl-3-chloro-phenyl}-2-ethoxy-propionic acid ethyl ester



The title compound was prepared from (S)-2-ethoxy-3-(3-chloro-4-hydroxy-phenyl)-propionic acid ethyl ester and [4-(3-bromo-propoxy)-phenyl]-phenyl-methanone (Example 256) using the Standard Procedure I. The product was purified by column chromatography on silica gel using a 4/1 Hexane/Ethyl acetate mixture as eluent to give the title product. MS(ES) for $C_{29}H_{31}ClO_6$ $[M+H]^+$: 511.1

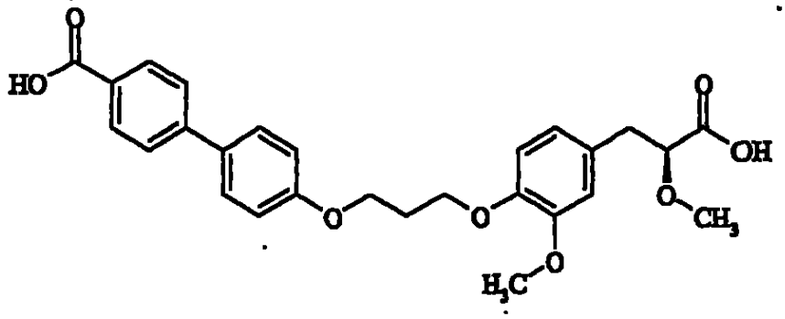
Step C

(2S)-3-{4-[3-(4-benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-ethoxy-propionic acid

The title compound was prepared from (S)-3-{4-[3-(4-benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-ethoxy-propionic acid methyl ester by the standard hydrolysis procedure C (LiOH). ^{1}H-NMR (200.15 MHz, $CDCl_3$): δ 7.82-7.72 (m, 4H), 7.56-7.43 (m, 3H), 7.07 (dd, 1H, *J*=8.8, 2.0), 6.97 (d, 2H, *J*=8.9), 6.86 (d, 2H, *J*=8.3), 4.31 (t, 2H, *J*=6.0), 4,21 (t, 2H, *J*=6.0), 4.10-4.02 (m, 1H), 3.66-3.44 (m, 2H), 3.10-2.87 (m, 2H), 2.33 (qn, 2H, *J*=6.2), 1.20 (t, 3H, *J*=7.0).

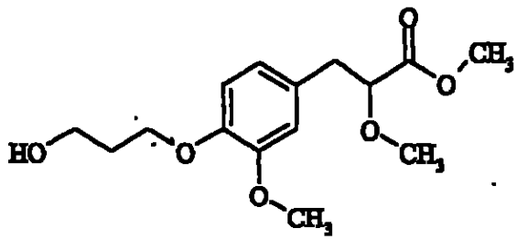
Example 259

(2S)-4'-{3-[4-(2-Carboxy-2-methoxy-ethyl)-2-methoxy-phenoxy]-propoxy}-biphenyl-4-carboxylic acid



Step A

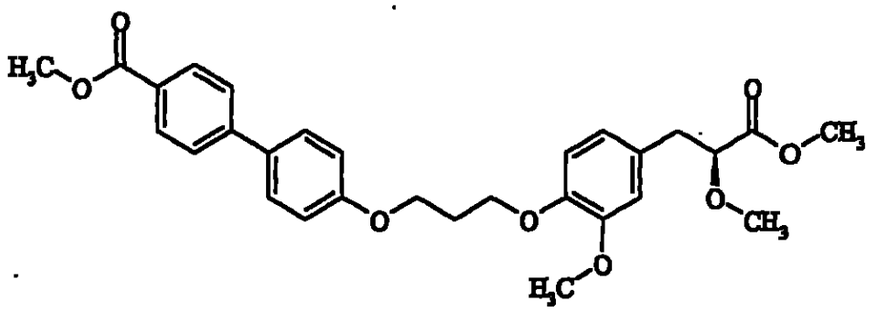
3-[4-(3-Hydroxy-propoxy)-3-methoxy-phenyl]-2-methoxypropionic acid methyl ester



A mixture of 3-(4-Hydroxy-3-methoxy-phenyl)-2-methoxypropionic acid methyl ester (Example 130, Step B) and 3-(*tert*-butyl-dimethyl-silanyloxy)-propan-1-ol were treated under Mitsunobu standard conditions B using DIAD and toluene. The product obtained was treated under Standard Procedure E for cleavage protected alcohols to give the title product. The 2*S* isomer was separated from the 2*R* isomer by chiral. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 6.84-6.72 (m, 3H), 4.17 (t, 2H, *J*= 5.9), 3.94 (dd, 2H, *J*= 7.0, 5.4), 3.87 (t, 2H, *J*= 5.4), 3.84 (s, 3H), 3.73 (s, 3H), 3.35 (s, 3H), 2.97-2.93 (m, 2H), 2.11-2.00 (m, 2H).

Step B

(2*S*)-4'-{3-[2-Methoxy-4-(2-methoxy-2-methoxycarbonyl-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid methyl ester



3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid methyl ester (Step A) and 4'-hydroxy-biphenyl-4-carboxylic acid methyl ester (Example 197, Step A) were treated under Mitsunobu standard conditions B. The crude was purified by chromatography on silica gel (hexanes/ethyl acetate 7:3) to afford the title compound.

^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 8.07 (d, 2H, *J*= 8.6), 7.58 (dd, 4H, *J*= 10.8, 8.9), 7.14 (d, 2H, *J*= 8.9), 6.99 (d, 2H, *J*= 8.9), 6.84 (d, 2H, *J*= 8.6), 4.24-4.12 (m, 6H), 3.94-3.90 (m, 4H), 3.35 (s, 3H), 2.97-2.94 (m, 2H), 2.27 (qn, 2H, *J*= 5.9), 1.23 (t, 3H, *J*= 7.0).

Step C

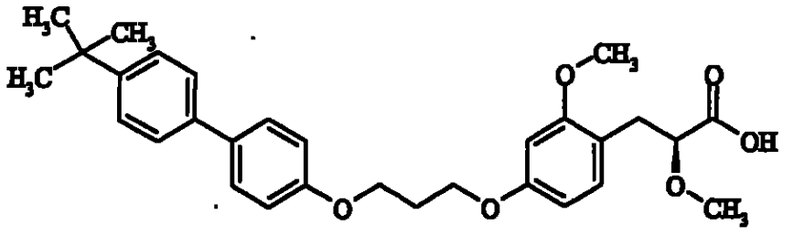
(2*S*)-4'-{3-[4-(2-Carboxy-2-methoxy-ethyl)-2-methoxy-phenoxy]-propoxy}-biphenyl-4-carboxylic acid

The title compound was prepared from 4'-{3-[2-methoxy-4-(2-methoxy-2-methoxycarbonyl-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid methyl ester (Step B) by standard hydrolysis procedure C (NaOH). ^{1}H-NMR (MeOD, 300.15 MHz):

δ 8.07 (d, 2H, *J*=8.5), 7.69 (d, 2H, *J*=8.5), 7.63 (d, 2H, *J*=8.7), 7.06 (d, 2H, *J*=8.7), 6.91-6.88 (m, 2H), 6.78 (dd, 1H, *J*=8.1, 1.6), 4.25 (t, 2H, *J*=6.3), 4.18 (t, 2H, *J*=6.0), 3.94 (dd, 1H, *J*=7.9, 4.4), 3.82 (s, 3H), 3.33 (s, 3H), 3.01 (dd, 1H, *J*=14.1, 4.4), 2.88 (dd, 1H, *J*=13.9, 7.7), 2.26 (qn, 2H, *J*=6.0).

Example 260

(2*S*)-3-{4-[3-(4'-*tert*-Butyl-biphenyl-4-yloxy)-propoxy]-2-methoxy-propionic acid



Step A

3-Bromo-propan-1-ol

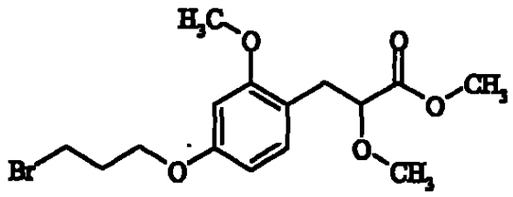


To a solution of 1,3-propanediol (5 g, 66 mmol) and benzene (132 mL) was added hydrobromic acid 48% (8 mL). The resulting mixture was heated at reflux for 20 hours while trapping the water formed using a Dean-Stark water separator. The mixture was washed with 2N NaOH solution, 5% HCl, water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. ^{1}H-NMR ($CDCl_3$,

300.15 MHz): δ 3.78 (2H, t, *J*= 6.0), 3.52 (2H, t, *J*= 6.0), 2.07 (2H, m).

Step B

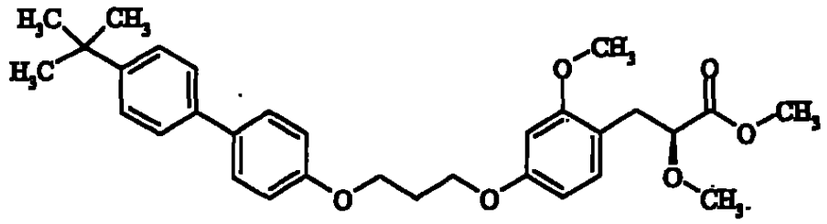
3-[4-(3-Bromo-propoxy)-2-methoxy-phenyl]-2-methoxy-propionic acid methyl ester



3-(4-Hydroxy-2-methoxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 188, Step C) and 3-bromo-propan-1-ol (Step A) were treated in the standard Mitsunobu conditions B (DIAD/toluene) to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.01 (d, 1H, *J*= 8.3), 6.39 (m, 2H), 4.06 (t, 2H, *J*= 5.9), 4.00-3.96 (m, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.57 (t, 2H, *J*= 6.4), 3.31 (s, 3H), 2.99 (dd, 1H, *J*= 13.7, 6.2), 2.91 (dd, 1H, *J*= 13.7, 7.5), 2.34-2.22 (m, 2H).

Step C

(2*S*)-3-{4-[3-(4'-*tert*-Butyl-biphenyl-4-yloxy)-propoxy]-2-methoxy-phenyl}-2-methoxy-propionic acid methyl ester



3-[4-(3-Bromo-propoxy)-2-methoxy-phenyl]-2-methoxy-propionic acid methyl ester (Step B) and 4'-*tert*-butyl-biphenyl-4-ol (Example 221, Step A) were treated under Standard Procedure K. The enantiomers were separated by chiral HPLC. The 2*S* isomer was separated from the 2*R* isomer by chiral HPLC (Chiralpack AD, Hexane 0.05% TFA/IPA, 75/25, isocratic mode, 1 mL/min; RT = 7.70 min). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.53-7.41 (m, 6H), 7.05-6.95 (m, 3H), 6.45-6.40 (m, 2H), 4.21 (d, 2H, *J*= 6.2), 4.14 (d, 2H, *J*= 6.2), 4.05-3.98 (m, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.33 (s, 3H), 3.01 (dd,1H,*J*= 13.4, 6.2), 2.92 (dd, 1H, *J*= 13.4, 7.5), 2.27 (qn,

2H, *J*= 6.2).

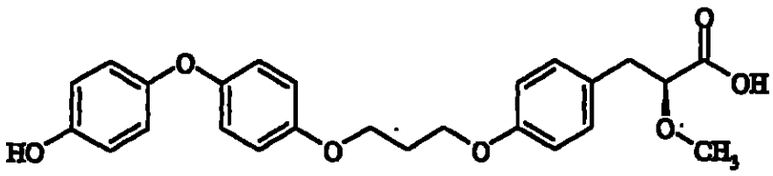
Step D

(2*S*)-3-{4-[3-(4'-*tert*-Butyl-biphenyl-4-yloxy)-propoxy]-2-methoxy-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2*S*)-3-{4-[3-(4'-*tert*-butyl-biphenyl-4-yloxy)-propoxy]2-methoxy-phenyl}-2-2-methoxy-propionic acid methyl ester (Step C) by standard hydrolysis procedure C (NaOH). ^{1}H-NMR (Acetone-d_6, 300.15 MHz): δ 7.57 (d, 2H, *J*=8.7), 7.53 (d, 2H, *J*=8.7), 7.45 (d, 2H, *J*=8.5), 7.06-7.02 (m, 3H), 6.55 (d, 1H, *J*=2.0), 6.46 (dd, 1H, *J*=8.3, 2.2), 4.26-4.17 (m, 4H), 3.96 (dd, 1H, *J*=7.9, 5.7), 3.81 (s, 3H), 3.26 (s, 3H), 2.25 (qn, 2H, *J*=6.3), 1.33 (s, 9H).

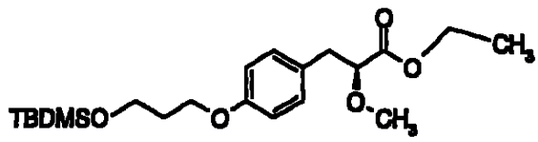
Example 261

(2*S*)-3-{4-[3-[4-(4-Hydroxy-phenoxy)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

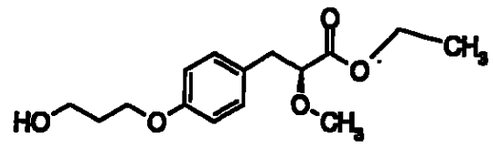
(2*S*)-3-{4-[3-(tert-Butyl-dimethyl-silanyloxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



A mixture of (2*S*)-3-(4-hydroxy-phenyl)-2-methoxy propionic acid ethyl ester and 3-(tert-Butyl-dimethyl-silanyloxy)-propan-1-ol were treated under Mitsounobu coupling standard conditions B using DIAD and toluene.

Step B

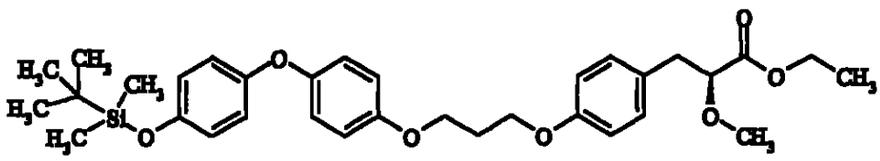
(2S)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester



A solution of (2S)-3-{4-[3-(tert-Butyl-dimethyl-silanyloxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester was treated under Standard Procedure E for cleaveage protected alcohols to give the title product.

Step C

3-(4-{3-[4'-(tert-Butyl-dimethyl-silanyloxy)-biphenyl-4-yloxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester



(2*S*)-3-[4-(3-Hydroxy-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester and 4'-(*tert*-butyl-dimethyl-silanyloxy)-biphenyl-4-ol (Example 196, Step A) were treated under Mitsunobu procedure B (DIAD, toluene), to afford the title compound.

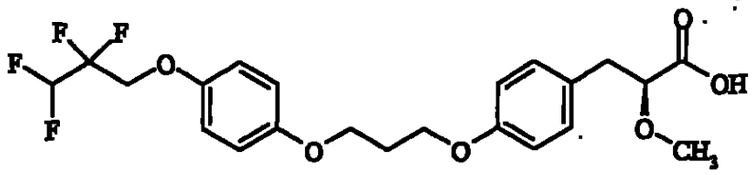
Step D

(2S)-3-(4-{3-[4-(4-Hydroxy-phenoxy)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

The title compound was prepared from 3-(4-{3-[4'-(tert-butyl-dimethyl-silanyloxy)-biphenyl-4-yloxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester (Step A) by standard hydrolysis procedure C (NaOH). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.15 (d, 2H, *J*=8.6), 6.92-6.74 (m, 10H), 4.15-4.09 (m, 4H), 3.98 (dd, 1H, *J*=7.3, 4.6), 3.39 (s, 3H), 3.09 (dd, 1H, *J*=14.2, 4.6), 2.95 (dd, 1H, *J*=14.2, 7.3), 2.23 (qn, 2H, *J*=5.9).

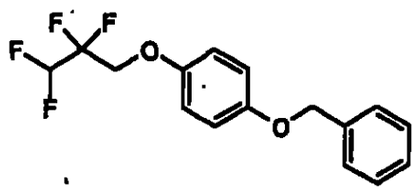
Example 262

(2S)-2-Methoxy-3-(4-{3-[4-(2,2,3,3-tetrafluoro-propoxy)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

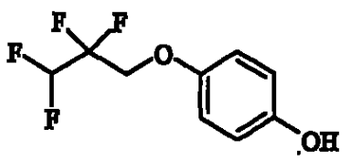
4-(2,2,3,3-tetrafluoro-propoxy)-1-benzyloxy-phenol



To a solution of methanesulfonic acid 2,2,3,3-tetrafluoro-propyl ester (obtained from 2,2,3,3-tetrafluoropropanol and methanesulfonyl chloride as described in (Example 268, Step A) (0.35 mmol, 74 mg) and 4-benzyloxy-phenol (0.175 mmol, 35 mg) in DMF (1mL) was added K_2CO_3, and the resulting mixture was stirred at 100°C for 20 hours. Water was added and the aqueous layer was extracted twice with hexane and once with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The crude was purified by chromatography on silica gel (hexane/ethyl acetate 4:1) to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.42-7.32 (m, 5H), 6.96-6.84 (m, 4H), 6.06 (tt, 1H, J= 53.0, 5.1), 5.03 (s, 2H), 4.29 (dt, J= 12.0, 1.6).

Step B

4-(2,2,3,3-Tetrafluoro-propoxy)-phenol

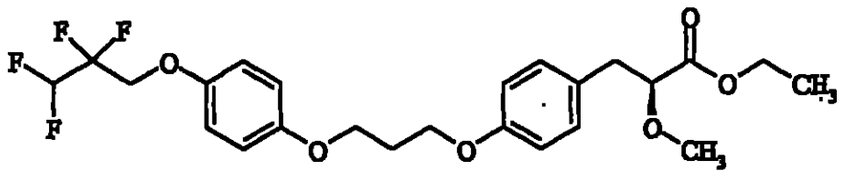


4-(2,2,3,3-tetrafluoro-propoxy)-benzyloxy-phenol (0.09 mmol, 28 mg) (Step A) was dissolved in MeOH (2 mL) and Pd(C) (40% weight, 10 mg) was added. The mixture

was stirred for 90 minutes under H_2 atmosphere (1 atm), and filtered through a celite pad (EtOH). The filtrate was concentrated to give the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 6.85-6.75 (m, 4H), 6.05 (dt, *J*= 53.2, 4.8), 4.28 (dt, 2H, *J*= 12.1, 1.6).

Step C

(2*S*)-2-Methoxy-3-(4-{3-[4-(2,2,3,3-tetrafluoro-propoxy)-phenoxy]-propoxy}-phenyl)-propionic acid ethyl ester



3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 173, Step A) and 4-(2,2,3,3-tetrafluoro-propoxy)-phenol (Step B) were treated under ester K to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.13 (d, 2H, *J*= 8.6), 6.85-6.80 (m, 6H), 6.05 (dt, 1H, *J*= 53.2, 5.1), 4.22-4.08 (m, 8H), 3.90 (dd, 1H, *J*= 7.0, 5.6), 3.35 (s, 3H), 3.04-2.86 (m, 2H), 2.22 (qn, 2H, *J*= 6.2).

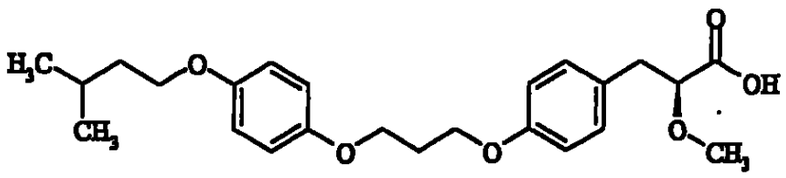
Step D

(2*S*)-2-Methoxy-3-(4-{3-[4-(2,2,3,3-tetrafluoro-propoxy)-phenoxy]-propoxy}-phenyl)-propionic acid

The title compound was prepared from (2*S*)-2-methoxy-3-(4-{3-[4-(2,2,3,3-tetrafluoro-propoxy)-phenoxy]-propoxy}-phenyl)-propionic acid ethyl ester (Step C) by standard hydrolysis procedure C (NaOH). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.14 (d, 2H, *J*= 8.6), 6.84-6.79 (m, 6H), 6.04 (tt, 1H, *J*= 53.0, 4.8), 4.27 (t, 2H, *J*= 12.0), 4.09 (t, 4H, *J*= 5.9), 3.97-3.91 (m, 1H), 3.34 (s, 3H), 3.11-2.87 (m, 2H), 2.20 (qn, 2H, *J*= 5.9).

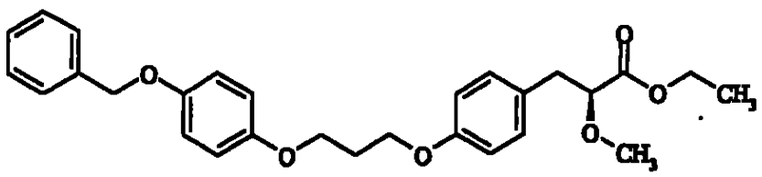
Example 263

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methyl-butoxy)-phenoxy]-propoxy}-phenyl)-propionic acid



Step A

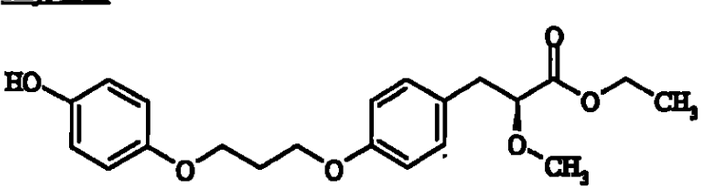
2*S*)-3-{4-[3-(4-benzyloxy-phenoxy]-propoxy}-phenyl)-2-methoxy propionic acid ethyl ester



3-[4-(3-Bromo-propoxy)-3-methoxy-phenyl]-2-methoxy-propionic acid methyl ester (Example 175, Step B) and 4-benzyloxy-phenol were treated under Mitsunobu standard conditions B to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.44-7.30 (m, 5H), 7.13 (d, 2H, *J*= 8.6), 6.93-6.73 (m, 6H), 5.01 (s, 2H), 4.20-4.06 (m, 6H), 3.90 (dd, 1H, *J*= 7.0, 5.6), 3.35 (s, 3H), 3.00-2.93 (m, 2H), 2.22 (qn, 2H, *J*= 6.2), 1.23 (t, 3H, *J*= 7.2).

Step B

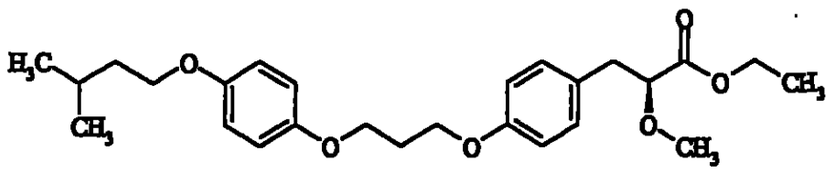
(2*S*)-3-{4-[3-(4-Hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



The title compound was obtained following the hydrogenation procedure (Example 261, Step B), starting from (2*S*)-3-{4-[3-(4-benzyloxy-phenoxy]-propoxy}-phenyl)-2-methoxy propionic acid ethyl ester. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.13 (d, 2H, *J*= 8.9), 6.84-6.71 (m, 6H), 4.23-4.06 (m, 6H), 3.91 (dd, 1H, *J*= 7.3, 5.9), 3.35 (s, 3H), 2.97-2.93 (m, 2H), 2.21 (qn, 2H, *J*= 6.2), 1.23 (t, 3H, *J*= 7.3).

Step C

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methyl-butoxy)-phenoxy]-propoxy}-phenyl)-propionic acid ethyl ester



(2*S*)-3-{4-[3-(4-Hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Step A) was reacted under Mitsunobu procedure B (DIAD, toluene) with 3-methyl-butanol to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.13 (d, 2H, *J*= 8.6), 6.85-6.81 (m, 6H), 4.18 (q, 4H, *J*= 7.0), 4.08 (d, 2H, *J*= 5.9), 3.96-3.87 (m, 3H), 3.35 (s, 3H), 2.97-2.93 (m, 2H), 2.22 (qn, 2H, *J*= 6.2), 1.86-1.60 (m, 3H), 1.23 (t, 5H, *J*= 7.0), 0.95 (d, 6H, *J*= 6.4).

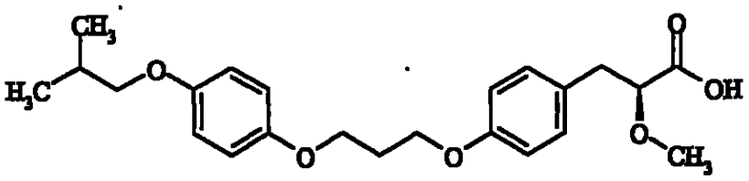
Step D

(2*S*)-2-Methoxy-3-(4-{3-[4-(3-methyl-butoxy)-phenoxy]-propoxy}-phenyl)-propionic acid

The title compound was prepared from (2*S*)-2-methoxy-3-(4-{3-[4-(3-methyl-butoxy)-phenoxy]-propoxy}-phenyl)-propionic acid ethyl ester (Step B) by standard hydrolysis procedure C (NaOH). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.12 (d, 2H, *J*=8.4), 6.84-6.80 (m, 6H), 4.09 (q, 4H, *J*= 6.2), 3.99-3.88 (m, 3H), 3.37 (s, 3H), 3.07 (dd, 1H, *J*= 14.3, 4.4), 2.93 (dd, 1H, *J*= 14.3, 7.0), 2.19 (qn, 2H, *J*= 6.2), 1.90-1.71 (m, 1H), 1.62 (q, 2H, *J*= 6.9), 0.93 (d, 6H, *J*= 6.6).

Example 264

(2*S*)-3-{4-[3-(4-Isobutoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

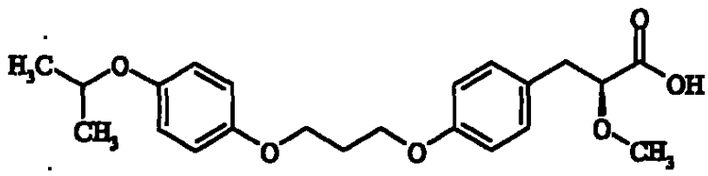


(2*S*)-(3-{4-[3-(4-Hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

ethyl ester (Example 263, Step B) was coupled under the ester *J* with 1-bromo-2-methylpropane to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.14 (d, 2H, *J*= 8.6), 6.86-6.82 (m, 6H), 4.11 (q, 4H, *J*=6.2), 3.98 (dd, 1H, *J*= 7.3, 4.6), 3.66 (d, 2H, *J*= 6.5), 3.40 (s, 3H), 3.10 (dd, 1H, *J*= 14.5, 4.6), 2.95 (dd, 1H, *J*= 14.5, 7.3), 2.21 (qn, 2H, *J*= 6.2), 2.11-1.98 (m, 1H), 1.01 (d, 6H, *J*= 6.7).

Example 265

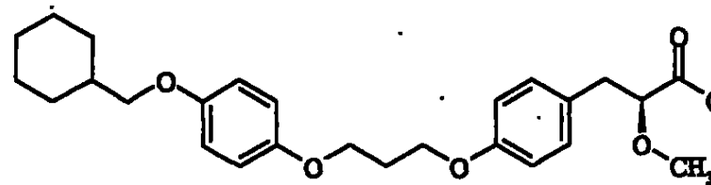
(2*S*)-3-{4-[3-(4-Isopropoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2*S*)-3-{4-[3-(4-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Example 263, Step B) and 2-bromopropene following the procedure described for Example 264. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.14 (d, 2H, *J*= 8.3), 6.86-6.82 (m, 6H), 4.40 (qn, 1H, *J*= 5.9), 4.11 (q, 4H, *J*= 5.9), 3.98 (dd, 1H, *J*= 7.3, 4.6), 3.40 (s, 3H), 3.10 (dd, 1H, *J*= 14.2, 4.3), 3.01-2.90 (dd, 1H, *J*= 14.2, 7.2), 2.22 (qn, 2H, *J*= 5.9), 1.30 (d, 6H, *J*= 6.2).

Example 266

(2*S*)-3-{4-[3-(4-Cyclohexylmethoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

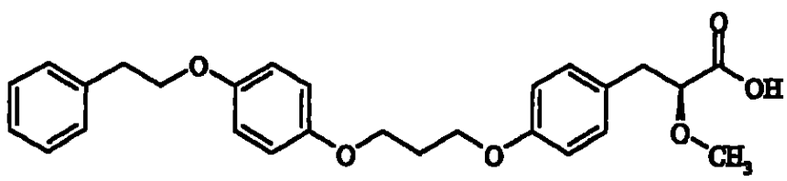


The title compound was prepared from (2*S*)-3-{4-[3-(4-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Example 263, Step B) and (bromomethyl)cyclohexane following the procedure described for Example 264.

^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.14 (d, 2H, J= 8.6), 6.86-6.81 (m, 6H), 4.11 (q, 4H, J= 6.2), 3.99 (dd, 1H, J= 7.3, 4.6), 3.70 (d, 2H, J= 6.2), 3.40 (s, 3H), 3.10 (dd, 1H, J= 14.5, 4.6), 2.96 (dd, 1H, J= 14.2, 7.3), 2.23 (qn, 2H, J= 6.2), 1.88-1.67 (m, 6H), 1.39-0.94 (m, 5H).

Example 267

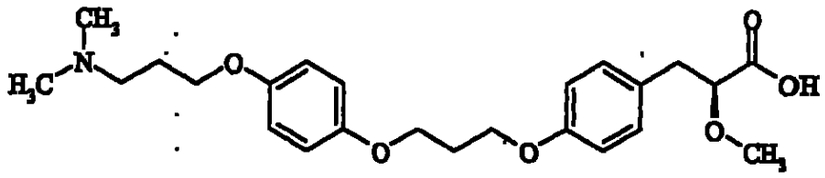
(2*S*)-2-Methoxy-3-{4-[3-(4-phenethyloxy-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2*S*)-3-{4-[3-(4-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Example 263, Step B) and (1-bromoethyl)benzene following the procedure described for Example 264. ^{1}H-NMR ($CDCl_3$, 300.15 MHz): δ 7.32-7.26 (m, 5H), 7.14 (d, 2H, J= 8.5), 6.86-6.82 (m, 6H), 4.15-4.08 (m, 6H), 4.00 (dd, 1H, J= 6.9, 4.4), 3.41 (s, 3H), 3.14-3.05 (m, 3H), 2.97 (dd, 1H, J= 14.5, 6.9), 2.22 (qn, 2H, J= 6.1).

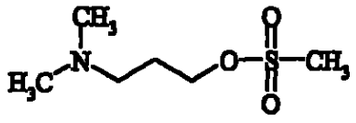
Example 268

(2*S*)-3-(4-{3-[4-(3-Dimethylamino-propoxy)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

Methanesulfonic acid 3-dimethylamino-propyl ester



3-Dimethylamino-1-propanol (0.98 mmol, 0.12 mL) was dissolved in THF (2 mL).

Triethylamine (1.47 mmol, 0.20 mL) was added, and the mixture was cooled at 0°C. Methanesulfonyl chloride (1.08 mmol, 0.08 mL) was added and the bath removed. The mixture was warmed to room temperature and stirred for 2 hours. Hexanes were added and the precipitates were removed by filtration through celite (hexanes). The filtrate was concentrated to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 4.29 (t, 2H, *J*= 6.4), 3.00 (s, 3H), 2.39 (t, 2H, *J*= 7.0), 2.22 (s, 6H), 1.90 (qn, 2H, *J*= 6.7).

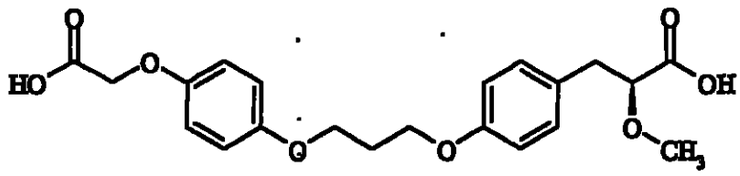
Step B

(2*S*)-3-{4-[3-[4-(3-Dimethylamino-propoxy)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid

The title compound was prepared from (2*S*)-3-{4-[3-(4-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Example 263, Step B) and methanesulfonic acid 3-dimethylamino-propyl ester (Step A) following the procedure described for Example 264. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.14 (d, 2H, *J*= 7.8), 6.83-6.77 (m, 6H), 4.10-4.04 (m, 5H), 3.95-3.89 (m, 4H), 3.37 (s, 3H), 3.16-3.13 (m, 2H), 3.06-2.99 (m, 2H), 2.77 (s, 6H), 2.21-2.15 (m, 4H).

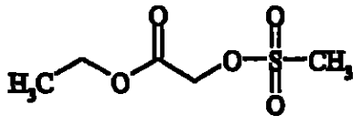
Example 269

(2*S*)-3-{4-[3-(4-Carboxymethoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

Methanesulfonyloxy-acetic acid ethyl ester

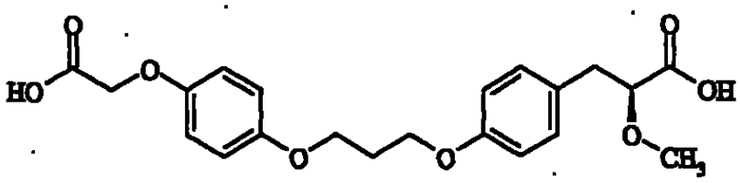


The title compound was prepared following the procedure described for

methanesulfonic acid 3-dimethylamino-propyl ester (Example 268, Step A) starting from ethyl glycolate. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 4.75 (s, 2H), 4.27 (q, 2H, *J*= 7.3), 3.20 (s, 3H), 1.31 (t, 3H, *J*= 7.3).

Step B

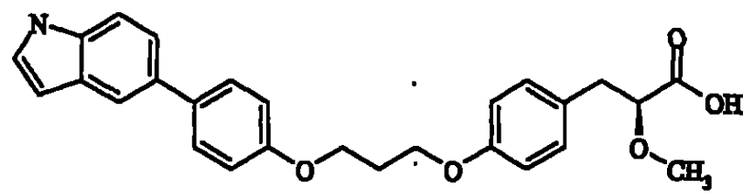
(2*S*)-3-{4-[3-(4-Carboxymethoxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2*S*)-3-{4-[3-(4-hydroxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Example 263, Step B) and methanesulfonyloxy-acetic acid ethyl ester (Step A) by following the procedure described for Example 264. ^{1}H-NMR (MeOD, 200.15 MHz): δ 7.13 (d, 2H, *J*= 8.6), 6.86-6.81 (m, 6H), 4.57 (s, 2H), 4.15-4.06 (m, 4H), 3.91 (dd, 1H, *J*= 7.8, 4.8), 3.31 (s, 3H), 2.99 (dd, 1H, *J*= 14.2, 4.6), 2.85 (dd, 1H, *J*= 14.2, 7.5), 2.17 (qn, 2H, *J*= 6.2).

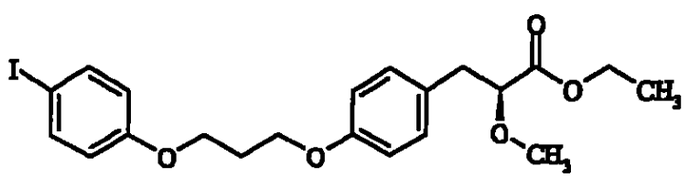
Example 270

(2*S*)-3-(4-{3-[4-(1H-Indol-5-yl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



Step A

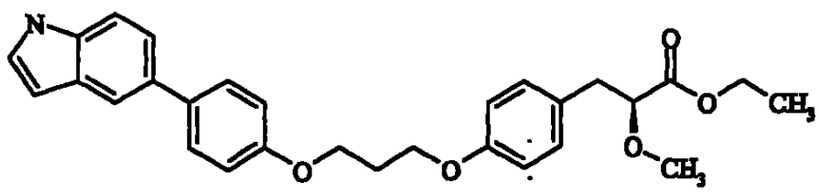
(2*S*)-3-{4-[3-(4-Iodo-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 173, Step A) and 4-iodo-phenol were treated under ester K (Cs_2CO_3) to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.54 (d, 2H, *J*= 8.9), 7.13 (d, 2H, *J*= 8.6), 6.82 (d, 2H, *J*= 8.9), 6.68 (d, 2H, *J*= 9.1), 4.23-4.08 (m, 6H), 3.90 (dd, 1H, *J*= 7.3, 5.9), 3.35 (s, 3H), 2.97-2.93 (m, 2H), 2.23 (qn, 2H, *J*= 6.2), 1.23 (t, 3H, *J*= 7.0).

Step B

(2*S*)-3-(4-{3-[4-(1H-Indol-5-yl)-phenoxyl-propoxy)-phenyl)-2-methoxy-propionic acid ethyl ester



To a stirred mixture of (2*S*)-3-{4-[3-(4-iodo-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (0.10 mmol, 50 mg) (Step A), 5-indolyl-boronic acid (0.114 mmol, 18 mg) and powered cesium carbonate (0.23 mmol, 35 mg) in DME (0.5 mL) was added $Pd(PPh_3)_4$ (0.003 mmol, 4 mg). The mixture was flushed with nitrogen and maintained under nitrogen while being heated at reflux in a 100°C oil bath. The mixture was stirred for 6 hours, and then cooled to room temperature and diluted with ethyl acetate and water. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography on silica gel (CH_2Cl_2/EtOAc 96:4) to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 8.20 (broad s, 1H), 7.80 (d, 1H, *J*= 0.8), 7.56 (d, 3H, *J*= 8.9), 7.41 (d, 2H, *J*= 1.6), 7.23 (dd, 1H, *J*= 3.2, 2.4), 7.15 (d, 3H, *J*= 8.6), 6.99 (d, 2H, *J*= 8.9), 6.85 (d, 3H, *J*= 8.6), 6.60-6.58 (m, 1H), 4.24-4.11 (m, 8H), 3.92 (dd, 1H, *J*= 7.3, 5.9), 3.35 (s, 4H), 2.98-2.94 (m, 3H), 2.28 (qn, 2H, *J*= 5.9), 1.24 (t, 4H, *J*= 7.3).

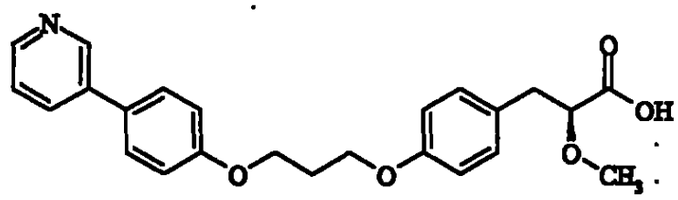
Step C

(2*S*)-3-(4-{3-[4-(1H-Indol-5-yl)-phenoxyl-propoxy)-phenyl)-2-methoxy-propionic acid

The title compound was obtained from (2*S*)-3-(4-{3-[4-(1H-indol-5-yl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid ethyl ester (Step B) by following the standard hydrolysis procedure C (NaOH). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 8.17 (broad s, 1H), 7.80 (s, 1H), 7.56 (d, 2H, *J*= 8.6), 7.42 (s, 2H), 7.24-7.21 (m, 1H), 7.15 (d, 2H, *J*= 8.6), 6.98 (d, 2H, *J*= 8.6), 6.86 (d, 2H, *J*= 8.6), 6.59-6.59 (m, 1H), 4.23-4.13 (m, 4H), 3.98 (dd, 1H, *J*= 7.3, 4.3), 3.39 (s, 3H), 3.10 (dd, 1H, *J*= 14.5, 4.0), 2.95 (dd, 1H, *J*= 14.5,7.3), 2.27 (qn, 2H, *J*= 6.2).

Example 271

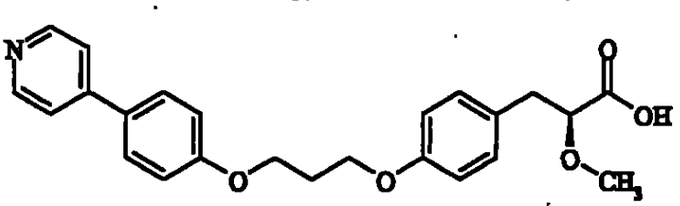
(2*S*)-2-Methoxy-3-{4-[3-(4-pyridin-3-yl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2*S*)-3-{4-[3-(4-iodo-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Example 270, Step A) and 3-pyridyl boronic acid by following the procedure described for Example 270 (Steps B and C). ^{1}H-NMR (MeOD, 300.15 MHz): δ 8.76 (s, 1H), 8.46 (s, 1H), 8.05 (d, 1H, *J*= 8.1), 7.60 (d, 2H, *J*= 8.7), 7.49 (dd, 1H, *J*= 7.7,4.8), 7.19 (d, 2H, *J*= 8.5), 7.09 (d, 2H, *J*= 8.7), 6.85 (d, 2H, *J*= 8.5), 4.24 (t, 2H, *J*= 6.1), 4.17 (t, 2H, *J*= 6.3), 3.74 (dd, 1H, *J*= 8.7, 3.8), 3.27 (s, 3H), 2.97 (dd, 1H, *J*= 14.3, 3.8), 2.81 (dd, 1H, *J*= 14.1, 8.5), 2.26 (qn, 2H, *J*= 6.0).

Example 272

(2*S*)-2-Methoxy-3-{4-[3-(4-pyridin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid

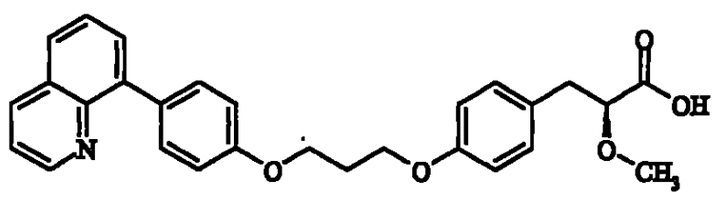


The title compound was prepared from (2*S*)-3-{4-[3-(4-iodo-phenoxy)-propoxy]-

phenyl}-2-methoxy-propionic acid ethyl ester (Example 270, Step A) and 4-pyridyl boronic acid by following the procedure described for Example 270 (Steps B and C). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 8.67-8.65 (m, 2H), 8.16 (d, 2H, *J*= 6.6), 7.90 (d, 2H, *J*= 8.8), 7.16-7.09 (m, 4H), 6.82 (d, 2H, *J*= 8.8), 4.26 (t, 2H, *J*= 6.2), 4.13 (t, 2H, *J*= 6.2), 3.90 (dd, 1H, *J*= 7.7, 4.8), 2.97 (dd, 1H, *J*= 14.3, 5.1), 2.83 (dd, 1H, *J*= 14.3, 7.7), 2.24 (qn, 2H, *J*= 5.9).

Example 273

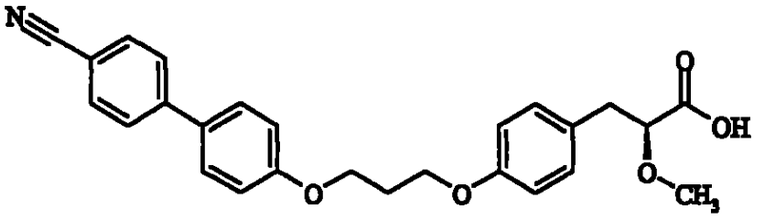
(2*S*)-2-Methoxy-3-{4-[3-(4-quinolin-8-yl-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2*S*)-3-{4-[3-(4-iodo-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Example 270, Step A) and 8-quinoline boronic acid by following the procedure described for Example 270 (Steps B and C). ^{1}H-NMR (MeOD, 300.15 MHz): δ 8.82 (d, 1H, *J*= 2.6), 8.39 (d, 1H, *J*= 8.1), 7.92 (d, 1H, *J*= 7.9), 7.74-7.63 (m, 2H), 7.58-7.51 (m, 3H), 7.18 (d, 2H, *J*= 8.5), 7.08 (d, 2H, *J*= 8.7), 6.88 (d, 2H, *J*= 8.7), 4.28 (t, 2H, *J*= 6.0), 4.20 (t, 2H, *J*= 6.3), 3.90-3.80 (m, 1H), 3.30 (s, 3H), 3.04-2.84 (m, 2H), 2.29 (qn, 2H, *J*= 6.3).

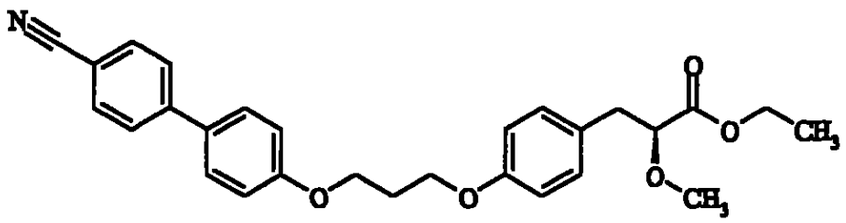
Example 274

(2*S*)-3-{4-[3-(4'-Cyano-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



Step A

(2*S*)-3-{4-[3-(4'-Cyano-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester



(2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 173, Step A) and 4'-hydroxy-4-biphenylcarbonitrile were treated under Mitsunobu standard conditions B (DIAD, toluene) to give the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.71-7.60 (m, 4H), 7.52 (d, 2H, *J*= 8.9), 7.14 (d, 2H, *J*= 8.9), 7.00 (d, 2H, *J*= 8.9), 6.83 (d, 2H, *J*= 8.6), 4.24-4.12 (m, 6H), 3.90 (dd, 1H, *J*= 7.3, 5.9), 3.34 (s, 3H), 2.97-2.93 (m, 2H), 2.27 (qn, 2H, *J*= 6.2), 1.23 (t, 3H, *J*= 7.3).

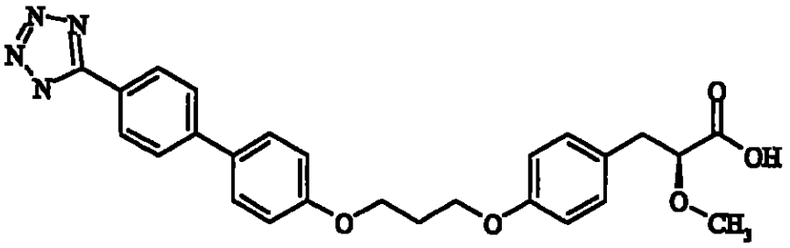
Step B

(2*S*)-3-{4-[3-(4'-Cyano-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid

The title compound was prepared from (2*S*)-3-{4-[3-(4'-cyano-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (Step A) via the standard hydrolysis procedure C (NaOH). ^{1}H-NMR (MeOD, 300.15 MHz): δ 7.77 (s, 4H), 7.64 (d, 2H, *J*= 8.7), 7.18 (d, 2H, *J*= 8.5), 7.07 (d, 2H, *J*= 8.7), 6.86 (d, 2H, *J*= 8.3), 4.24 (t, 2H, *J*= 6.3), 4.17 (t, 2H, *J*= 6.3), 3.84-3.74 (m, 1H), 3.03-2.81 (m, 2H), 2.26 (qn, 2H, *J*= 6.0).

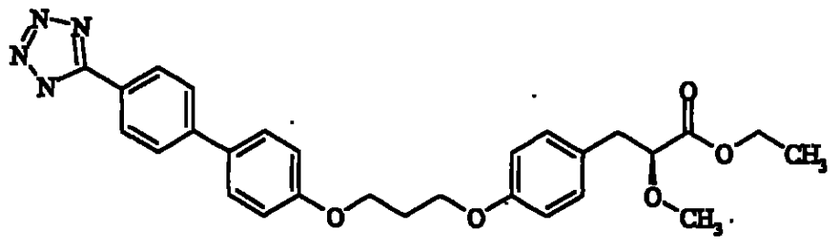
Example 275

(2*S*)-2-Methoxy-3-(4-{3-[4'-(1*H*-tetrazol-5-yl)biphenyl-4-yloxy]-propoxy}-phenyl)-propionic acid



Step A

(2*S*)-2-Methoxy-3-(4-{3-[4'-(1*H*-tetrazol-5-yl)biphenyl-4-yloxy]-propoxy}-phenyl)-propionic acid ethyl ester



Azidotributyltin (0.72 mmol, 0.2 mL) was added to a solution of (2*S*)-3-{4-[3-(4'-cyano-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid ethyl ester (0.36 mmol, 0.17 g) (Example 274, Step A) in toluene (1 mL). The mixture was heated at 60°C for 48 hours. The mixture was allowed to reach room temperature and 1N HCl was added. The mixture was heated at reflux for 24 additional hours. Upon cooling, water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by chromatography on silica gel (hexanes/ethyl acetate/acetic acid 3:2:10%) to afford the title product. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 8.12 (d, 2H, *J*= 8.3), 7.65 (d, 2H, *J*= 8.6), 7.51 (d, 2H, *J*= 8.9), 7.11 (d, 2H, *J*= 8.6), 6.95 (d, 2H, *J*= 8.6), 6.79 (d, 2H, *J*= 8.6), 4.25-4.06 (m, 7H), 3.97 (dd, 1H, *J*= 7.0, 5.4), 3.37 (s, 3H), 2.99-2.96 (m, 2H), 2.22 (qn, 2H, *J*= 5.9), 1.25 (t, 3H, *J*= 7.2).

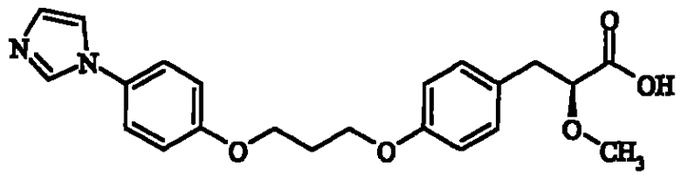
Step B

(2*S*)-2-Methoxy-3-(4-{3-[4'-(1*H*-tetrazol-5-yl)biphenyl-4-yloxy]-propoxy}-phenyl)-propionic acid

The title compound was prepared from (2*S*)-2-methoxy-3-(4-{3-[4'-(1*H*-tetrazol-5-yl)biphenyl-4-yloxy]-propoxy}-phenyl)-propionic acid ethyl ester (Step A) via the standard hydrolysis procedure C (NaOH). ^{1}H-NMR (MeOD, 300.15 MHz): δ 8.09 (d, 2H, *J*= 8.3), 7.70 (d, 2H, *J*= 8.3), 7.62 (d, 2H, *J*= 8.7), 7.18 (d, 2H, *J*= 8.5), 7.05 (d, 2H, *J*= 8.7), 6.86 (d, 2H, *J*= 8.7), 4.23 (t, 2H, *J*= 6.0), 4.17 (t, 2H, *J*= 6.1), 3.83 (dd, 1H, *J*= 8.3, 4.2), 3.36 (s, 3H), 2.99 (dd, 1H, *J*= 14.1, 4.0), 2.84 (dd, 1H, *J*= 13.9, 8.1), 2.26 (qn, 2H, *J*= 6.3).

Example 276

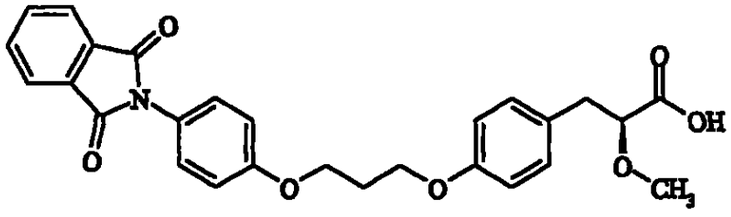
(2*S*)-3-{4-[3-(4-Imidazol-1-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 173, Step A) and 4-(imidazol-1-yl) phenol were treated under ester J to give the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 8.11 (s, 1H), 7.31-7.16 (m, 7H), 6.99 (d, 2H, *J*= 8.9), 6.82 (d, 2H, *J*= 8.6), 4.19 (t, 2H, *J*= 6.2), 4.12 (t, 2H, *J*= 5.9), 3.95 (dd, 1H, *J*= 7.3, 4.8), 3.39 (s, 3H), 3.08 (dd, 1H, *J*= 14.4, 4.8), 2.96 (dd, 1H, *J*= 14.2, 7.6), 2.26 (qn, 2H, *J*= 5.9).

Example 277

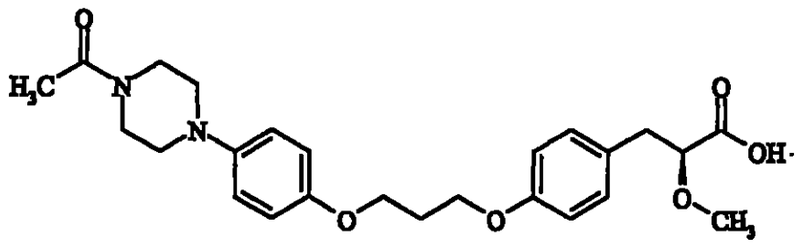
(2*S*)-3-{4-[3-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



The title compound was obtained from (2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 173, Step A) and N-(4-hydroxyphenyl) phtalimide by following the procedure described for Example 276. ^{1}H-NMR ($CDCl_3$, 300.15 MHz): δ 7.97-7.92 (m, 2H), 7.81-7.77 (m, 2H), 7.32 (d, 2H, *J*= 8.9), 7.15 (d, 2H, *J*= 8.5), 7.02 (d, 2H, *J*= 8.9), 6.85 (d, 2H, *J*= 8.5), 4.20 (t, 2H, *J*= 6.0), 4.16 (t, 2H, *J*= 6.0), 3.99 (dd, 1H, *J*= 7.3, 4.4), 3.41 (s, 3H), 3.11 (dd, 1H, *J*= 14.3, 4.4), 2.97 (dd, 1H, *J*= 14.3, 7.1), 2.27 (qn, 2H, *J*= 6.0).

Example 278

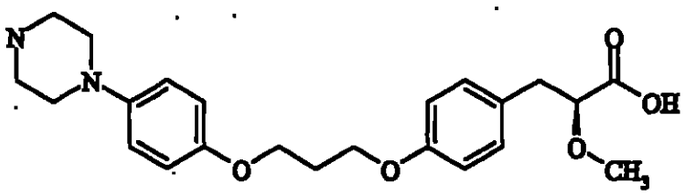
(2*S*)-3-{4-{3-[4-(4-Acetyl-piperazin-1-yl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid



The title compound was obtained from (2*S*)-3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 173, Step A) and 1-acetyl-4-(4-hydroxyphenyl)piperazine by following the procedure described for Example 276. ^{1}H-NMR (CDCl$_3$, 300.15 MHz): δ 7.14 (d, 2H, *J*= 8.5), 6.90-6.80 (m, 5H), 4.15-4.09 (m, 3H), 3.98 (dd, 1H, *J*= 6.7, 4.9), 3.79-3.76 (m, 2H), 3.63-3.60 (m, 2H), 3.40 (s, 3H), 3.11-2.93 (m, 6H), 2.14 (s, 3H).

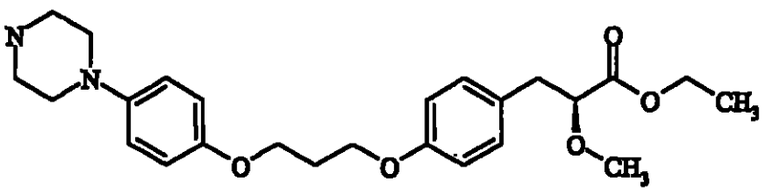
Example 279

(2*S*)-2-Methoxy-3-{4-[3-(4-piperazin-1-yl-phenoxy)-propoxy]-phenyl}-propionic acid



Step A

(2*S*)-2-Methoxy-3-{4-[3-(4-piperazin-1-yl-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester



3-[4-(3-Bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 173, Step A) and 1-(4-hydroxyphenyl)-piperazine were treated under ester K to give

the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 8.01 (s, 1H), 7.13 (d, 2H, *J*= 8.6), 6.88-6.75 (m, 6H), 4.30 (t, 2H, *J*= 6.4), 4.17 (q, 2H, *J*= 7.0), 4.02 (t, 2H, *J*= 5.9), 3.94-3.87 (m, 1H), 3.64-3.60 (m, 4H), 3.34 (s, 3H), 2.98-2.96 (m, 4H), 2.18-2.04 (m, 2H), 1.23 (t, 3H, *J*= 7.3).

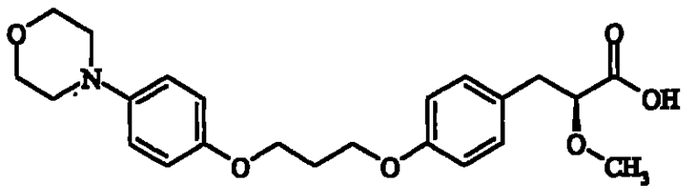
Step B

(2*S*)-2-Methoxy-3-{4-[3-(4-piperazin-1-yl-phenoxy)-propoxy]-phenyl}-propionic acid

The title compound was prepared from (2*S*)-2-methoxy-3-{4-[3-(4-piperazin-1-yl-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester (Step A) by standard hydrolysis procedure C (NaOH). ^{1}H-NMR (MeOD, 300.15 MHz): δ 7.18 (d, 2H, *J*= 8.5), 6.89-6.83 (m, 4H), 6.72 (d, 2H, *J*= 9.1), 4.30 (t, 2H, *J*= 6.3), 4.07 (t, 2H, *J*= 6.1), 3.86-3.82 (m, 1H), 3.62-3.59 (m, 4H), 3.36 (s, 3H), 3.07-2.83 (m, 6H), 2.12 (qn, 2H, *J*= 6.3).

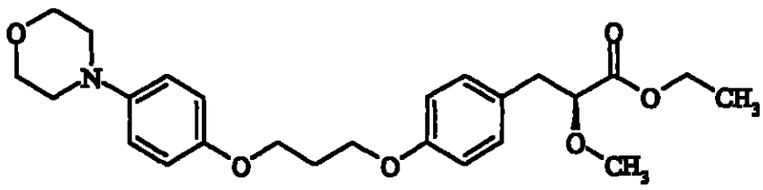
Example 280

(2*S*)-2-Methoxy-3-{4-[3-(4-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid



Step A

(2*S*)-2-Methoxy-3-{4-[3-(4-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester



A mixture of (2*S*)-3-{4-[3-(4-iodo-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic

acid ethyl ester (1.03 mmol, 0.5 g), morpholine (1.24 mmol, 0.11 mL), $Pd(OAc)_2$ (0.05 mmol, 12 mg), 2,2'-bis(diphenylphsphino)-1,1'-binaphthyl (0.08 mmol, 48 mg) and cesium carbonate (1.45 mmol, 471 mg) in DMF (2 mL) was heated at 110°C for 14 hours. The mixture was purified through a silica gel column (hexanes/ethyl acetate 7:3) to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.11 (d, 2H, *J*= 8.8), 6.85 (broad s, 2H), 6.80 (d, 4H, *J*= 8.8), 4.21-4.04 (m, 6H), 3.91-3.80 (m, 5H), 3.32 (s, 3H), 3.10-2.95 (m, 4H), 2.94-2.91 (m, 2H), 2.20 (qn, 2H, *J*= 5.9), 1.23 (t, 3H, *J*= 7.2).

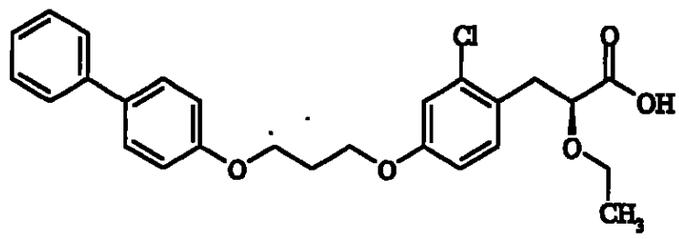
Step B

(2*S*)-2-Methoxy-3-{4-[3-(4-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid

The title compound was prepared from (2*S*)-2-methoxy-3-{4-[3-(4-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid ethyl ester (Step A) by standard hydrolysis procedure C (NaOH). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 9.90 (s, 1H), 7.30 (d, 2H, *J*= 9.1), 7.10 (d, 2H, *J*= 8.4), 6.91 (d, 2H, *J*= 9.1), 6.75 (d, 2H, *J*= 8.8), 4.18-3.90 (m, 9H), 3.43-3.33 (m, 7H), 3.02 (dd, 1H, *J*= 14.3, 4.8), 2.90 (dd, 1H, *J*= 14.3, 7.0), 2.18 (qn, 2H, *J*= 5.9).

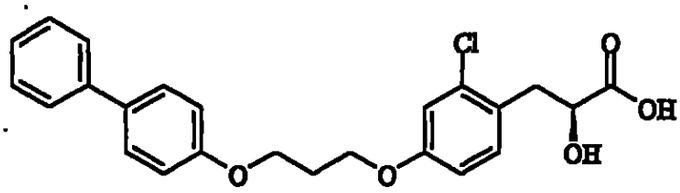
Example 281

(2*S*)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-ethoxy-propionic acid



Step A

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-hydroxy-propionic acid



Boron tribromide (0.03 mmol, 0.03 mL) was added to a solution of 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid (0.06 mmol, 25.5 mg) (Example 191) in CH_2Cl_2 (0.4 mL) at -78°C. The mixture was warmed to temperature gradually and stirred for 12 hours. The solvent was concentrated to dryness to afford the title compound. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): δ 7.56-7.18 (m, 8H), 6.99-6.95 (m, 3H), 6.79-6.75 (m, 1H), 4.58-4.42 (m, 1H), 4.25-4.12 (m, 4H), 3.34-2.92 (m, 2H), 2.30-2.22 (m, 2H).

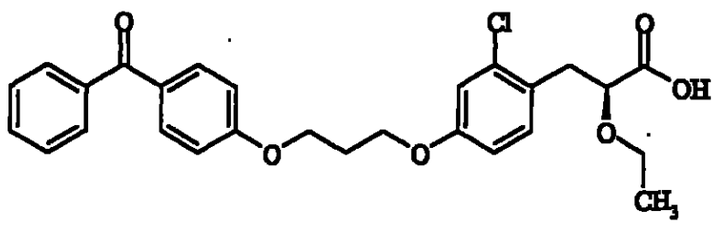
Step B

3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-ethoxy-propionic acid

Ethyl iodide (0.6 mmol, 0.05 mL) was added to a solution of 3-{4-[3-(biphenyl-4-yloxy)-propoxy]-2-chloro-phenyl}-2-hydroxy-propionic acid (Step A) and Ag_2O (0.09 mmol, 21 mg) in DMF (0.5 mL). The mixture was heated at 50°C for 24 hours. The mixture was warmed to room temperature, and 1N HCl was added until pH 3. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The crude was purified by chromatography on silica gel (CH_2Cl_2) to afford the title compound. ^{1}H-NMR ($CDCl_3$, 300.15 MHz): δ 7.56-7.51 (m, 4H), 7.44-7.39 (m, 2H), 7.30 (t, 1H, *J*= 7.3), 7.20 (d, 1H, *J*= 8.5), 6.99 (d, 2H, *J*= 8.7), 6.95 (d, 1H, *J*= 2.4), 6.77 (dd, 1H, *J*= 8.5, 2.4), 4.21-4.13 (m, 5H), 3.64-3.54 (m, 1H), 3.44-3.34 (m, 1H), 3.29 (dd, 1H, *J*= 14.1, 4.2), 3.01 (dd, 1H, *J*= 14.1, 8.7), 2.28 (qn, 2H, *J*=6.0), 1.12 (t, 3H, *J*= 6.9).

Example 282

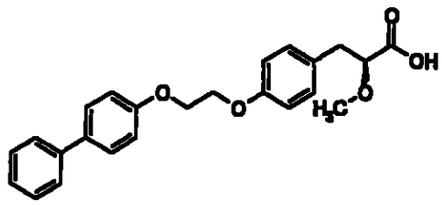
3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-chloro-phenyl}-2-ethoxy-propionic acid



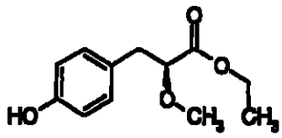
The title compound was prepared from 3-{4-[3-(4-benzoyl-phenoxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid (Example 193) by following the same procedure as in Example 281 (Steps A and B). ^{1}H-NMR ($CDCl_3$, 300.15 MHz): δ 7.82 (d, 2H, *J*= 8.7), 7.76 (d, 2H, *J*= 8.1), 7.61-7.55 (m, 1H), 7.50-7.45 (m, 2H), 7.18 (d, 1H, *J*= 8.5), 6.99-6.95 (m, 3H), 6.77 (dd, 1H, *J*= 8.5, 2.4), 4.25 (t, 2H, *J*= 5.9), 4.17-4.14 (m, 3H), 3.61-3.38 (m, 2H), 3.29 (dd, 1H, *J*= 14.1, 4.9), 3.02 (dd, 1H, *J*= 14.1, 8.1), 2.31 (qn, 2H, *J*= 5.9), 1.14 (t, 3H, *J*= 7.1).

EXAMPLE 283

(2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



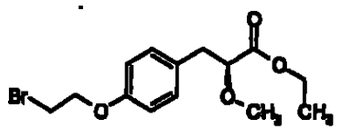
Step 1: (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester



The compound of (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid (5.1 mmol) was dissolved in 50 ml of ethanol and 0.3 ml (5.6 mmol) of sulfuric acid was added. The mixture was stirred at room temperature for 18 hours and then concentrated. The mixture was diluted with water (55 ml) and $NaHCO_3$ was added (310 mg, 3.7 mmol). This mixture was extracted with ethyl acetate (4 x 20 mL), and the combined organic layers were dried ($MgSO_4$) and then concentrated to produce a yellow oil. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.07 (d, 2H, J=8.6), 6.72 (d, 2H, J=8.6),

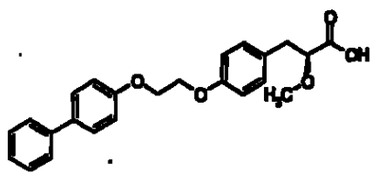
5.42 (br s, 1H), 4.18 (q, 2H, J=7.3), 3.92 (dd, 1H, J=6.7, 5.9), 3.36 (s, 3H), 2.95 (d, 2H, J=6.7), 1.23 (t, 3H; J=7.3).

Step2: (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester



A mixture containing (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester obtained in Step 1 (0.223 mol, 50 mg), potassium carbonate (0.446 mol, 50 mg), magnesium sulfate (powdered, 50 mg, 1 g/g), ethylene dibromide (3.35 mol, 628 mg) and EtOH (25 mL) was heated at reflux (78-76°C) for 24 hours and cool to room temperature. The mixture was heated again to reflux (76.5-77°C) and 2 mL of ethylene dibromide was added. The mixture was heated for another 12 hours at 79.5-80.1°C and then cooled to room temperature and vacuum filtered. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 6:1, Rf 0.27) to produce a colorless oil. MS (ES) for $C_{14}H_{19}BrO_4$ $[M+Na]^+$: 353.0.

Step 3: (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid

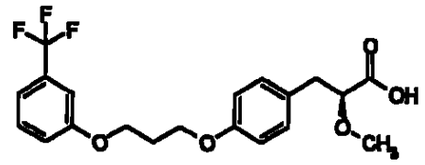


A solution of biphenyl-4-ol (0.39 mmol, 68 mg) in 10 ml of DMF in was treated with (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester obtained in Step 2 (0.33 mmol, 100 mg) and cesium carbonate (0.66 mmol, 214 mg) in a round bottom flask. The reactants were filtered and washed with DMF several times and the solvent was evaporated under vacuo. The residue was reconstituted in a mixture of ethanol (20 ml) and NaOH (1M) (8 ml), and then stirred at room temperature until TLC indicated the disappearance of starting material. Ethanol was removed under vacuum, and the aqueous solution was diluted with 20 mL of brine and washed with diethyl ether (3 x 15 mL). The aqueous phase was acidified with

1N HCl (pH 1-2) and extracted with ethyl acetate (3 x 15 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to yield the title compound. MS (ES) for $C_{24}H_{24}O_5$ $[M+Na]^+$: 415.4.

Example 284

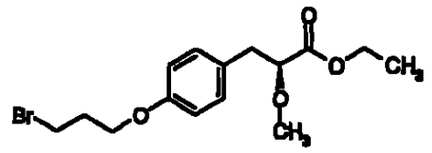
(2S)-2-methoxy-3-{4-[3-(3-trifluoromethyl-phenoxy)-propoxyl-phenyl}-propionic acid



Step 1: 3-bromo-propan-1-ol

The compound of 1,3-propanodiol (10.26 g, 134.8 mmol) was dissolved in benzene (150 mL), and HBr 48% (16.84 mL) was added. The mixture was refluxed under aceotropic removal of water for 24 hours. The solvent was distilled at atmospheric pressure, and the residue was diluted with ether and (150 mL) and washed with water (3 x 50) mL. The organic layer was dried over $MgSO_4$ and concentrated to afford a yellowish oil. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 3.80 (t, 2H, J=6.4), 3.54 (t, 2H, J=6.5), 2.10 (qn, 2H, J=6.4).

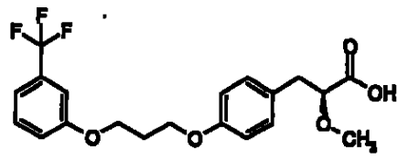
Step 2: (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester



A solution of triphenylphosphine (4.77 mmol, 1250 mg) in 50 mL of dry toluene was treated at 0°C with diisopropilazodicarboxylate (4.77 mmol, 964.5 mg) and stirred for about 20 minutes. A solution of (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (Example 283, Step 1) (4.46 mmol, 1000 mg) and 3-bromo-propan-1-ol (4.77 mmol, 663 mg) in 10 mL of dry THF was added, and the mixture was stirred at room temperature overnight. The mixture was concentrated to dryness under vacuum and purified by silica gel chromatography (silica gel,

hexanes/ethyl acetate 6:1). The fraction with Rf 0.4 corresponding to the coupled compound was combined and concentrated to dryness to afford a yellow oil. MS (ES) for $C_{15}H_{21}BrO_4$ $[M+Na]^+$: 367.2.

Step 3: (2S)-2-methoxy-3-{4-[3-(3-trifluoromethyl-phenoxy)-propoxy]-phenyl}-propionic acid

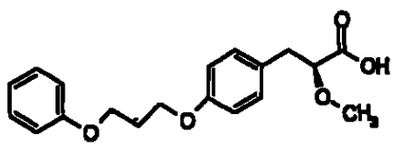


The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 3-trifluoromethyl-phenol via the same procedure used for the preparation of (2S)-3-{4-[2-(Biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3) to produce a yellow solid.

MS (ES) for $C_{20}H_{21}F_3O_5$ $[M+NH_4]^+$: 421.4.

Example 285

(2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid

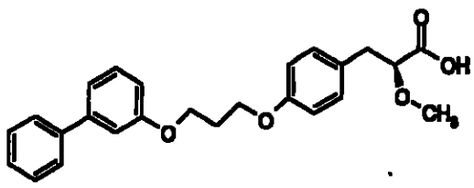


A solution of (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) (0.1 mmol, 32 mg) in 0.7 ml of DMF in a 16 x 100 mm tube was treated with phenol (0.15 mmol, 15 mg), cesium carbonate (0.3 mmol, 95 mg). The mixture was stirred at room temperature overnight, and the reactants were filtered and washed with DMF a several times. The solvent was evaporated under vacuum, and the residue was reconstituted in a mixture of ethanol (2 ml) and NaOH (1M, 1 ml), which was stirred at room temperature until reaction was completed by HPLC-MS. Upon completion, HCl (1M) was added (pH=3) and the solvents were eliminated under vacuum. The residue was reconstituted in CH_2Cl_2/H_2O and filtered through a hidrofobic syringer. The organic layer was separated, concentrated and

purified by HPLC-MS to afford the title compound as a colorless oil. MS (ES) for $C_{19}H_{22}O_5$ $[M+NH_4]^+$: 348.4.

Example 286

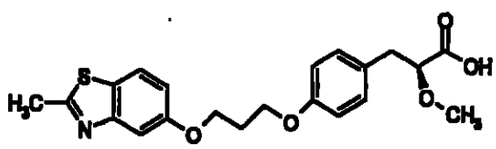
(2S)-3-{4-[3-(biphenyl-3-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and biphenyl-3-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{25}H_{26}O_5$ $[M+Na]^+$: 429.4.

Example 287

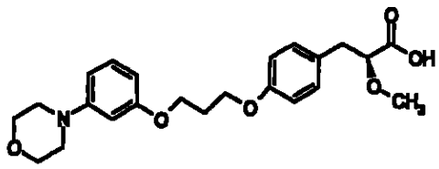
(2S)-2-methoxy-3-{4-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 2-methyl-benzothiazol-5-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.
MS (ES) for $C_{21}H_{23}NO_5S$ $[M+H]^+$: 402.4.

Example 288

(2S)-2-methoxy-3-{4-[3-(3-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid

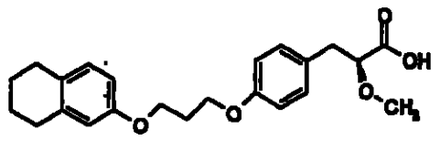


The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 3-Morpholin-4-yl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.

MS (ES) for $C_{23}H_{29}NO_6$ $[M+H]^+$: 416.4.

Example 289

(2S)-2-methoxy-3-{4-[3-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid

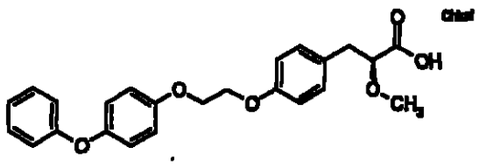


The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 5,6,7,8-tetrahydro-naphthalen-2-ol via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3), to produce a white solid.

MS (ES) for $C_{23}H_{28}O_5$ $[M+Na]^+$: 402.4.

Example 290

2-methoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid

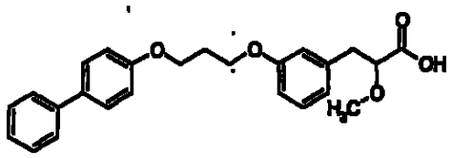


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 4-phenoxy-phenol via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3) to produce a white solid.

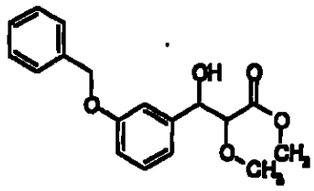
MS (ES) for $C_{24}H_{24}O_6$ $[M+NH_4]^+$: 426.0.

Example 291

3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)



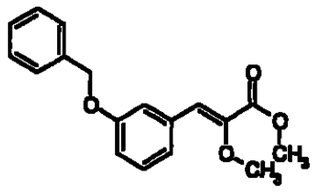
Step 1: 3-(3-benzyloxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester



Sodium trimethylsilylamide 1M in THF (20.73 mL, 20.73 mmol) was added to a 2-neck round bottom flask under nitrogen. The flask was placed in an acetone bath cooled to about -78°C. A solution of methyl 2-methoxyacetate (2.34 mL, 23.55 mmol) and 3-benzyloxybenzaldehyde (4.0 g, 18.85 mmol) in dry THF (24 mL) was added dropwise via cannula over 10 minutes. The mixture was stirred at -78°C for 3 hours. HPLC-MS showed the presence of starting aldehyde at this time. Additional 10mL of NaHDMS were added, and the mixture was stirred for another hour, and then HCl 3N (50 mL) was added to the mixture at -78°C. The bath was removed, and the mixture was extracted with diethyl ether (4 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford an oil that was purified by

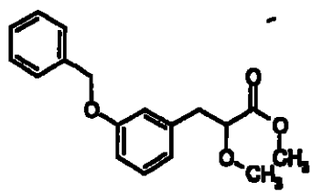
chromatography (silica gel, hexanes/ethyl acetate 3:1). Rf. 0.13. (two isomers) ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.45-7.22 (m, 12H), 7.05-6.89 (m, 6H), 5.07 (d, 4H, J=1.1), 4.93 (dd, 2H, J=11.8, 5.9), 3.97 (d, 1H, J=5.6), 3.89 (d, 1H, J=5.4), 3.67 (s, 3H), 3.65 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 2.92 (br s, 1H), 2.83 (br s, 1H).

Step 2: 3-(3-benzyloxy-phenyl)-2-methoxy-acrylic acid methyl ester



The compounds of 3-(3-benzyloxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester (Example 291, Step 1) (4.06 g, 12.84 mmol), triethylamine (7.15 mL, 51.33 mmol) and 4-(N,N-dimethylamino)pyridine (0.157 g, 1.28 mmol) were dissolved in dichloromethane (20 mL) in a round bottom flask and then cooled to 0 °C under ice bath. Mesyl chloride (1.093 mL, 14.1 mmol) was added dropwise via syringe, and the mixture was stirred at room temperature until no starting aldol is observed by HPLC-MS (4 days, 0.2 additional mL of MsCl were added each day). The mixture was diluted with 200 mL of diethyl ether, washed with HCl (1N, 3 x 40 mL) and 40 mL of brine, and dried over $MgSO_4$. Concentration of the mixture afforded 3.96 g of a 2.5:1 mixture of the acrylate and a single isomer of the mesylate intermediate which was directly used in the next Step. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.46-7.26 (m, 8H), 6.99-6.93 (m, 1H), 5.10 (s, 2H), 3.85 (s, 3H), 3.72 (s, 3H).

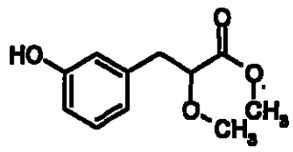
Step 3: 3-(3-benzyloxy-phenyl)-2-methoxy-propionic acid methyl ester



A solution of 3-(3-benzyloxy-phenyl)-2-methoxy-acrylic acid methyl ester (Example 291, Step 2) (3.96 g) in methanol (10 mL) was placed in a round bottom flask

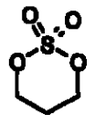
equipped with a reflux condenser. The mixture was cooled to 0°C and Mg turnings (6.45 g) were added. The mixture was initially stirred vigorously and then further stirred at room temperature for about an hour. The solvent was evaporated under vacuum, and 100 mL of diethyl ether were added to the resulting solid. HCl (3N, 100 mL) was added and the solution was stirred for one minute. The organic layer was separated from the slurry, and 100 mL of diethyl ether and HCl (3N, 100 mL) were added to the remaining slurry. The procedure was repeated until the entire solid was dissolved. The combined ethereal extracts were washed with brine and dried over $MgSO_4$. Concentration of the mixture afforded a yellow oil which was about 90% pure by NMR. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.45-7.17 (m, 6H), 6.88-6.81 (m, 3H), 5.05 (s, 2H), 3.97 (dd, 1H, J=7.3, 5.4), 3.72 (s, 3H), 3.34 (s, 3H), 3.00 (d, 1H, J=5.1), 2.99 (d, 1H, J=7.8).

Step 4: 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester



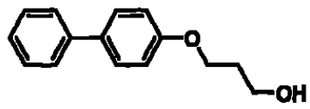
The compounds of 3-(3-benzyloxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 3) (3.15 g, 10.49 mmol) and Pd 10% on activated carbon (0.558 g, 0.524 mmol) were placed in a 250-ml round bottom flask equipped with a magnetic stirring bar. 100 mL of methanol was added, and hydrogen was bubbled through the solution for 10 minutes. The flask was sealed with a rubber septum, and a balloon containing 250 mL of hydrogen was connected to the flask through a needle. The mixture was stirred at room temperature for 5 hours and then concentrated to dryness under vacuum. The residue was taken up in ethyl acetate and filtered through a pad of celite. Concentration of the mixture afforded an oil. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.15 (dt, 1H, J=1.1, 7.0), 6.79-6.68 (m, 3H), 5.27 (br s, 1H), 3.98 (dd, 1H, J=7.5, 5.6), 3.73 (s, 3H), 3.35 (s, 3H), 2.97 (d, 1H, J=3.8), 2.97 (d, 1H, J=9.1).

Step 5: [1,3,2]dioxathiane 2,2-dioxide



Thionyl chloride (36 mL, 491 mmol) was added to a solution of 1,3-propanodiol (30 g, 394 mmol) in CCl_4 (278 mL) via syringe. The mixture was heated at reflux for 1.5 hours and cooled to 0°C to evaporate the solvent under vacuum. The residue was dissolved in a mixture of $CCl_4/CH_3CN/H_2O$ (2:2:3=500 mL) and cooled to 0°C. Ruthenium trichloride trihydrate (0.556 g, 2.68 mmol) was added followed by addition of solid $NaIO_4$ (14.35 g, 197 mmol). The mixture was stirred at room temperature for 1 hour and then H_2O (1 L) was added. The aqueous phase was extracted with diethyl ether (4 x 300 mL). The combined organic layers were washed with brine (2 x 100 mL), dried ($MgSO_4$), and filtered through a pad of silica gel to remove the ruthenium salts. The solvent was evaporated, and hexanes (200 mL) was added to the resulting oil. After cooling, a gray solid was precipitated, which was filtered and washed with hexanes. Recrystallization from hexanes/ether yielded a white crystalline solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): d 4.73 (t, 4H, J=5.6), 2.13 (qn, 2H, J=5.6).

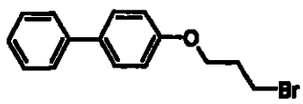
Step 6: 3-(biphenyl-4-yloxy)-propan-1-ol



A solution of 4-phenylphenol (4.9 g, 29.0 mmol) and potassium tert-butoxide (3.64 g, 30.3 mmol) in THF (100 mL) was stirred at room temperature for 30 minutes. The solution was cooled at 0°C and [1,3,2]dioxathiane 2,2-dioxide (Example 291, Step 5) (3.6 g, 26.34 mmol) in THF (25 mL) was added. The mixture was stirred at room temperature for 5 hours, and the solvent was removed under vacuum. The residue was dissolved in 6N HCl (15 mL) and heated at 100°C for 16 hours. The mixture was cooled to room temperature, and the aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with H_2O (3 x 25 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to produce a

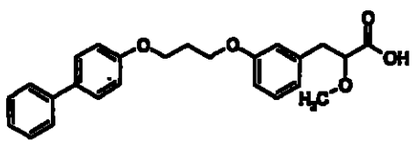
white solid. ^{1}H-NMR (200.15 MHz, $CDCl_3$): d 7.57-7.49 (m, 4H), 7.45-7.37 (m, 3H), 6.98 (dd, 2H, J=6.72, 2.14), 4.17 (t, 2H, J=5.9), 3.88 (q, 2H, J=5.9), 2.07 (qn, 2H, J=5.9).

Step 7: 4-(3-bromo-propoxy)-biphenyl



Triphenylphosphine (1.61 g, 6.14 mmol) was added to a solution of 3-(biphenyl-4-yloxy)-propan-1-ol (Example 291, Step 6) (1.00 g, 4.38 mmol) and carbon tetrabromide (1.81 g, 5.47 mmol) in CH2Cl2 (20 mL) at 0°C. The mixture was warmed to room temperature and stirred for about an hour and then extracted with ethyl acetate (50 mL). The organic layer was washed with H_2O (3 x 50 mL) and brine (3 x 25 mL), and then dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel column chromatography (silica gel, hexanes/ethyl acetate, 9:1) to produce 4-(3-bromo-propoxy)-biphenyl. ^{1}H-NMR (200.15 MHz, $CDCl_3$): d 7.57-7.29 (m, 7H), 6.98 (dd, 2H, J=6.72, 1.88), 4.15 (t, 2H, J=5.92), 3.62 (t, 2H, J=6.44), 2.34 (qn, 2H, J=5.92).

Step 8: 3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (Isomer 1)

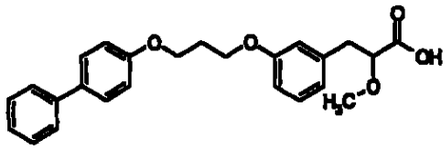


The title compound was prepared from 4-(3-bromo-propoxy)-biphenyl (Example 291, Step 7) and 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 4) (0.3 g, 1.42 mmol) via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3). The crude material was submitted to chiral HPLC separation to afford the single enantiomer of isomer 1. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.57-7.17 (m, 7H), 6.99 (dd, 2H, J=6.7, 2.2), 6.85-6.80 (m, 3H), 4.19

(dd, 4H, J=13.4, 6.4), 4.03 (dd, 1H, J=7.3, 4.3), 3.40 (s, 3H), 0.14 (dd, 1H, J=14.0, 4.3), 2.98 (dd, 1H, J=14.8, 7.5), 2.28 (qui, 2H, J=5.9).

Example 292

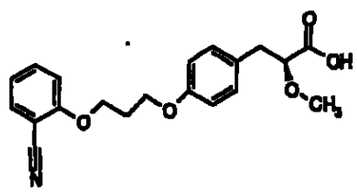
3-{3-[3-(biphenyl-4-yloxy)-propoxyl-phenyl}-2-methoxy-propionic acid (Isomer 2)



The title compound was prepared from 4-(3-bromo-propoxy)-biphenyl (Example 291, Step 7), and 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 4) via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3). The crude material was submitted to chiral HPLC separation to afford the single enantiomer of isomer 2. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.57-7.17 (m, 7H), 6.99 (dd, 2H, J=6.7, 2.2), 6.85-6.80 (m, 3H), 4.19 (dd, 4H, J=13.4, 6.4), 4.03 (dd, 1H, J=7.3, 4.3), 3.40 (s, 3H), .14 (dd, 1H, J=14.0, 4.3), 2.98 (dd, 1H, J=14.8, 7.5), 2.28 (qn, 2H, J=5.9).

Example 293

(2S)-3-{4-[3-(2-cyano-phenoxy)-propoxyl-phenyl}-2-methoxy-propionic acid

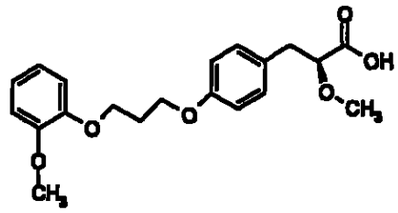


The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 2-hydroxy-benzonitrile via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.

MS (ES) for $C_{20}H_{21}NO_5$ $[M+NH_4]^+$: 373.4.

Example 294

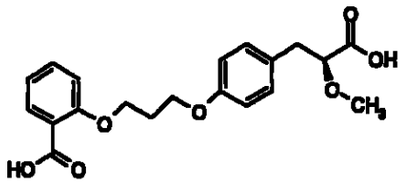
(2S)-2-methoxy-3-{4-[3-(2-methoxy-phenoxy)-propoxyl-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 2-methoxy-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.
MS (ES) for $C_{20}H_{24}O_6$ $[M+NH_4]^+$: 378.4.

Example 295

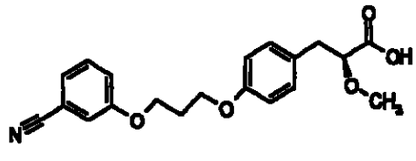
(2S)-2-{3-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 2-hydroxy-benzoic acid methyl ester via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.
MS (ES) for $C_{20}H_{22}O_7$ $[M+H]^+$: 375.2.

Example 296

(2S)-3-{4-[3-(3-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

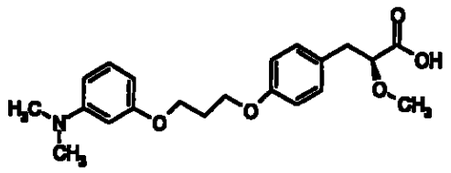


The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 3-hydroxy-benzonitrile via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.

MS (ES) for $C_{20}H_{21}NO_5$ $[M+NH_4]^+$: 373.4.

Example 297

(2S)-3-{4-[3-(3-dimethylamino-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid

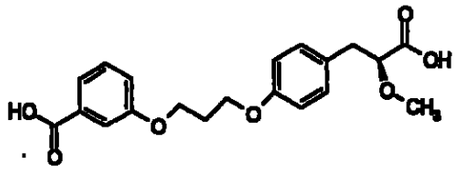


The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 3-dimethylamino-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.

MS (ES) for $C_{21}H_{27}NO_5$ $[M+H]^+$: 374.4.

Example 298

(2S)-3-{3-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid

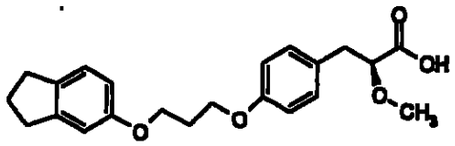


The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 3-hydroxy-benzoic acid methyl ester via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.

MS (ES) for $C_{20}H_{22}O_7$ [M+Na]$^+$: 397.4.

Example 299

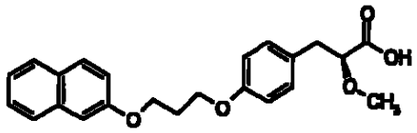
(2S)-3-{4-[3-(indan-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and indan-5-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{22}H_{26}O_5$ [M+Na]$^+$: 393.4.

Example 300

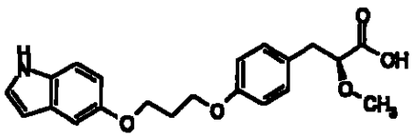
(2S)-2-methoxy-3-{4-[3-(naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and naphthalen-2-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{23}H_{24}O_5$ [M+Na]$^+$: 403.4.

Example 301

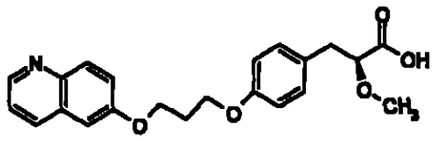
(2S)-3-{4-[3-(1H-indol-5-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 1H-indol-5-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{21}H_{23}NO_5$ $[M+H]^+$: 370.4.

Example 302

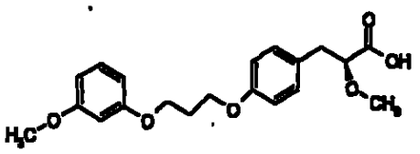
(2S)-2-methoxy-3-{4-[3-(quinolin-6-yloxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and quinolin-6-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{22}H_{23}NO_5$ $[M+H]^+$: 382.4.

Example 303

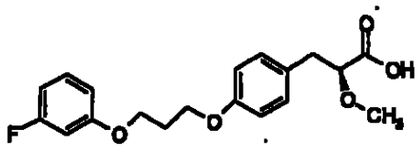
(2S)-2-methoxy-3-{4-[3-(3-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 3-methoxy-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{20}H_{24}O_6$ $[M+H]^+$: 361.4.

Example 304

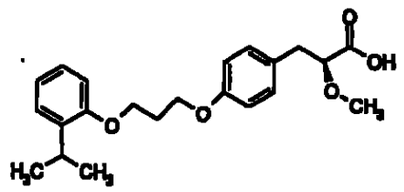
(2S)-3-{4-[3-(3-fluoro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 3-fluoro-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{19}H_{21}FO_5$ $[M+Na]^+$: 371.4.

Example 305

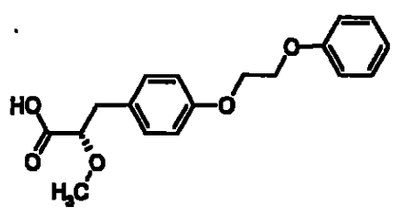
(2S)-3-{4-[3-(2-isopropyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2) and 2-isopropyl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{22}H_{28}O_5$ $[M+NH_4]^+$: 390.4.

Example 306

(2S)-2-methoxy-3-[4-(2-phenoxy-ethoxy)-phenyl]-propionic acid

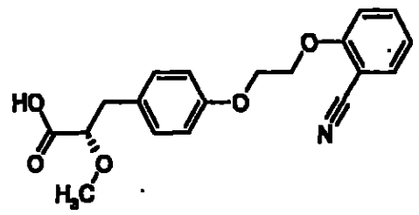


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and phenol via the same

procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{18}H_{20}O_5$ $[M+Na]^+$: 339.3.

Example 307

(2S)-3-{4-[2-(2-cyano-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid

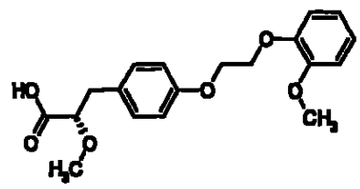


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2-hydroxy-benzonitrile via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.

MS (ES) for $C_{19}H_{19}NO_5$ $[M-H]^-$: 340.3.

Example 308

(2S)-2-methoxy-3-{4-[2-(2-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid

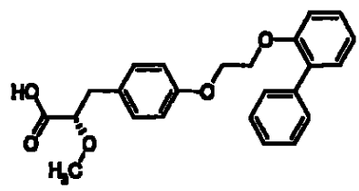


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2-methoxy-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{19}H_{22}O_6$ $[M+Na]^+$: 369.4.

Example 309

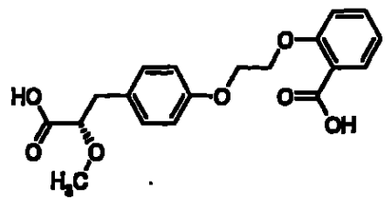
(2S)-3-{4-[2-(biphenyl-2-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and biphenyl-2-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{24}H_{24}O_5$ [M+Na]$^+$: 415.4.

Example 310

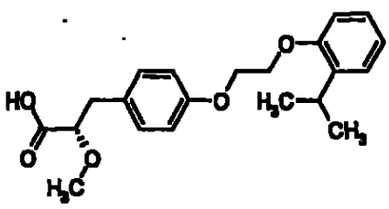
(2S)-2-{2-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-ethoxy}-benzoic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2-hydroxy-benzoic acid methyl ester via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{19}H_{20}O_7$ [M+Na]$^+$: 383.3.

Example 311

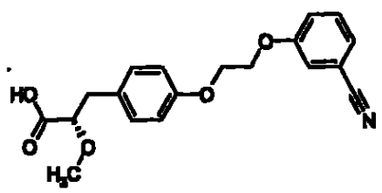
(2S)-3-{4-[2-(2-isopropyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2-isopropyl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.
MS (ES) for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.4.

Example 312

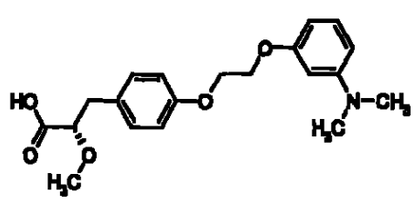
(2S)-3-{4-[2-(3-cyano-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 3-hydroxy-benzonitrile via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.
MS (ES) for $C_{19}H_{19}NO_5$ $[M-H]^-$: 340.3.

Example 313

(2S)-3-{4-[2-(3-dimethylamino-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



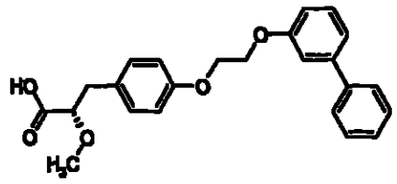
The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 3-dimethylamino-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-

phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a yellow oil.

MS (ES) for $C_{21}H_{26}O_5$ $[M+H]^+$: 360.4.

Example 314

(2S)-3-{4-[2-(biphenyl-3-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid

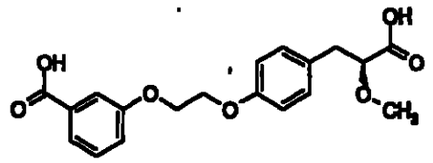


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and biphenyl-3-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{24}H_{24}O_5$ $[M-H]^-$: 391.4.

Example 315

(2S)-3-{2-[4-(2-carboxy-2-methoxy-ethyl)-phenoxy]-ethoxy}-benzoic acid

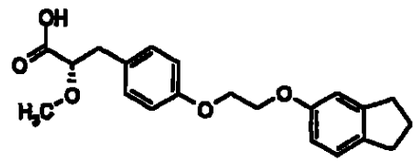


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 3-hydroxy-benzoic acid methyl ester via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{19}H_{20}O_7$ $[M-H]^-$: 359.3.

Example 316

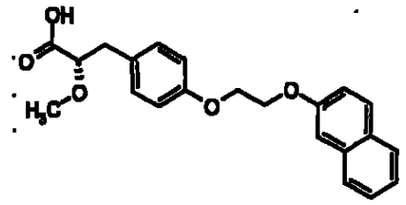
(2S)-3-{4-[2-(indan-5-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and indan-5-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{21}H_{24}O_5$ [M-H]$^-$: 355.3.

Example 317

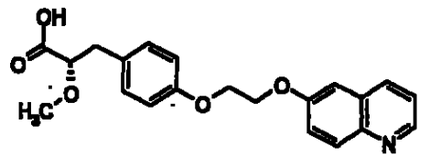
(2S)-2-methoxy-3-{4-[2-(naphthalen-2-yloxy)-ethoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and naphthalen-2-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{22}H_{22}O_5$ [M+Na]$^+$: 389.3.

Example 318

(2S)-2-Methoxy-3-{4-[2-(quinolin-6-yloxy)-ethoxy]-phenyl}-propionic acid

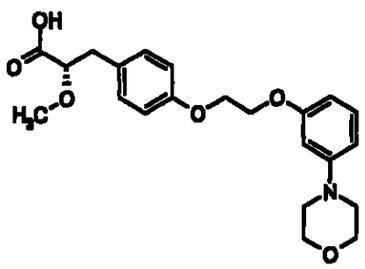


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and quinolin-6-ol via the

same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.
MS (ES) for $C_{21}H_{21}NO_5$ $[M+H]^+$: 368.3.

Example 319

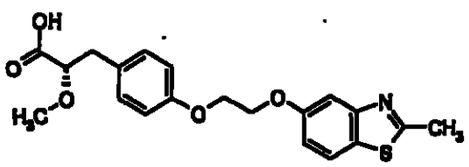
(2S)-2-Methoxy-3-{4-[2-(3-morpholin-4-yl-phenoxy)-ethoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 3-morpholin-4-yl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a yellow oil.
MS (ES) for $C_{22}H_{27}NO_6$ $[M+H]^+$: 402.4.

Example 320

(2S)-2-methoxy-3-{4-[2-(2-methyl-benzothiazol-5-yloxy)-ethoxy]-phenyl}-propionic acid

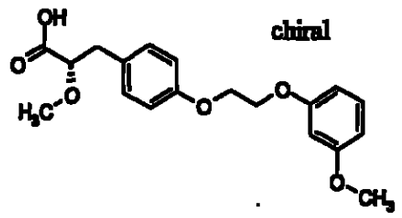


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2-methyl-benzothiazol-5-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a yellow oil.

MS (ES) for $C_{20}H_{21}NO_5S$ $[M+H]^+$: 388.3.

Example 321

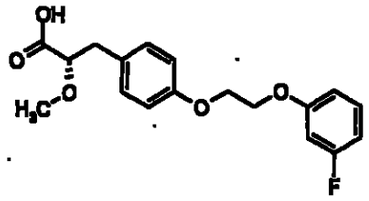
(2S)-2-methoxy-3-{4-[2-(3-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 3-methoxy-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{19}H_{22}O_6$ $[M-H]^-$: 345.3.

Example 322

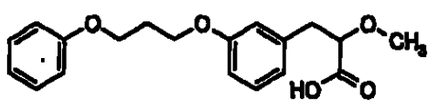
(2S)-3-{4-[2-(3-fluoro-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



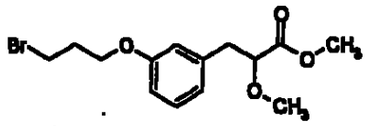
The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 3-fluoro-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{18}H_{19}FO_5$ $[M-H]^-$: 333.3.

Example 323

2-methoxy-3-[3-(3-phenoxy-propoxy)-phenyl]-propionic acid (isomer 1)

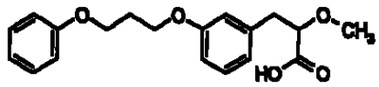


Step 1: 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester



The title compound was prepared from 3-bromo-propan-1-ol (Example 284, Step 1) and 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 4) via the same procedure used for the preparation of (2S)-3-[4-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 284, Step 2). ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.26-7.16 (m, 1H), 6.80 (t, 3H, J=7.3), 4.09 (t, 2H, J=5.9), 3.97 (dd, 1H, J=7.3, 5.4), 3.73 (s, 3H), 3.60 (t, 2H, J=6.4), 3.36 (s, 3H), 3.00 (s, 1H), 2.97 (d, 1H, J=3.2), 2.31 (qn, 2H, J=6.2).

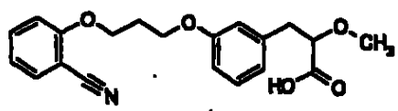
Step 2: (Isomer-1) 2-methoxy-3-[3-(3-phenoxy-propoxy)-phenyl]-propionic acid



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{19}H_{22}O_5$ $[M+Na]^+$: 353.3.

Example 324

3-{3-[3-(2-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)

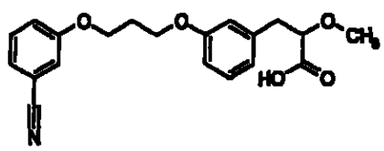


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-cianophenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-

phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378.3.

Example 325

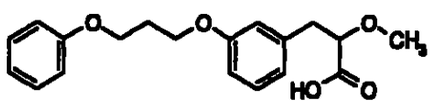
3-{3-[3-(3-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3-cianophenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378.3.

Example 326

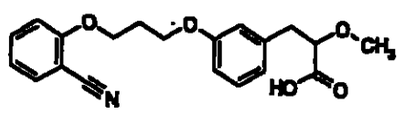
2-methoxy-3-[3-(3-phenoxy-propoxy)-phenyl]-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enantiomers were separated by chiral HPLC.
MS (ES) for $C_{19}H_{22}O_5$ $[M+Na]^+$: 353.3.

Example 327

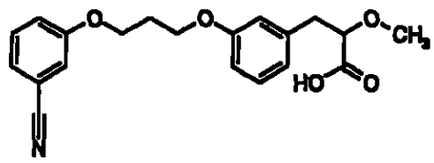
3-{3-[3-(2-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-cianophenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378.3

Example 328

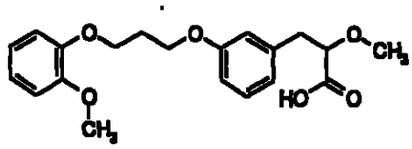
3-{3-[3-(3-cyano-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3-cianophenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378.3

Example 329

2-methoxy-3-{3-[3-(2-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 1)

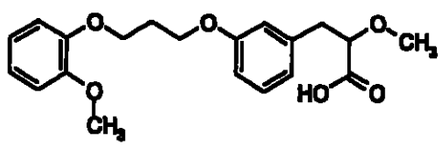


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-methoxyphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-

propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.4.

Example 330

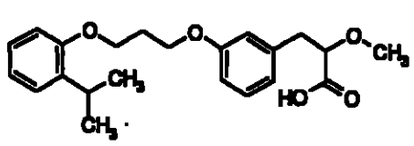
2-methoxy-3-{3-[3-(2-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-methoxyphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.4.

Example 331

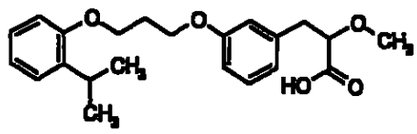
3-{3-[3-(2-isopropyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-isopropylphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{22}H_{28}O_5$ $[M+Na]^+$: 395.4.

Example 332

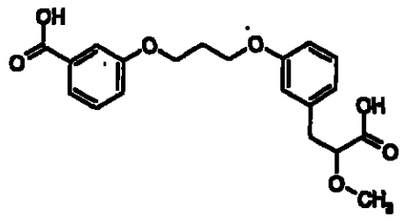
3-{3-[3-(2-isopropyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-isopropylphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{22}H_{28}O_5$ $[M+Na]^+$: 395.4.

Example 333

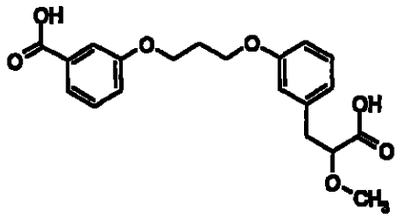
3-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3-hydroxybenzoic acid methyl ester via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{22}O_7$ $[M+Na]^+$: 397.4.

Example 334

3-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer2)

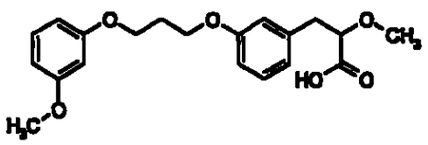


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3-hydroxybenzoic acid

methyl ester via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{22}O_7$ $[M+Na]^+$: 397.4.

Example 335

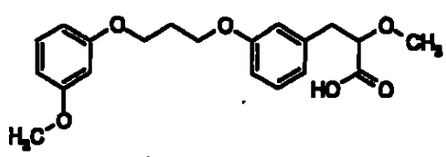
2-methoxy-3-{3-[3-(3-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3-methoxyphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.3.

Example 336

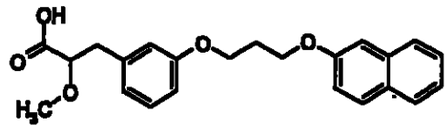
2-methoxy-3-{3-[3-(3-methoxy-phenoxy)-propoxy]-phenyl}-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3-methoxyphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.3.

Example 337

2-methoxy-3-{3-[3-(naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (isomer 1)

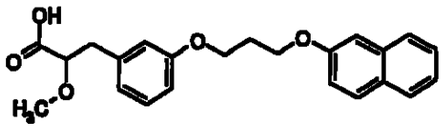


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-naphthol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC.

^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.78-7.69 (m, 3H), 7.47-7.12 (m, 5H), 6.84-6.81 (m, 3H), 4.28 (t, 2H, J=5.9), 4.19 (t, 2H, J=5.9), 4.02 (dd, 1H, J=7.5, 4.0), 3.38 (s, 3H), 3.13 (dd, 1H, J=14.2, 4.3), 2.97 (dd, 1H, J=14.2, 7.5), 2.33 (qn, 2H, J=6.2). MS (ES) for $C_{23}H_{24}O_5$ $[M+H]^+$: 381.2.

Example 338

2-methoxy-3-{3-[3-(naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid (isomer 2)

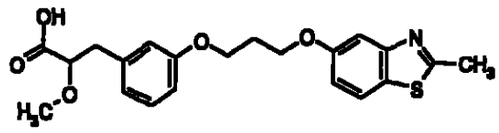


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-naphthol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC.

^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.78-7.69 (m, 3H), 7.47-7.12 (m, 5H), 6.84-6.81 (m, 3H), 4.28 (t, 2H, J=5.9), 4.19 (t, 2H, J=5.9), 4.02 (dd, 1H, J=7.5, 4.0), 3.38 (s, 3H), 3.13 (dd, 1H, J=14.2, 4.3), 2.97 (dd, 1H, J=14.2, 7.5), 2.33 (qn, 2H, J=6.2). MS (ES) for $C_{23}H_{24}O_5$ $[M+H]^+$: 381.2.

Example 339

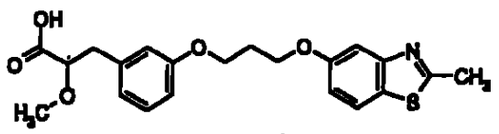
2-methoxy-3-{3-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-methyl-benzothiazol-5-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{21}H_{23}NO_5S$ $[M+H]^+$: 402.1.

Example 340

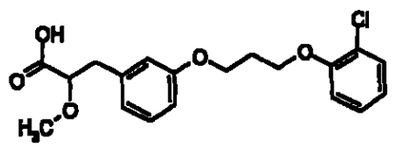
2-methoxy-3-{3-[3-(2-methyl-benzothiazol-5-yloxy)-propoxy]-phenyl}-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-methyl-benzothiazol-5-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{21}H_{23}NO_5S$ $[M+H]^+$: 402.1.

Example 341

3-{3-[3-(2-chloro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)

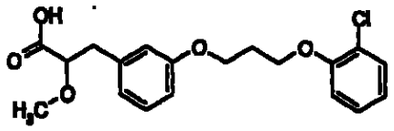


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-chlorophenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.35 (dd, 1H, J=8.1, 1.9), 7.24-7.16 (m, 2H), 6.97-6.80 (m, 5H), 4.22 (t, 2H, J=5.9), 4.20 (t, 2H, J=5.9), 4.02 (dd, 1H, J=7.3, 4.0), 3.39 (s, 3H), 3.13 (dd, 1H, J=14.2, 3.8), 2.97 (dd, 1H, J=14.0, 7.8), 2.30 (qn, 2H, J=6.2).

MS (ES) for $C_{19}H_{21}ClO_5$ $[M+Na]^+$: 387.2.

Example 342

3-{3-[3-(2-chloro-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)

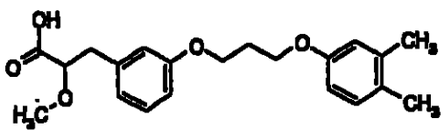


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-chlorophenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.35 (dd, 1H, J=8.1, 1.9), 7.24-7.16 (m, 2H), 6.97-6.80 (m, 5H), 4.22 (t, 2H, J=5.9), 4.20 (t, 2H, J=5.9), 4.02 (dd, 1H, J=7.3, 4.0), 3.39 (s, 3H), 3.13 (dd, 1H, J=14.2, 3.8), 2.97 (dd, 1H, J=14.0, 7.8), 2.30 (qn, 2H, J=6.2).

MS (ES) for $C_{19}H_{21}ClO_5$ $[M+Na]^+$: 387.2.

Example 343

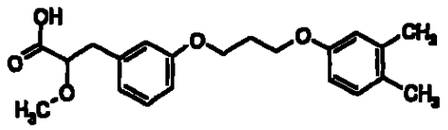
3-{3-[3-(3,4-dimethyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3,4-dimethylphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.18 (d, 1H, J=7.5), 7.02 (d, 1H, J=8.3), 6.84-6.62 (m, 5H), 4.14 (t, 2H, J=6.4), 4.12 (t, 2H, J=5.9), 4.02 (dd, 1H, J=7.3, 4.0), 3.39 (s, 3H), 3.13 (dd, 1H, J=14.2, 4.6), 2.97 (dd, 1H, J=14.0, 7.5), 2.23 (q, 1H, J=6.2.1), 2.22 (s, 3H), 2.18 (s, 3H). MS (ES) for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.2.

Example 344

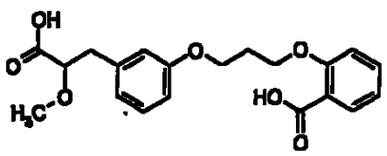
3-{3-[3-(3,4-dimethyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 3,4-dimethylphenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.18 (d, 1H, J=7.5), 7.02 (d, 1H, J=8.3), 6.84-6.62 (m, 5H), 4.14 (t, 2H, J=6.4), 4.12 (t, 2H, J=5.9), 4.02 (dd, 1H, J=7.3, 4.0), 3.39 (s, 3H), 3.13 (dd, 1H, J=14.2, 4.6), 2.97 (dd, 1H, J=14.0, 7.5), 2.23 (q, 1H, J=6.2.1), 2.22 (s, 3H), 2.18 (s, 3H). MS (ES) for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.2.

Example 345

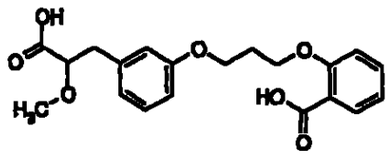
2-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-hydroxy-benzoic acid via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{22}O_7$ $[M+H]^+$: 375.2.

Example 346

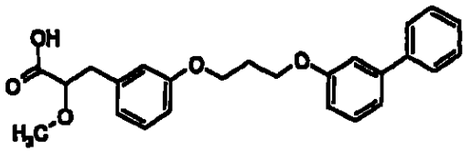
2-{3-[3-(2-carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-benzoic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and 2-hydroxy-benzoic acid via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{20}H_{22}O_7$ $[M+H]^+$: 375.2.

Example 347

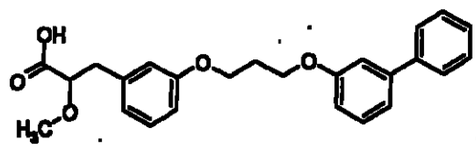
3-{3-[3-(biphenyl-3-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and biphenyl-3-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{25}H_{26}O_5$ $[M+Na]^+$: 429.2.

Example 348

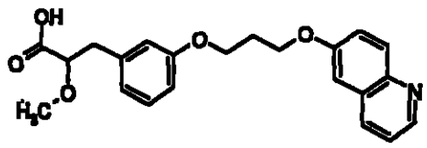
3-{3-[3-(biphenyl-3-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and biphenyl-3-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{25}H_{26}O_5$ $[M+Na]^+$: 429.2.

Example 349

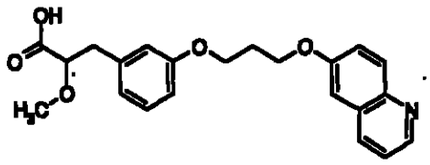
2-methoxy-3-{3-[3-(quinolin-6-yloxy)-propoxyl-phenyl}-propionic acid (isomer 1)



The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and quinolin-6-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{22}H_{23}NO_5$ $[M+H]^+$: 382.2.

Example 350

2-methoxy-3-{3-[3-(quinolin-6-yloxy)-propoxyl-phenyl}-propionic acid (isomer 2)

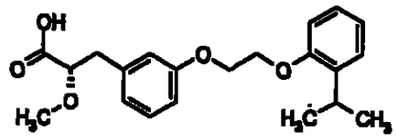


The title compound was prepared from 3-[3-(3-bromo-propoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 323, Step 1) and quinolin-6-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-

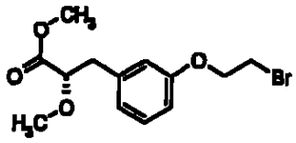
phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{22}H_{28}NO_5$ $[M+H]^+$: 382.2.

Example 351

3-{3-[2-(2-isopropyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)

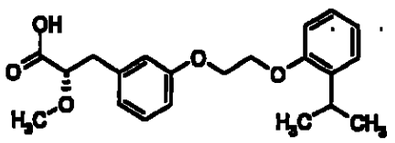


Step 1: 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester



The title compound was prepared from 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 4) (4.76 mol, 1000 mg) via the same procedure used for the preparation of (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2). MS (ES) for $C_{13}H_{17}BrO_4$ $[M+NH_4]^+$: 334.2.

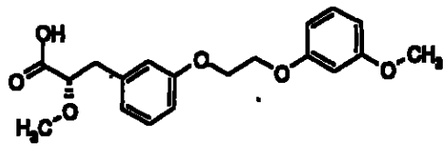
Step 2: 3-{3-[2-(2-isopropyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)



The title compound was prepared from 2-isopropyl-phenol and 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 351, Step 1) via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{21}H_{26}O_5$ $[M-H]^-$: 357.2.

Example 352

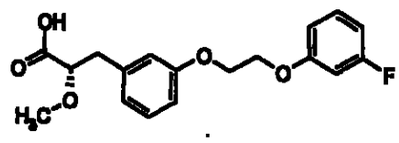
2-methoxy-3-{3-[2-(3-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (isomer 1)



The title compound was prepared from 3-methoxy-phenol and 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 351, Step 1) via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{19}H_{22}O_6$ [M-H]$^-$: 345.1.

Example 353

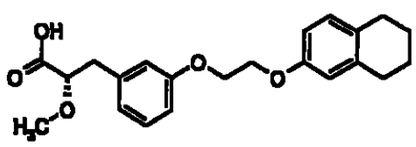
3-{3-[2-(3-fluoro-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (isomer 1)



The title compound was prepared from 3-fluoro-phenol and 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 351, Step 1) via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{18}H_{19}FO_5$ [M-H]$^-$: 333.1.

Example 354

2-methoxy-3-{3-[2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-ethoxy]-phenyl}-propionic acid (isomer 1)

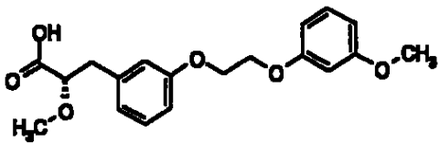


The title compound was prepared from 5,6,7,8-tetrahydro-naphthalen-2-ol and 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 351,

Step 1) via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{22}H_{26}O_5$ [M-H]$^-$: 369.2.

Example 355

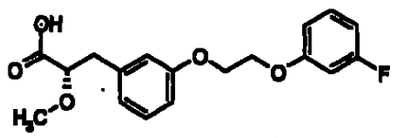
2-methoxy-3-{3-[2-(3-methoxy-phenoxy)-ethoxy]-phenyl}-propionic acid (isomer 2)



The title compound was prepared from 3-methoxy-phenol and 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 351, Step 1) via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{19}H_{22}O_6$ [M-H]$^-$: 345.1.

Example 356

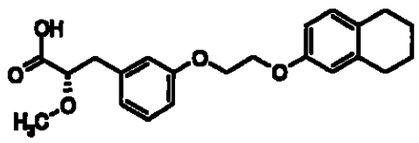
3-{3-[2-(3-fluoro-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (isomer 2)



The title compound was prepared from 3-fluoro-phenol and 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 351, Step 1) via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{18}H_{19}FO_5$ [M-H]$^-$: 333.1.

Example 357

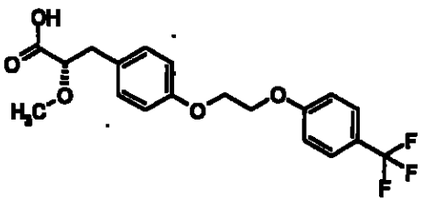
2-methoxy-3-{3-[2-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-ethoxy]-phenyl}-propionic acid (isomer 2)



The title compound was prepared from 5,6,7,8-tetrahydro-naphthalen-2-ol and 3-[3-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid methyl ester (Example 351, Step 1) via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1). The enatiomers were separated by chiral HPLC. MS (ES) for $C_{22}H_{26}O_5$ [M-H]$^-$: 369.2.

Example 358

(2S)-2-methoxy-3-{4-[2-(4-trifluoromethyl-phenoxy)-ethoxy]-phenyl}-propionic acid

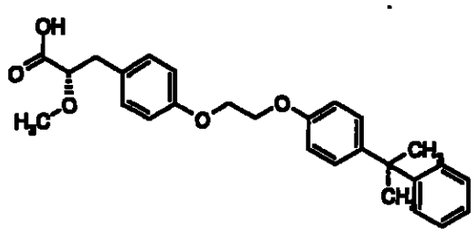


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 4-trifluoromethyl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{19}H_{19}F_3O_5$ [M+Na]$^+$: 407.2.

Example 359

(2S)-2-methoxy-3-(4-{2-[4-(1-methyl-1-phenyl-ethyl)-phenoxy]-ethoxy}-phenyl)-propionic acid

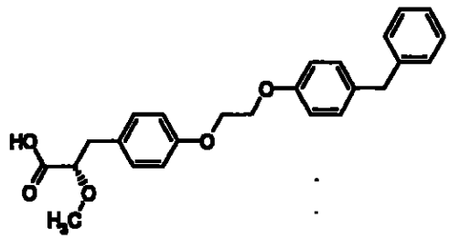


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 4-(1-methyl-1-phenyl-ethyl)-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{27}H_{30}O_5$ $[M+Na]^+$: 457.2.

Example 360

(2S)-3-{4-[2-(4-benzyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid

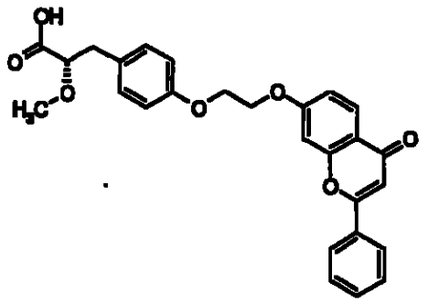


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 4-benzyl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{25}H_{26}O_5$ $[M+Na]^+$: 429.3.

Example 361

(2S)-2-methoxy-3-{4-[2-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-ethoxy]-phenyl}-propionic acid

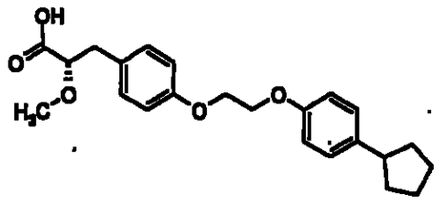


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 7-hydroxy-2-phenyl-chromen-4-one via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a yellow solid.

MS (ES) for $C_{27}H_{24}O_7$ $[M+H]^+$: 461.3.

Example 362

(2S)-3-{4-[2-(4-cyclopentyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid

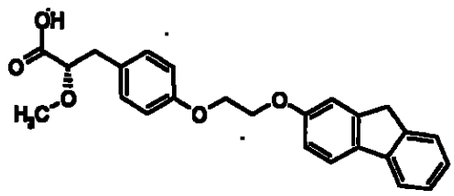


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 1-cyclopentyl-4-methoxy-benzene via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{23}H_{28}O_5$ $[M+Na]^+$: 407.3.

Example 363

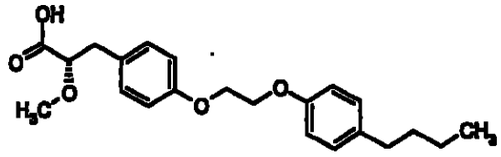
(2S)-3-{4-[2-(9H-fluoren-2-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 9H-fluoren-2-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{25}H_{24}O_5$ $[M+Na]^+$: 427.3.

Example 364

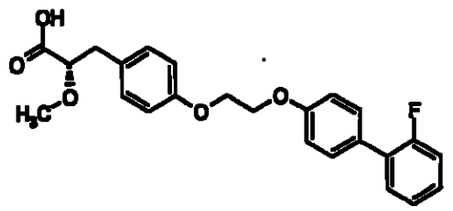
(2S)-3-{4-[2-(4-butyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 4-butyl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{22}H_{28}O_5$ $[M+Na]^+$: 395.3.

Example 365

(2S)-3-{4-[2-(2'-fluoro-biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid

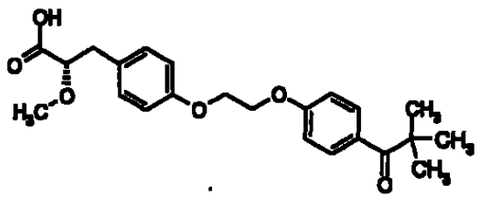


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2'-fluoro-biphenyl-4-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

MS (ES) for $C_{24}H_{23}FO_5$ $[M+Na]^+$: 433.3.

Example 366

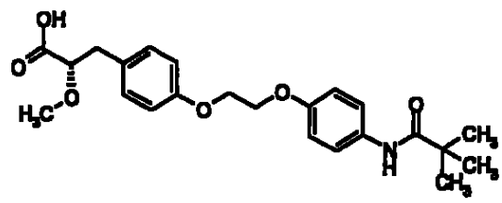
(2S)-3-{4-[2-[4-(2,2-dimethyl-propionyl)-phenoxy]-ethoxy}-phenyl)-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 1-(4-hydroxy-phenyl)-2,2-dimethyl-propan-1-onel via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil. MS (ES) for $C_{23}H_{28}O_5$ $[M+H]^+$: 401.4.

Example 367

3-{4-[2-[4-(2,2-dimethyl-propionylamino)-phenoxy]-ethoxy}-phenyl)-2-methoxy-propionic acid

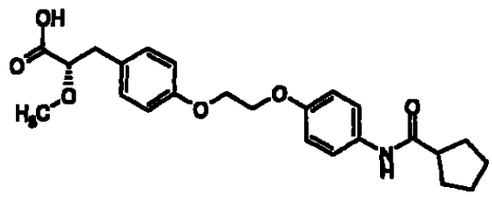


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and N-(4-hydroxy-phenyl)-2,2-dimethyl-propionamide via the same procedure used for the preparation

of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{23}H_{29}NO_6$ $[M+H]^+$: 416.4.

Example 368

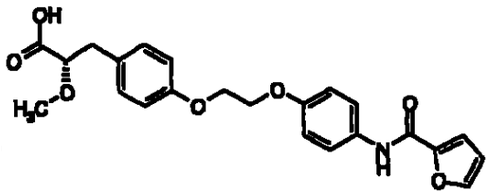
(2S)-3-(4-{2-[4-(cyclopentanecarbonyl-amino)-phenoxy]-ethoxy}-phenyl)-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and cyclopentanecarboxylic acid (4-hydroxy-phenyl)-amide via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{24}H_{29}NO_6$ $[M+H]^+$: 428.3.

Example 369

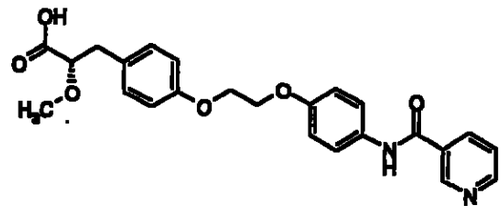
(2S)-3-[4-(2-{4-[(furan-2-carbonyl)-amino]-phenoxy}-ethoxy)-phenyl]-2-methoxy-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and furan-2-carboxylic acid (4-hydroxy-phenyl)-amide via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{23}H_{23}NO_7$ $[M+H]^+$: 426.3.

Example 370

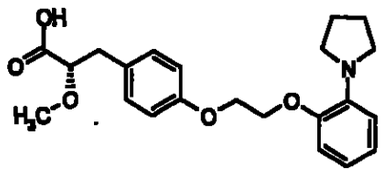
(2S)-2-methoxy-3-[4-(2-{4-[(pyridine-3-carbonyl)-amino]-phenoxy}-ethoxy)-phenyl]-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and N-(4-hydroxy-phenyl)-nicotinamide via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid. MS (ES) for $C_{24}H_{24}N_2O_6$ [M+H]+: 437.3.

Example 371

(2S)-2-methoxy-3-{4-[2-(2-pyrrolidin-1-yl-phenoxy)-ethoxy]-phenyl}-propionic acid

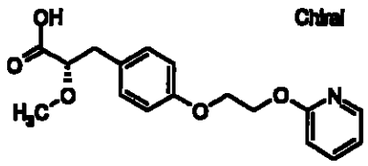


The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2-pyrrolidin-1-yl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a yellow oil.

MS (ES) for $C_{22}H_{27}NO_5$ $[M+H]^+$: 386.3.

Example 372

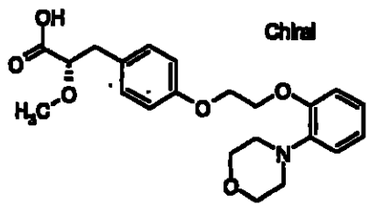
(2S)-2-methoxy-3-{4-[2-(pyridin-2-yloxy)-ethoxy]-phenyl}-propionic acid



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and yyridin-2-ol via the same procedure used for the preparation of (2S)-2-Methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.
MS (ES) for $C_{17}H_{19}NO_5$ $[M+H]^+$: 318.3.

Example 373

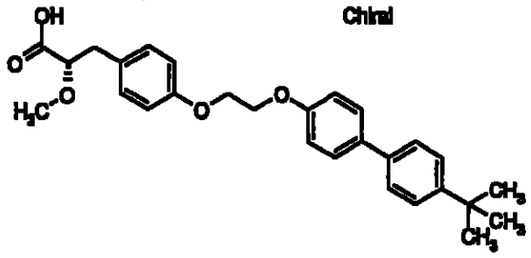
(2S)-2-methoxy-3-{4-[2-(2-morpholin-4-yl-phenoxy)-ethoxy]-phenyl}-propionic acid.



The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 2-morpholin-4-yl-phenol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a colorless oil.
MS (ES) for $C_{22}H_{27}NO_6$ $[M+H]^+$: 402.3.

Example 374

(2S)-3-{4-[2-(4'-tert-butyl-biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid



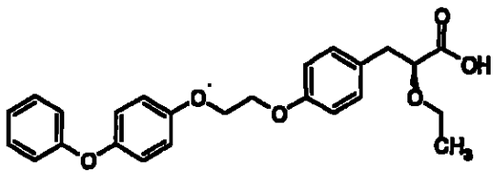
Chiral

The title compound was prepared from (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) and 4'-tert-butyl-biphenyl-4-ol via the same procedure used for the preparation of (2S)-2-methoxy-3-[4-(3-phenoxy-propoxy)-phenyl]-propionic acid (Example 285, Step 1), to produce a white solid.

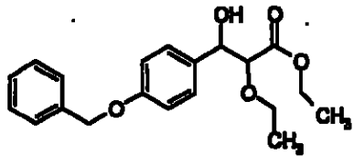
MS (ES) for $C_{28}H_{32}O_5$ [M-H]$^-$: 447.2.

Example 375

(2S)-2-ethoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid

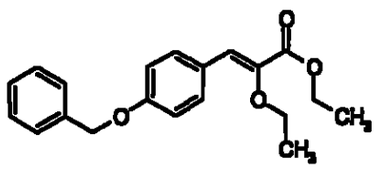


Step 1: 3-(4-benzyloxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid ethyl ester



The title compound was prepared from 4-benzyloxybenzaldehyde, lithium diisopropylamide and ethyl 2-ethoxyacetate via the same procedure used for the preparation of 3-(3-benzyloxy-phenyl)-3-hydroxy-2-methoxy propionic acid methyl ester (Example 291, Step 1). MS (ES) for $C_{20}H_{24}O_5$ [M+H_2O-H]$^+$: 327, [M+Na]$^+$: 367.4.

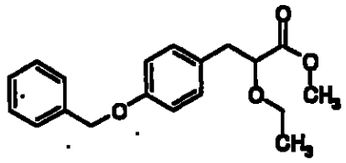
Step 2: 3-(4-benzyloxy-phenyl)-2-ethoxy-acrylic acid ethyl ester



The title compound was prepared from 3-(4-benzyloxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid ethyl ester (Example 375, Step 1) via the same procedure used for the preparation of 3-(4-benzyloxy-phenyl)-2-ethoxy-acrylic acid methyl ester.

MS (ES) for $C_{20}H_{22}O_4$ $[M+H]^+$: 327.2.

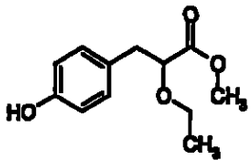
Step 3: 3-(4-benzyloxy-phenyl)-2-ethoxy-propionic acid methyl ester



The title compound was prepared from 3-(4-benzyloxy-phenyl)-2-ethoxy-acrylic acid ethyl ester (Example 375, Step 2) (3.3 gr, 10.12 mmol) via the same procedure used for the preparation of 3-(3-benzyloxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 3) to produce an oil that was purified by chromatography (silica gel, hexanes/ethyl acetate 6:1) to produce two compounds: 3-(4-benzyloxy-phenyl)-propionic acid methyl ester (1.5 gr, Rf aprox. 0.65) and the desired compound (1.5 gr, Rf aprox. 0.2).

MS (ES) for $C_{19}H_{22}O_4$ $[M+NH_4]^+$: 332.3.

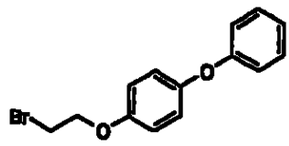
Step 4: 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid methyl ester



The title compound was prepared from 3-(4-benzyloxy-phenyl)-2-ethoxy-propionic acid methyl ester (Example 375, Step 3) via the same procedure used for the preparation of 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester

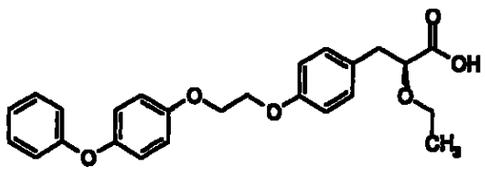
(Example 291, Step 4) to produce a yellow oil. MS (ES) for $C_{12}H_{16}O_4$ $[M+H]^+$: 225.2, $[M+NH_4]^+$: 242.2, $[M+Na]^+$: 247.2.

Step 5: 4-(2-bromo-ethoxy)-phenoxyphenyl



The title compound was prepared from 4-phenoxy-phenol via the same procedure used for the preparation of (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) to produce a white solid. MS (ES) for $C_{14}H_{13}BrO_2$ $[M-H]^-$: 291.0.

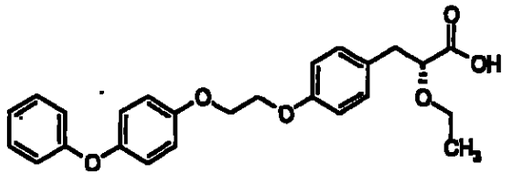
Step 6: (2S)-2-ethoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid



The title compound was prepared from 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid methyl ester (Example 375, Step 4) and 4-(2-bromo-ethoxy)-phenoxyphenyl (Example 375, Step 5) via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3). The crude material was submitted to chiral HPLC separation to afford the single enantiomer isomer 2. MS (ES) for $C_{25}H_{26}O_6$ $[M-H]^-$: 421.4.

Example 376

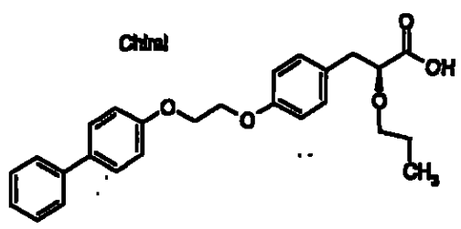
(2R)-2-ethoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid



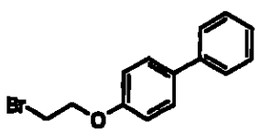
The title compound was prepared from 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid methyl ester (Example 375, Step 4) and 4-(2-bromo-ethoxy)-phenoxyphenyl (Example 375, Step 5) via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3). The crude material was submitted to chiral HPLC separation to afford the single enantiomer isomer 1. MS (ES) for $C_{25}H_{26}O_6$ [M-H]$^-$: 421.4.

Example 377

(2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-propoxy-propionic acid

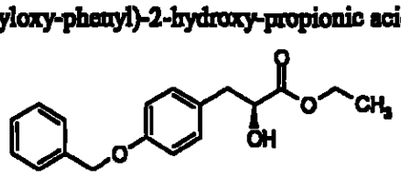


Step 1: 4-(2-bromo-ethoxy)-biphenyl



The title compound was prepared from biphenyl-4-ol via the same procedure used for the preparation of (2S)-3-[4-(2-bromo-ethoxy)-phenyl]-2-methoxy-propionic acid ethyl ester (Example 283, Step 2) to produce a white solid. MS (ES) for $C_{14}H_{13}BrO$ [M-H]$^-$: 279.1.

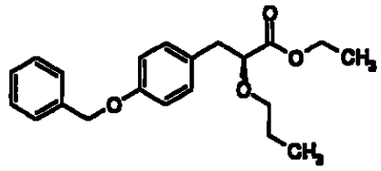
Step 2: (2S)-3-(4-benzyloxy-phenyl)-2-hydroxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-(4-benzyloxy-phenyl)-2-hydroxy-propionic acid via the same procedure used for the preparation of (2S)-3-(4-hydroxy-phenyl)-2-methoxy-propionic acid ethyl ester (Example 283, Step 1) to afford the product as a yellow oil. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.35-7.55 (m, 5H), 7.20 (d,

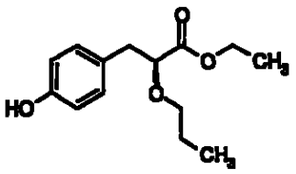
2H, J = 8.3), 6.79 (d, 2H, J = 8.3), 4.99 (s, 2H), 4.41 (dd, 1H, J= 6.5, 4.4), 4.19 (q, 2H, J = 6.9), 2.92 (2dd, 2H, J= 16.1, 4.4), 1.23 (t, 3H, J= 6.9).

Step 3: (2S)-3-(4-benzyloxy-phenyl)-2-propoxy-propionic acid ethyl ester



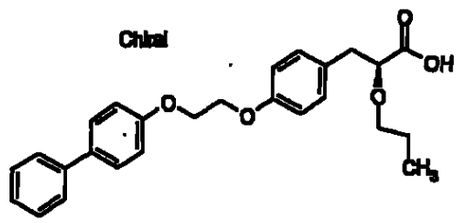
Propyl iodide (41.6 mmol) was added at room temperature to a solution of (2S)-3-(4-benzyloxy-phenyl)-2-hydroxy-propionic acid ethyl ester (Example 377, Step 2) (8.3 mmol) and silver oxide (12.45 mmol) in 40 mL of DMF. The mixture was heated at 50°C for 24 hours. After that the mixture was cooled to room temperature, 300 ml of ethyl acetate and 200 ml of water were added. The aqueous layer was separated and the organic layer were washed with brine (3 X 100 ml), and then dried over ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by chromatography (silica gel, hexanes/ethyl acetate 6:1) to produce a yellow oil. ^{1}H-NMR ($CDCl_3$, 200.15 MHz): 7.42-7.31 (m, 5 H), 7.17 (d, 2 H, J = 8.6 Hz), 6.90 (d, 2 H, J = 8.6 Hz), 5.05 (s, 2 H), 4.17 (q, 2 H, J = 7.0 Hz), 3.97 (dd, 1 H, J = 7.0, 6.2 Hz), 3.53 (dt, 1 H, J = 8.9, 6.4 Hz), 3.23 (dt, 1 H, J = 9.1, 6.7 Hz), 2.97 (d, 2 H, J = 6.7 Hz), 1.66-1.48 (m, 2 H), 1.23 (t, 3 H, J = 7.3 Hz), 0.86 (t, 3 H, J = 7.5 Hz).

Step 4: (2S)-3-(4-hydroxy-phenyl)-2-propoxy-propionic acid ethyl ester



The title compound was prepared from (2S)-3-(4-benzyloxy-phenyl)-2-propoxy-propionic acid ethyl ester (Example 377, Step 3) via the same procedure used for the preparation of 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 4) to produce a yellow oil. MS (ES) for $C_{14}H_{20}O_4$ $[M+H]^+$: 253.1.

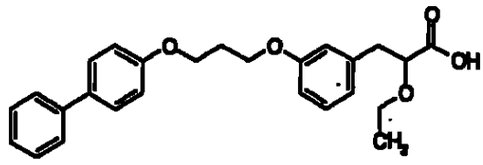
Step 5: (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-propoxy-propionic acid



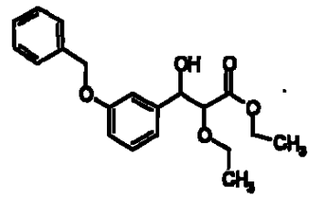
The title compound was prepared from 4-(2-bromo-ethoxy)-biphenyl (Example 377, Step 1) and (2S)-3-(4-hydroxy-phenyl)-2-propoxy-propionic acid ethyl ester (Example 377, Step 4) via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3) to produce a white solid. MS (ES) for $C_{25}H_{28}O_5$ $[M+H]^+$: 421.0, $[M+NH_4]^+$: 438.0, $[M+Na]^+$: 443.0, $[M-H]^-$: 3239.2.

Example 378

3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-ethoxy-propionic acid (isomer 1)

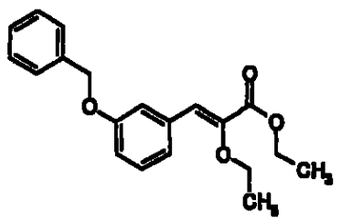


Step 1: 3-(3-benzyloxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid ethyl ester



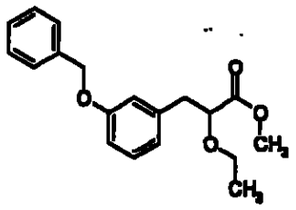
The title compound was prepared from 3-benzyloxy-benzaldehyde and ethyl ethoxyacetate via the same procedure used for the preparation of 3-(3-benzyloxy-phenyl)-3-hydroxy-2-methoxy-propionic acid methyl ester (Example 291, Step 1) to afford the title compound as a colorless oil.

Step 2: 3-(3-benzyloxy-phenyl)-2-ethoxy-acrylic acid ethyl ester



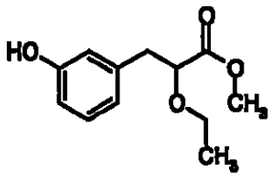
The title compound was prepared from 3-(3-benzyloxy-phenyl)-2-ethoxy-3-hydroxy-propionic acid ethyl ester (Example 378, Step 1) via the same procedure used for the preparation of 3-(3-benzyloxy-phenyl)-2-methoxy-acrylic acid methyl ester (Example 291, Step 2) to afford the title compound as a colorless oil.

Step 3: 3-(3-benzyloxy-phenyl)-2-ethoxy-propionic acid methyl ester



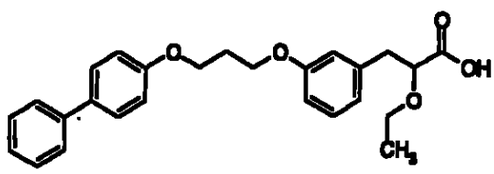
The title compound was prepared from 3-(3-benzyloxy-phenyl)-2-ethoxy-acrylic acid ethyl ester (Example 378, Step 2) via the same procedure used for the preparation of 3-(3-benzyloxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 3) to afford the title compound as a colorless oil.

Step 4: 2-ethoxy-3-(3-hydroxy-phenyl)-propionic acid methyl ester



The title compound was prepared from 3-(3-benzyloxy-phenyl)-2-ethoxy-propionic acid methyl ester (Example 378, Step 3) via the same procedure used for the preparation of 3-(3-hydroxy-phenyl)-2-methoxy-propionic acid methyl ester (Example 291, Step 4) to afford the title compoud as a yellow oil. MS (ES) for $C_{12}H_{16}O_4$ $[M+H]^+$: 225.1.

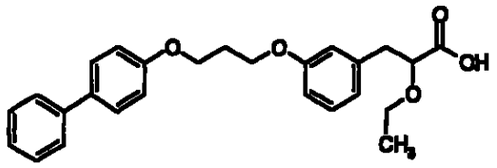
Step 5: (3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-ethoxy-propionic acid (isomer 1)



The title compound was prepared from 3-(biphenyl-4-yloxy)-propan-1-ol (Example 291, Step 6) and 2-ethoxy-3-(3-hydroxy-phenyl)-propionic acid methyl ester (Example 378, Step 4) via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3) to produce a white solid. The crude material was submitted to chiral HPLC separation to afford the single enantiomer isomer 1. (ES) for $C_{26}H_{28}O_5$ $[M+NH_4]^+$: 438.0, $[M+Na]^+$: 443.0.

Example 379

3-{3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-ethoxy-propionic acid (isomer 2)



The title compound was prepared from 3-(biphenyl-4-yloxy)-propan-1-ol (Example 291, Step 6) and 2-ethoxy-3-(3-hydroxy-phenyl)-propionic acid methyl ester (Example 378, Step 4) via the same procedure used for the preparation of (2S)-3-{4-[2-(biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid (Example 283, Step 3) to produce a white solid. The crude material was submitted to chiral HPLC separation to afford the single enantiomer isomer 2. MS (ES) for $C_{26}H_{28}O_5$ $[M+NH_4]^+$: 438.0, $[M+Na]^+$: 443.0.

Example 380

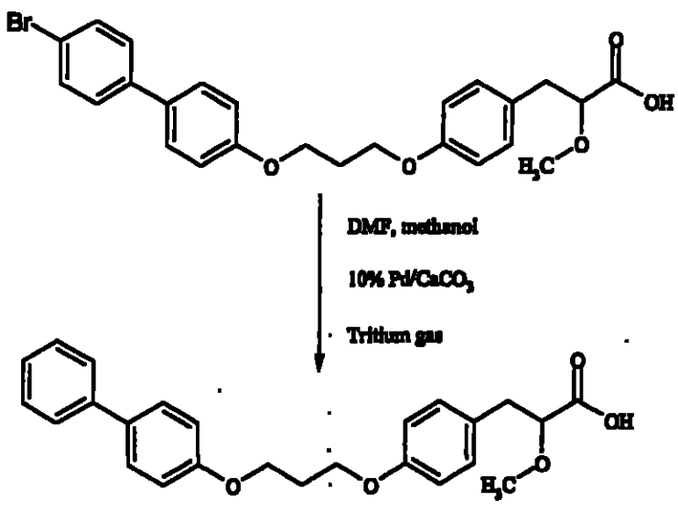
Binding assay:

DNA-dependent binding was carried out using Scintillation Proximity Assay (SPA) technology. PPARγ as well as its heterodimeric partner RXRα were prepared using

a baculovirus expression system. A biotinylated complementary oligonucleotide duplex representing the human consensus PPR response element was used for binding receptor dimer to Yttrium silicate streptavidin-coated SPA beads. The 5'-3' strand had the sequence: 5'TAATGTAGGTAATAGTTCAATAGGTCAAAGG3' (SEQ ID NO: 1); biotin was bound to the first A at the 3' end of the complementary 3'-5' strand. The PPARγ labeled ligand was ^{3}H-(s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid with specific activiy of 24 Ci/mmol. The binding assay was carried out on 96 well dishes. Per well, 100ng of oligonucleotide was preincubated with 3 μg SPA beads in a binding buffer containing 10 mM HEPES pH 7.8, 80 mM KCl, 0.5 mM $MgCl_2$, 1 mM DTT, 0.5% CHAPS and 16.6 μg bovine serum albumin for 30 minutes at room temperature. The mixture was then spun at 2000 rpm for 3 minutes to pellet the beads-oligo mix. The supernatant was removed, and the beads-oligo pellet was resuspended in the same binding buffer as above but also containing 14% glycerol, 5 μg sheared salmon sperm DNA and 2.5 μg of each receptor, PPARγ and RXRα . A saturation binding assay was carried out using increasing amounts of ^{3}H-(s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid in the reaction to obtain 0.39nM to 402nM of ^{3}H-(s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid. Non-specific binding was measured in the presence of 10 μM of unlabeled (s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid. A K_d value was calculated from the saturation binding experiments after plotting specific binding versus concentration of labeled ligand. Competition binding reactions were carried in the presence of 30,000 cpm of ^{3}H-(s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid and 5nM to 10 μM of competing compounds. The IC_{50} (nM) values for competing compounds were calculated after deduction of non-specific binding (measured in the presence of 10μM unlabeled ^{3}H-(s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid), and the data normalized to total binding (in the absence of any unlabeled compound). The ^{3}H-(s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid was effective in determining the binding affinity of PPAR subtypes in the range of 5nM to 10000nM. For example, PPAR compounds with

IC_{50} values less than 500 nM were identified as ligands for PPAR gamma.

Preparation of ^{3}H-(s)-3-{4-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid



In a reaction vessel (s)-3-{4-[3-(4'-bromo-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid (6.1 mg) was combined with 10% $Pd/CaCO_3$ (18.6 mg), DMF (0.5ml) and methanol (0.5 ml). The mixture was stirred under 10Ci of tritium gas for about 4.5 hours. The catalyst was removed by filtration, and the labile activity was removed by repeated rotary evaporations with methanol. The final residue was dissolved in ethanol. The crude product was purified by reverse phase HPLC eluting with a water/acetonitrile/TFA gradient system. The major UV and radioactive peak was collected and rotary evaporated to dryness. The resulting residue was dissolved in ethanol (yield: 102 mCi)

Example 381

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPARα and PPARγ receptors were determined by the procedures detailed below. DNA-dependent binding (ABCD binding) was carried out using Scintillation Proximity Assay (SPA)

technology with PPAR receptors. Tritium-labeled PPARα and PPARγ agonists were used as radioligands for generating displacement curves and IC_{50} values with compounds of the present invention. Cotransfection assays were carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs and RXRα were constitutively expressed using plasmids containing the CMV promoter. Since for PPARα and PPARβ/δ, interference by endogenous PPARγ in CV-1 cells is an issue, in order to eliminate such interference, a GAL4 chimeric system was used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element was utilized in place of the AOX PPRE. Cotransfection efficacy was determined relative to PPAR-isotope specific reference compounds. Efficacies were determined by computer fit to a concentration-response curve, or in some cases at a single high concentration of agonist (10 μM). Typical range for concentration determination IC_{50} is in the range of 1 nM to 10 μM. For binding or cotransfection studies with receptors other than PPARs, similar assays were carried out using appropriate ligands, receptors, reporter constructs for that particular receptor.

These studies were carried out to evaluate the ability of compounds of the present invention to bind to and/or activate various nuclear transcription factors, particularly huPPARα ("hu" indicates "human") and huPPARγ. These studies provided in-vitro data concerning efficacy and selectivity of compounds of the present invention. Furthermore, binding and cotransfection data for compounds of the present invention were compared with corresponding data for marketed compounds that act on either huPPARα or huPPARγ. Binding and cotransfection data for representative compounds of the present invention were compared with corresponding data for reference compounds to determine the binding.

The concentration of test compound required to effect 50% maximal activation of PPARα ($IC_{50\alpha}$) and PPARγ ($IC_{50\gamma}$) was determined. Many of the compounds of the present invention are selective agonists for PPARγ or are co-agonists of PPARα/PPARγ.

Evaluation of Triglyceride and Cholesterol Levels in HuapoAI Transgenic Mice

Five to six week old male mice, transgenic for human apoAI [C57Bl/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME] were housed five per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5001) and water available at all times. After an acclimation period of 2 weeks, animals were individually identified by ear notches, weighed and assigned to groups based on body weight. Beginning the following morning, mice were dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments were test compounds (30 mg/kg), a positive control (fenofibrate, 100 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.2 ml/mouse]. Prior to termination on day 7, mice were weighed and dosed. Three hours after dosing, animals were anesthetized by inhalation of isoflurane (2-4%) and blood obtained via cardiac puncture (0.7-1.0 ml). Whole blood was transferred to serum separator tubes (Vacutainer SST), chilled on ice and permitted to clot. Serum was obtained after centrifugation at 4°C and frozen until analysis for triglycerides, total cholesterol, compound levels and serum lipoprotein profiled by fast protein liquid chromatography (FPLC) coupled to an inline detection system. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads were excised and weighed.

The animals dosed with vehicle had average triglycerides values of about 60 to 80 mg/dl, which were reduced by the positive control fenofibrate (33-58 mg/dl with a mean reduction of 37%). The animals dosed with vehicle have average total serum cholesterol values of about 140 to180 mg/dl, which were increased by fenofibrate (about 190 to 280 mg/dl with a mean elevation of 41%). When subject to FPLC analysis, pooled sera from vehicle-treated hu apoAI transgenic mice had a high-density lipoprotein cholesterol (HDLc) peak area which ranged from 47v-sec to 62v-sec. Fenofibrate increased the amount of HDLc (68-96v-sec with a mean percent increase of 48%). Test compounds were evaluated in terms of percent increase in the area under the curve. Representative compounds of the present invention were tested using the above method or substantially similar methods.

Evaluation of Glucose Levels in db/db Mice

Five week old male diabetic (db/db) mice [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates (db+) were housed 6 per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5015) and water available at all times. After an acclimation period of 2 weeks, animals were individually identified by ear notches, weighed and bled via the tail vein for determination of initial glucose levels. Blood was collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube balanced on the edge of the bench. Sample was discharged into a heparinized microtainer with gel separator (VWR) and retained on ice. Plasma was obtained after centrifugation at 4°C and glucose was measured immediately. Remaining plasma was frozen until the completion of the experiment, and glucose and triglycerides were assayed in all samples. Animals were grouped based on initial glucose levels and body weights. Beginning the following morning, mice were dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments were test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice were weighed and bled (tail vein) for about 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals were bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 were assayed for glucose. After 24 hour bleed, animals were weighed and dosed for the final time. Three hours after dosing on day 8, animals were anesthetized by inhalation of isoflurane, and blood obtained was via cardiac puncture (0.5-0.7 ml). Whole blood was transferred to serum separator tubes, chilled on ice and permitted to clot. Serum was obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads were excised and weighed.

The animals dosed with vehicle had average triglycerides values of about 170 to 230 mg/dl, which were reduced by the positive PPARγ control (about 70 to 120 mg/dl with a mean reduction of 50%). Male db/db mice are hyperglycemic (average

glucose of about 680 to 730 mg/dl on the 7th day of treatment), while lean animals have average glucose levels between about 190 and 230 mg/dl. Treatment with the positive control agent reduced glucose significantly (about 350 to 550 mg/dl with a mean decrease towards normalization of 56%).

Glucose was measured colorimetrically by using commercially purchased reagents (Sigma #315-500). According to the manufacturers, the procedures were modified from published work (McGowan et al. *Clin Chem*, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte coupled with a color reaction first described by Trinder (Trinder, P. *Ann Clin Biochem*, 6:24 (1969)). The absorbance of the dye produced was linearly related to the analyte in the sample. The assays was further modified for use in a 96 well format. Standards (Sigma #339-11, Sigma #16-11, and Sigma #CC0534 for glucose, triglycerides and total cholesterol, respectively), quality control plasma (Sigma # A2034), and samples (2 or 5 µl/well) were measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates were incubated at room temperature (18, 15, and 10 minutes for glucose, triglycerides and total cholesterol, respectively) on a plate shaker and absorbance read at 500 nm (glucose and total cholesterol) or 540 nm (triglycerides) on a plate reader. Sample absorbance was compared to a standard curve (100-800, 10-500, and 100-400 mg/dl for glucose, triglycerides and total cholesterol, respectively). Values for the quality control sample were consistently within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment were assayed at the same time to minimize inter-assay variability.

Serum lipoproteins were separated and cholesterol was quantitated with an in-line detection system. Sample was applied to a Superose® 6 HR 10/30 size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16 ml/min was mixed with the column effluent through a T-

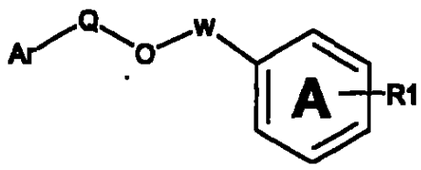
connection, and the mixture was passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37°C water bath. The colored product produced in the presence of cholesterol was monitored in the flow stream at 505 nm, and the analog voltage from the monitor was converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration was plotted against time, and the area under the curve corresponding to the elution of VLDL, LDL and HDL was calculated (Perkin Elmer Turbochrome software).

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by the following structural formula:



or pharmaceutically acceptable salts, hydrates, stereoisomers and solvates thereof, wherein:

Ar is a substituted or unsubstituted aromatic group;

Q is a covalent bond, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$;

W is a substituted or unsubstituted alkylene group two to ten atoms in length or a substituted or unsubstituted heteroalkylene group, wherein the heteroalkylene group is an alkylene group from two to ten atoms in length in which one or more methylene groups have been replaced with a functional group selected from -CH=CH-, -C≡C-, -O-, -CO-, $-NR_7-$, $-NR_7CO-$, $-C(=NOH)-$, -S-, -S(O)-, $-S(O)_2-$ or $-CH(NR_7R_8)-$;

phenyl Ring A is optionally substituted with up to four substituents in addition to R_1;

R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ or $-(CH)=C(Y)-(CH_2)_mE$; wherein E is $COOR_3$, C_1-C_3 -alkylnitrile, carboxamide, sulfonamide, acylsulfonamide or tetrazole and wherein sulfonamide, acylsulfonamide and tetrazole are optionally substituted with one or more substituents independently selected from: C1-C6 alkyl, C1-C6 haloalkyl and aryl-C0-4-alkyl;

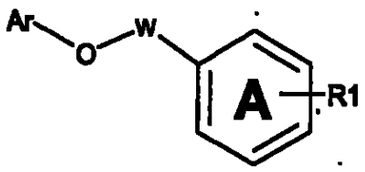
R_2 is -H, an aliphatic group, a substituted aliphatic group, haloalkyl, an aralkyl group, a substituted aralkyl group, an aromatic group, a substituted aromatic group, $-COR_4$, $-COOR_4$, $-CONR_5R_4$, $-C(S)R_4$, $-C(S)OR_4$ or $-C(S)NR_5R_6$;

Y is –O-, $-CH_2-$, $-CH_2CH_2-$ or a –CH=CH- group which is bonded to a carbon atom in Phenyl Ring A that is *ortho* to R_1;

R_3-R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group; and

n and m are independently 0, 1 or 2.

2. A compound represented by the following structural formula:



or pharmaceutically acceptable salts, hydrates and solvates thereof, wherein:

Ar is a substituted or unsubstituted aromatic group;

W is a substituted or unsubstituted alkylene linking group or a substituted or unsubstituted heteroalkylene linking group from two to ten atoms in length;

phenyl Ring A is optionally substituted with up to four substituents in addition to R_1;

R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ or $-(CH)=C(Y)-(CH_2)_mCOOR_3$;

R_2 is -H, an aliphatic group, a substituted aliphatic group, an aryl group, a substituted aryl group, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ or $-C(S)NR_5R_6$;

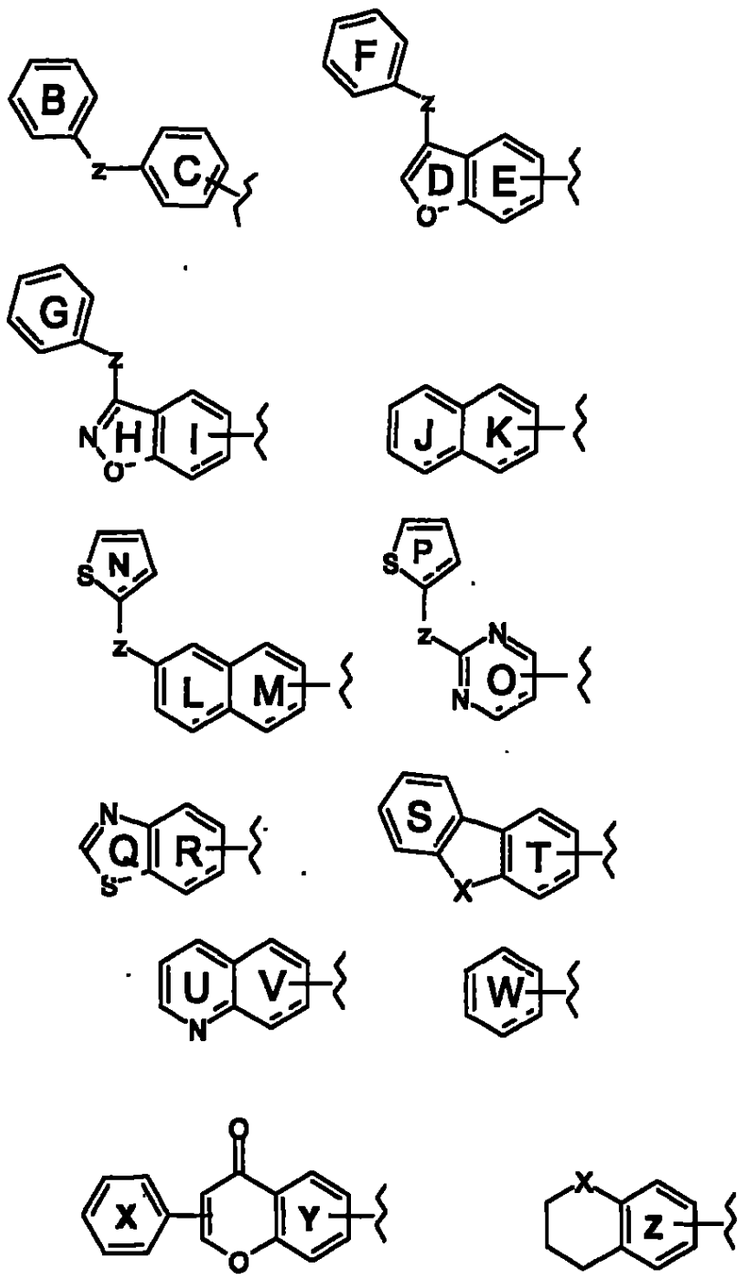
Y is –O-, $-CH_2-$, $-CH_2CH_2-$ or a –CH=CH- group which is bonded to a carbon atom in Phenyl Ring A that is *ortho* to R_1;

R_3-R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group; and

n and m are independently 0, 1 or 2.

3. The compound of Claim 1 or 2 wherein Ar is represented by a structural

formula selected from:



wherein:

Rings B-Z are independently substituted or unsubstituted;

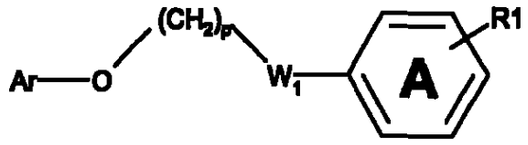
X is –O-, -S-, $-CH_2-$ or –C(O)-;

Z is a covalent bond, -O-, $(-CH_2)_q-$, $-CH(CH_3)(CH_2)_q-$, $-C(CH_3)_2(CH_2)_q-$, $-(CH_2)_qCH(CH_3)-$, $-(CH_2)_qC(CH_3)_2-$, $-O(CH_2)_q-$, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, $-(CH_2)_qNH-$, $-(CH_2)_qCHR_{20}-$, $-CHR_{20}(CH_2)_q-$, $-(CH_2)_qCR_{20}R_{20}-$, $-(CH_2)_qCR_{20}R_{20}-$, $-(CH_2)_qNR_{20}-$, $-NR_{20}(CH_2)_q-$, $-(CH_2)_qC(=NOH)-$, $-C(=NOH)(CH_2)_q-$, $-CH(OH)-(CH_2)_q-$, $-(CH_2)_q-CH(OH)-$, $-CO-(CH_2)_q-$, $-(CH_2)_q-CO-$, $-COO-(CH_2)_q-$, $-OCO-(CH_2)_q-$, $-(CH_2)_q-OCO-$, $-(CH_2)_q-COO-$, $-(CH_2)_qCO-NH-$, $-(CH_2)_qNH-CO-$, $-(CH_2)_qCONR_{20}-$, $-CONR_{20}(CH_2)_q-$, $-(CH_2)_qNR_{20}CO-$ or $-NR_{20}CO(CH_2)_q-$;

q is 0, 1, 2 or 3; and

each R_{20} is independently a C1-C5 alkyl group or a halogenated C1-C5 alkyl group.

4. The compound of Claim 3 wherein the compound is represented by the following structural formula:



;

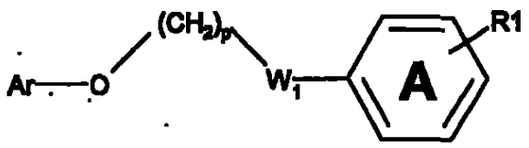
wherein:

p is an integer from one to nine

W_1 is -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- or $-CH(NR_7R_8)-$; and

R_7 and R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group.

5. The compound of Claim 3 wherein the compound is represented by the following structural formula:



;

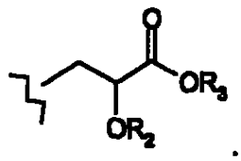
wherein:

p is an integer from one to four;

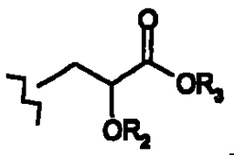
W_1 is -O-, -C(O)-, $-OCH_2$-, $-CH_2$-, $-NR_8$-, $-NR_8CO$-, $-NR_8CH$-, -C(=NOH)- or $-CH(NR_7R_8)$-; and

R_7 and R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group.

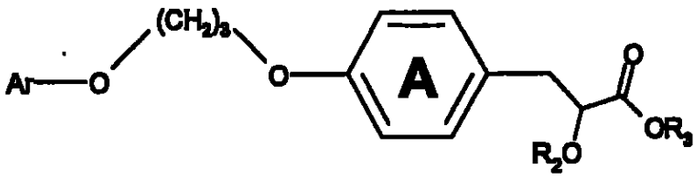
6. The compound of Claim 5 wherein R_1 is *para* to W_1 and is represented by the following structural formula:

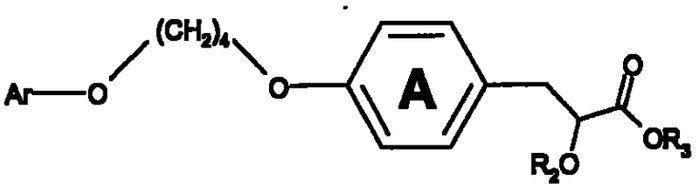


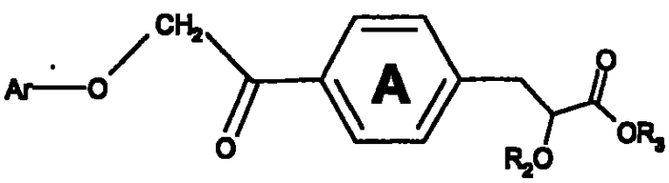
7. The compound of Claim 5 wherein R_1 is *meta* to W_1 and is represented by the following structural formula:

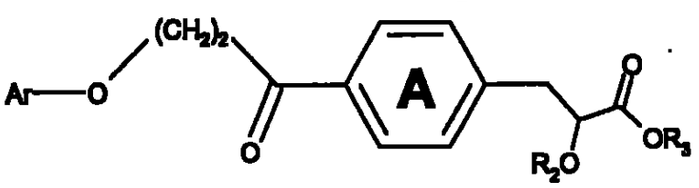


8. The compound of Claim 6 wherein the compound is represented by a structural formula selected from:

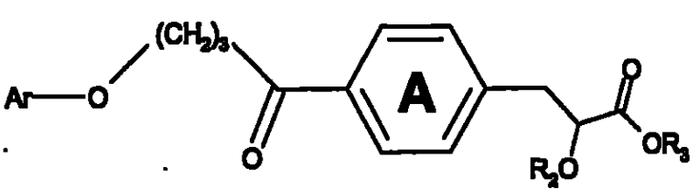


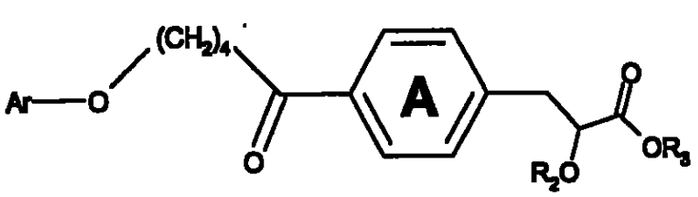


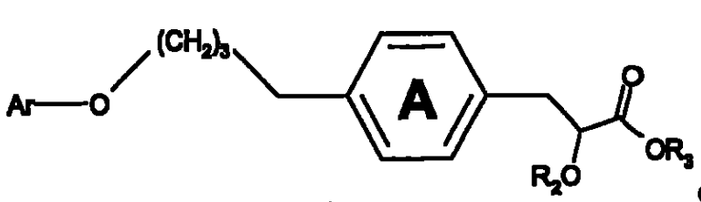




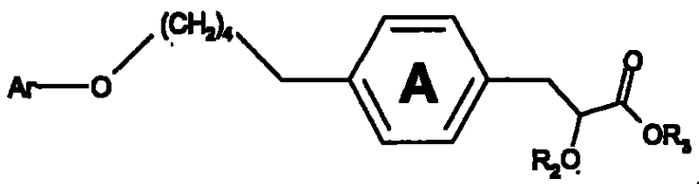
5



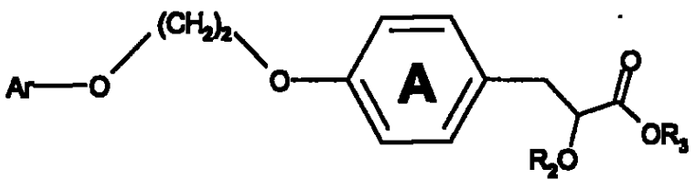




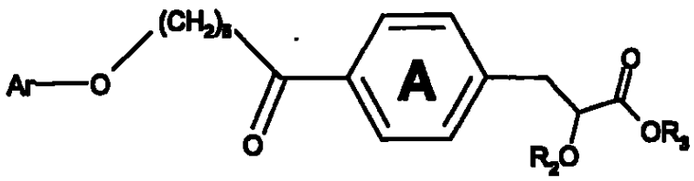
or



9. The compound of Claim 4 wherein the compound is represented by a structural formula selected from:

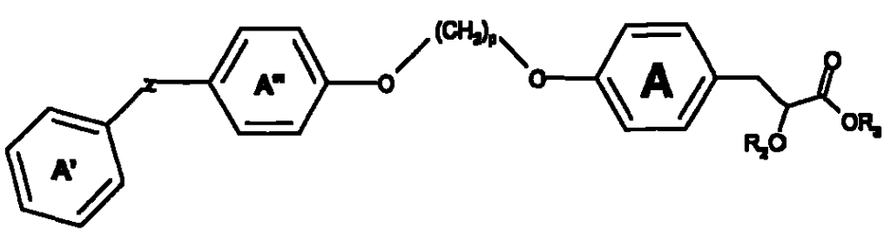


; or



10. The compound of Claim 8 wherein R_2 is a C1-C6 alkyl group, phenyl, benzyl or benzoyl; and R_3 is -H or a C1-C6 alkyl group.

11. The compound of Claim 10 wherein the compound is represented by the following structural formula:



;

wherein:

Phenyl Rings A' and A'' independently substituted or unsubstituted and Z is –O- or –CO- and p is 3 or 4.

12. The compound of Claim 11 wherein Phenyl Rings A' and A'' are independently substituted with one or more groups selected from halogen, $-R_9$, $-OR_9$, $-COR_9$, $-COOR_9$, -CN, a non-aromatic heterocyclic group, an allyl group, $-(CH_2)_aCH(OR_{30})(CH_2)_bCOOR_{31}$, or $-NR_9C(O)R_9$, R_9 is –H, a C1-C10 alkyl group, a C1-C10 halogenated alkyl group, a cycloalkyl group or an aromatic group, R_{30} is a C1-C6 alkyl group or a halogenated C1-C6 alkyl group, R_{31} is -H, a C1-C6 alkyl group or a halogenated C1-C6 alkyl group, and a and b are independently 0, 1 or 2.

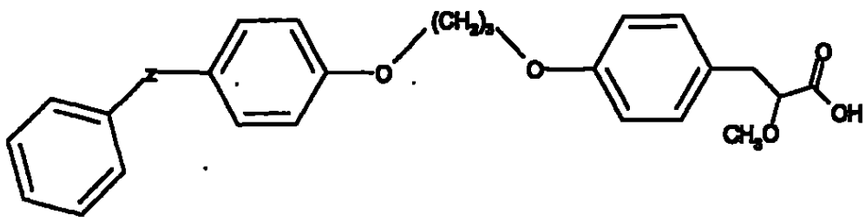
13. The compound of Claim 12 wherein Phenyl Rings A' and A'' are independently substituted with one or more groups selected from halogen, C1-C8 straight chained or branched alkyl, C3-C8 cycloalkyl, C1-C8 straight chained or branched alkanoyl, C1-C8 straight chained or branched alkoxy, -Br, -F, *N*-morpholino, -CN, -COOH, -OH, $-CF_3$ or $-OCF_3$.

14. The compound of Claim 13 wherein Phenyl Ring A is substituted with one or more groups selected from halogen, $-OR_{10}$, $-R_{10}$, aromatic group, substituted aromatic group, aralkyl, substituted aralkyl, aralkenyl, substituted aralkenyl, allyl or substituted allyl and R_{10} is a C1-C10 alkyl group or a C1-C10 halogenated alkyl group.

15. The compound of Claim 14 wherein Phenyl Ring A is substituted with one or more groups selected from -F, -Cl, $-OCH_3$, $-OCF_3$, $-CH_3$, ethyl, *n*-propyl, *iso*-propyl, allyl, 2-phenylethenyl, 2-phenylethyl, phenyl, -*o*-biphenyl, -*m*-biphenyl, -*p*-biphenyl, $-o-C_6H_4OCH_3$, $-m-C_6H_4OCH_3$, $-p-C_6H_4OCH_3$, $-o-C_6H_4F$, $-m-C_6H_4F$ or $-p-C_6H_4F$.

16. The compound of Claim 11 wherein R_2 is methyl and R_3 is hydrogen.

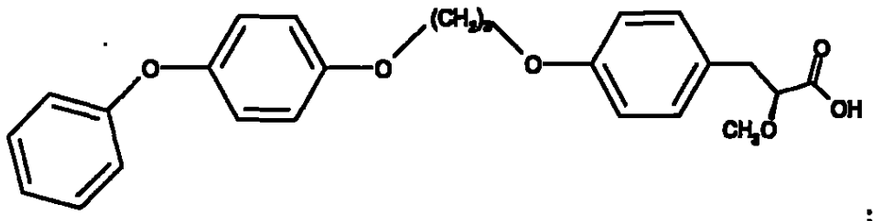
17. A compound represented by the following structural formula:



;

or pharmaceutically acceptable salts, hydrates, stereoisomers and solvates thereof, wherein Z is –O- or –CO-.

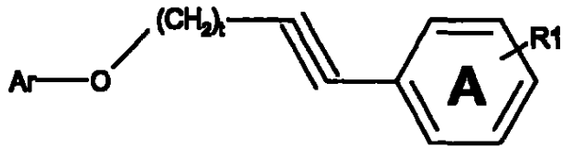
18. A compound represented by the following structural formula



;

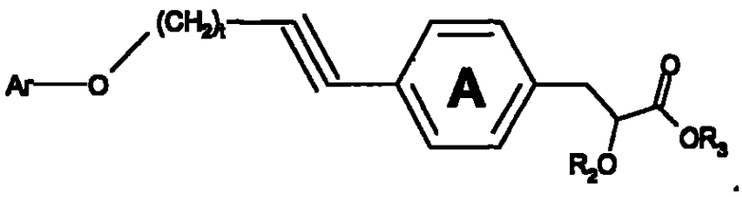
or pharmaceutically acceptable salts, hydrates and solvates thereof.

19. The compound of Claim 1 or 2, wherein the compound is represented by the following structural formula:



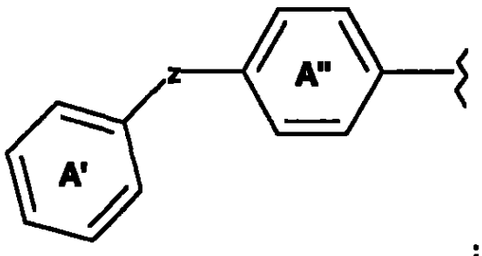
wherein t is an integer from 1 to about 5.

20. The compound of Claim 19 wherein the compound is represented by the following structural formula:



21. The compound of Claim 20 wherein R_2 is a C1-C6 alkyl group, phenyl, benzyl or benzoyl; and R_3 is -H or a C1-C6 alkyl group.

22. The compound of Claim 21 wherein Ar is represented by the following structural formula:



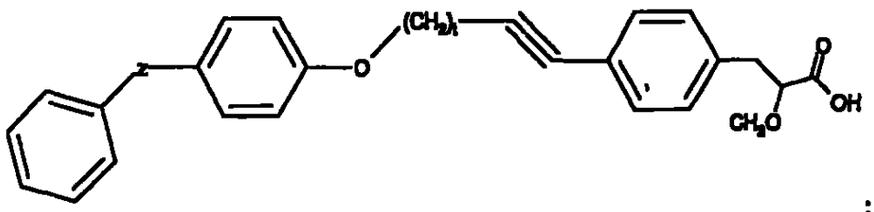
wherein Phenyl Rings A' and A" independently substituted or unsubstituted and Z is –O- or –CO-.

23. The compound of Claim 22 wherein Phenyl Rings A' and A" are independently substituted with one or more groups selected from $-R_9$, $-OR_9$, $-COR_9$, $-COOR_9$, -CN, a non-aromatic heterocyclic group, an allyl group, $-(CH_2)_a CH(OR_{30})(CH_2)_b COOR_{31}$, or $-NR_9C(O)R_9$, R_9 is -H, a C1-C10 alkyl group, a C1-C10 halogenated alkyl group, a cycloalkyl group or an aromatic group, R_{30} is a C1-C6 alkyl group or a halogenated C1-C6 alkyl group, R_{31} is -H, a C1-C6 alkyl group or a halogenated C1-C6 alkyl group, and a and b are independently 0, 1 or 2.

24. The compound of Claim 23 wherein R_2 is methyl and R_3 is –H.

25. A compound represented by the following structural formula:

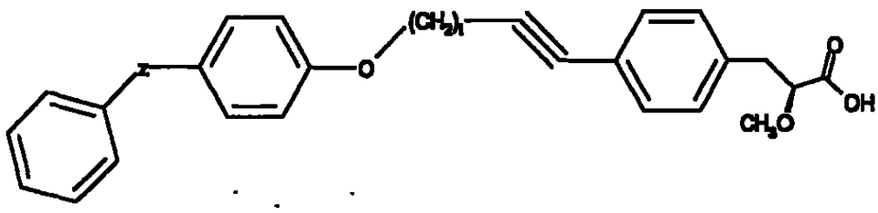
459



;

or pharmaceutically acceptable salts, hydrates, stereoisomers and solvates thereof, wherein Z is –O-, -CO-, -C(=NOH) or a bond and t is 1, 2 or 3.

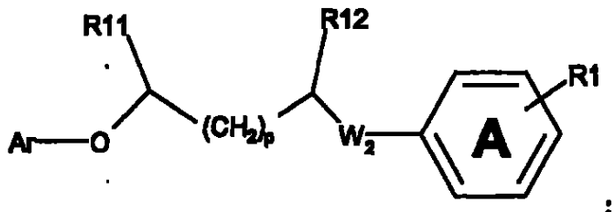
26. A compound represented by the following structural formula:



;

or pharmaceutically acceptable salts, hydrates and solvates thereof, wherein Z is –O-, -CO- or a bond and t is 1, 2 or 3.

27. The compound of Claim 1 or 2 wherein the compound is represented by the following structural formula:



;

wherein:

p is zero, one or two;

W_2 is -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- or $-CH(NR_7R_8)-$;

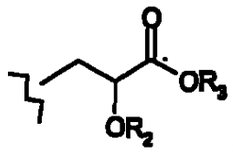
R_7 and R_8 are independently -H, an aliphatic group, a substituted

aliphatic group, an aromatic group or a substituted aromatic group; and

R_{11} and R_{12} are independently a C1-C6 alkyl group, or, taken together are a substituted or unsubstituted ethylene, propylene or butylene group.

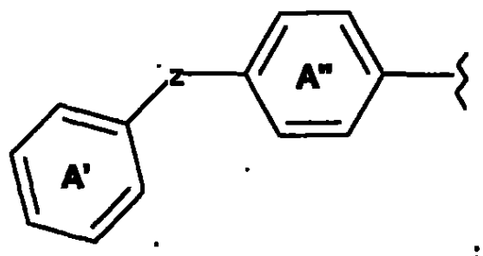
28. The compound of Claim 27 wherein W_2 is -O-.

29. The compound of Claim 28 wherein R_1 is *para* to the carbon atom bonded to W_2 and is represented by the following structural formula:



wherein R_2 is a C1-C6 alkyl group, phenyl, benzyl or benzoyl; and R_3 is -H or a C3-C6 alkyl group.

30. The compound of Claim 29 wherein Ar is represented by the following structural formula:



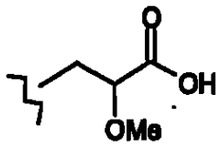
;

wherein Phenyl Rings A' and A'' independently substituted or unsubstituted and Z is –O- or –CO-.

31. The compound of Claim 30 wherein Phenyl Rings A' and A'' are independently substituted with one or more groups selected from $-R_9$, $-OR_9$, -$-COR_9$, $-COOR_9$, -CN, a non-aromatic heterocyclic group, an allyl group, $-(CH_2)_nCH(OR_{30})(CH_2)_bCOOR_{31}$, or $-NR_9C(O)R_9$, and wherein R_9 is –H, a C1-C10 alkyl group, or a C1-C10 halogenated alkyl group, a cycloalkyl

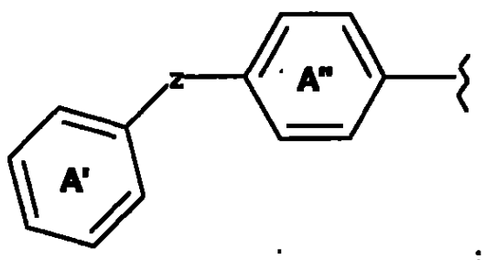
group or an aromatic group, R_{30} is a C1-C6 alkyl group or a halogenated C1-C6 alkyl group, R_{31} is -H, a C1-C6 alkyl group or a halogenated C1-C6 alkyl group, and a and b are independently 0, 1 or 2.

32. The compound of Claim 31 wherein R_1 is represented by the following structural formula:



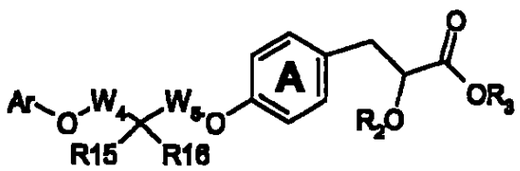
33. The compound of Claim 27 wherein: 1) p is one and R_{11} and R_{12}, taken together, are ethylene or propylene; 2) p is zero and R_{11} and R_{12}, taken together, are propylene or butylene; or 3) p is zero, one or two and R_{11} and R_{12} are independently methyl, ethyl or propyl.

34. The compound of Claim 33 wherein Ar is represented by the following structural formula:



Phenyl Rings A, A' and A'' are unsubstituted and Z is –O–, -C(O)- or a bond.

35. The compound of Claim 1 or 2 wherein the compound is represented by the following structural formula:



wherein:

W_4 and W_5 are independently methylene or ethylene;

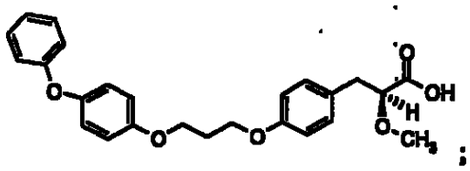
R_2 is a C1-C6 alkyl group, phenyl, benzyl or benzoyl;

R_3 is –H or a C1-C3 alkyl group.

R_{15} is H and R_{16} is a C1-C6 alkyl group, or R_{15} and R_{16}, taken together, are =O or =CH_2.

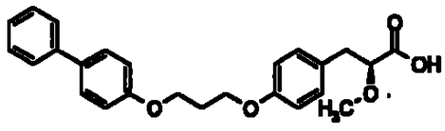
36. The compound of Claim 35 wherein R_{15} is H and R_{16} is methyl, ethyl or propyl, or R_{15} and R_{16}, taken together, are =O or =CH_2.

37. A compound selected from the group consisting of (S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



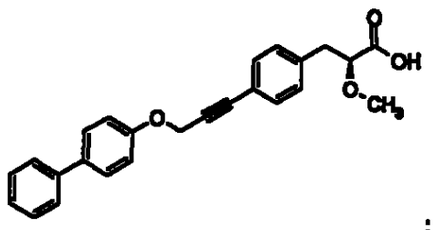
;

(S)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



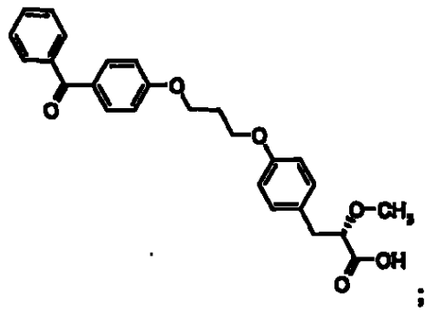
;

(S)-3-{4-[3-(Biphenyl-4-yloxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



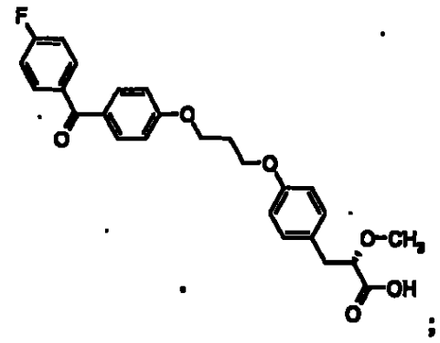
;

(S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



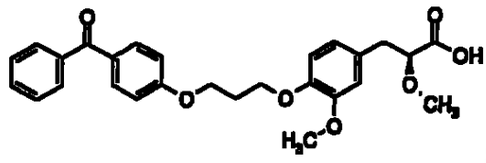
;

(S)-3-(4-{3-[4-(4-Fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid, represented by the following structural formula:



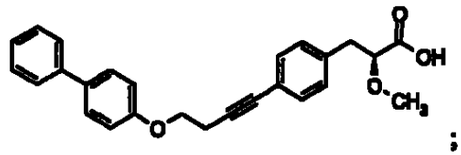
;

(S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid, which is represented by the following structural formula:



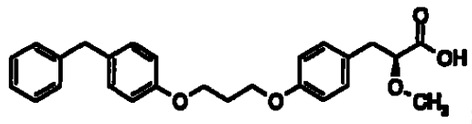
;

(S)-3-{4-[4-(Biphenyl-4-yloxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid, which is represented by the following structural formula:



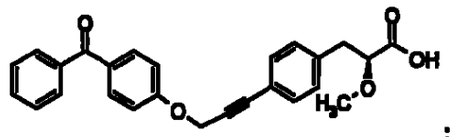
;

(S)-3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid, which is represented by the following structural formula:



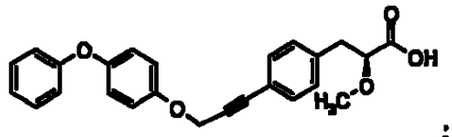
;

(S)-3-{4-[3-(4-Benzoyl-phenoxy)-prop-1-ynyl]-phenyl}-2-methoxy-propionic acid, which is represented by the following structural formula:



;

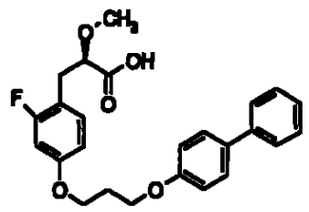
(S)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-prop-1-ynyl]-phenyl}-propionic acid, which is represented by the following structural formula:



;

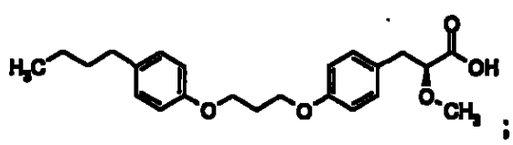
(S)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-2-fluoro-phenyl}-2-methoxy-

propionic acid, which is represented by the following structural formula:



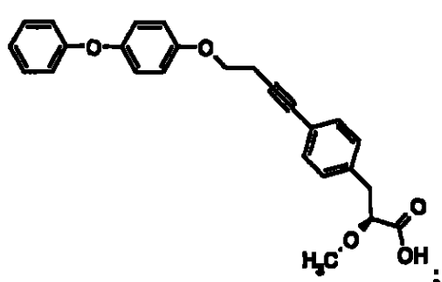
;

(S)-3-{4-[3-(4-Butyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid, which is represented by the following structural formula:



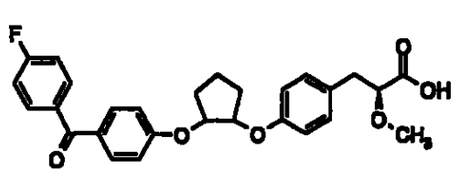
;

(S)-2-Methoxy-3-{4-[4-(4-phenoxy-phenoxy)-but-1-ynyl]-phenyl}-propionic acid, which is represented by the following structural formula:



;

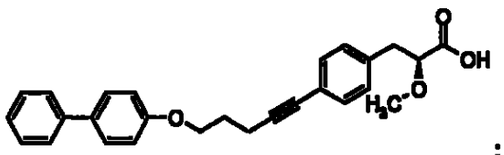
(2S)-3-(4-{2-[4-(4-Fluoro-benzoyl)-phenoxy]-cyclopentyloxy}-phenyl)-2-methoxy-propionic acid, which is represented by the following structural formula:



;

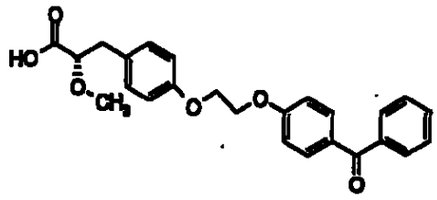
(S)-3-{4-[5-(Biphenyl-4-yloxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic

acid, which is represented by the following structural formula:



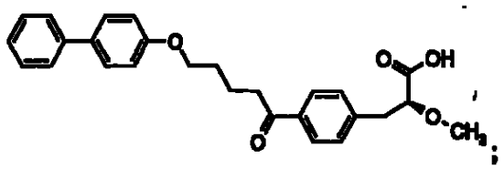
;

(S)-3-{4-[2-(4-Benzoyl-phenoxy)-ethoxy]-phenyl}-2-methoxy-propionic acid, which is represented by the following structural formula:



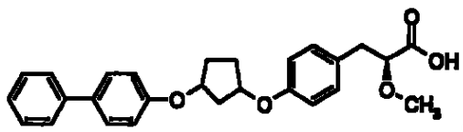
;

(S)-3-{4-[5-(Biphenyl-4-yloxy)-pentanoyl]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



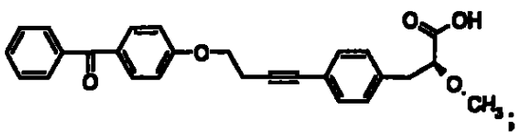
;

(S)-3-{4-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:

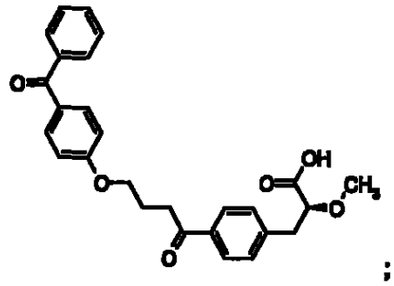


;

(S)-3-{4-[4-(4-Benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:

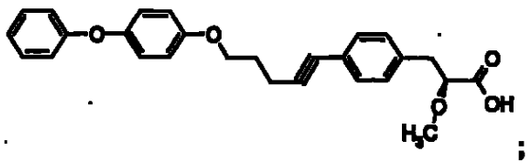


(S)-3-{4-[4-(4-Benzoyl-phenoxy)-butyryl]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



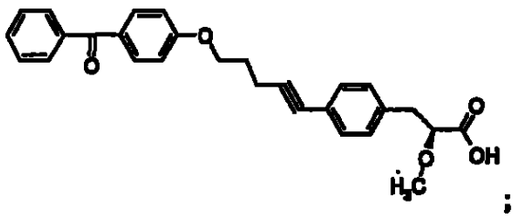
;

(S)-2-Methoxy-3-{4-[5-(4-phenoxy-phenoxy)-pent-1-ynyl]-phenyl}-propionic acid, represented by the following structural formula:



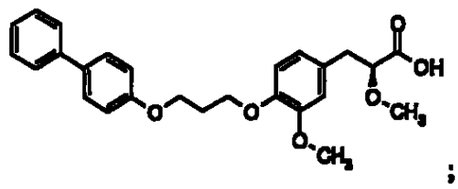
;

(S)-3-{4-[5-(4-Benzoyl-phenoxy)-pent-1-ynyl]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



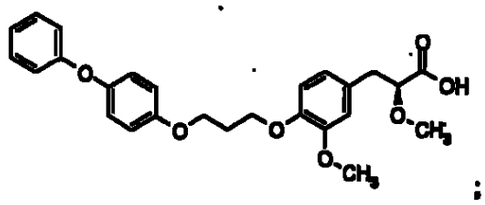
;

(S)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-3-methoxy-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



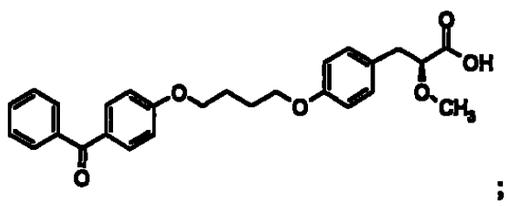
;

(S)-2-Methoxy-3-{3-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



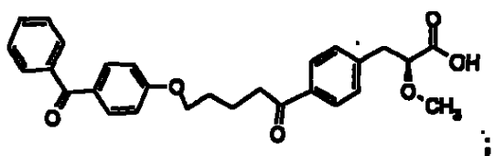
;

(S)-3-{4-[4-(4-Benzoyl-phenoxy)-butoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



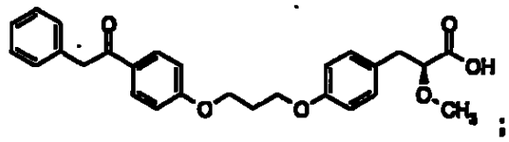
;

(S)-3-{4-[5-(4-Benzoyl-phenoxy)-pentanoyl]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



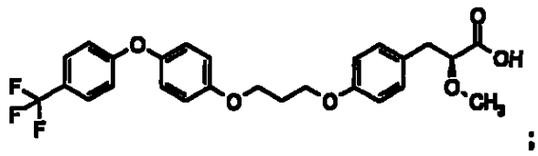
;

(S)-2-Methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



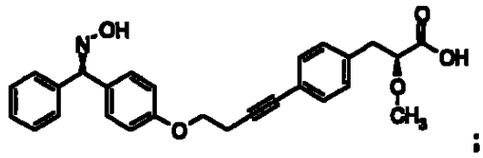
;

2-Methoxy-3-(4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-propoxy}-phenyl)-propionic acid, represented by the following structural formula:



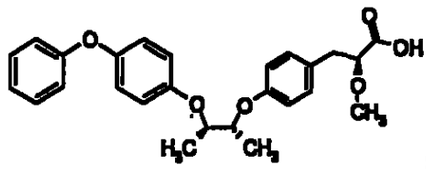
;

3-(4-{4-[4-(Hydroxyimino-phenyl-methyl)-phenoxy]-but-1-ynyl}-phenyl)-2-methoxy-propionic acid, represented by the following structural formula:



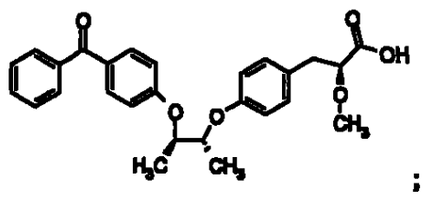
;

2-Methoxy-3-{4-[1-methyl-2-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



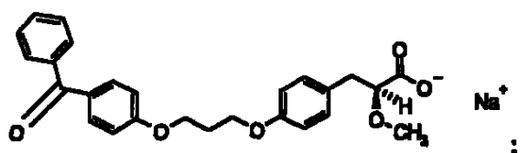
;

3-{4-[2-(4-Benzoyl-phenoxy)-1-methyl-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



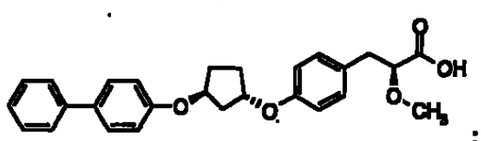
;

Sodium 3-{4-[3-(4-benzoyl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionate, represented by the following structural formula:



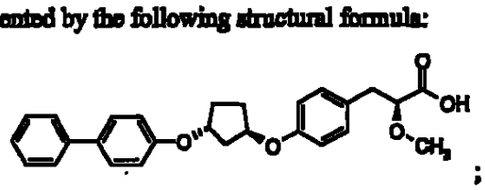
;

3-{4-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-phenyl}-2*S*-methoxy-propionic acid, represented by the following structural formula:



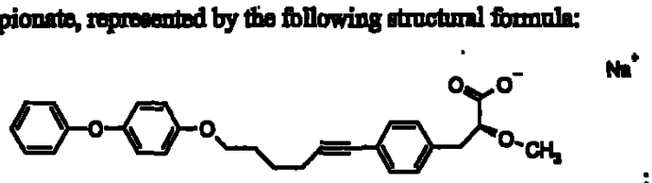
;

3-{4-[3-(Biphenyl-4-yloxy)-cyclopentyloxy]-phenyl}-2*S*-methoxy-propionic acid, represented by the following structural formula:



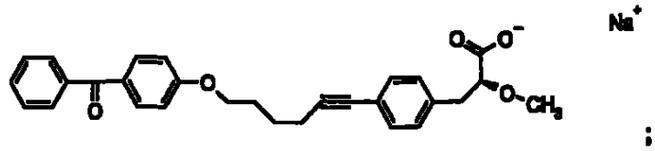
;

Sodium (S)-2-methoxy-3-{4-[6-(4-phenoxy-phenoxy)-hex-1-ynyl]-phenyl}-propionate, represented by the following structural formula:

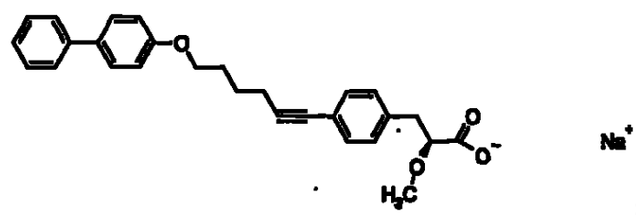


;

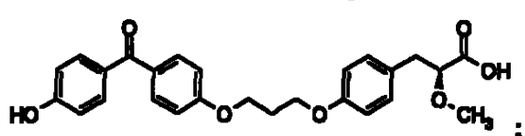
Sodium (S)-3-{4-[6-(4-benzoyl-phenoxy)-hex-1-ynyl]-phenyl}-2-methoxy-propionate, represented by the following structural formula:



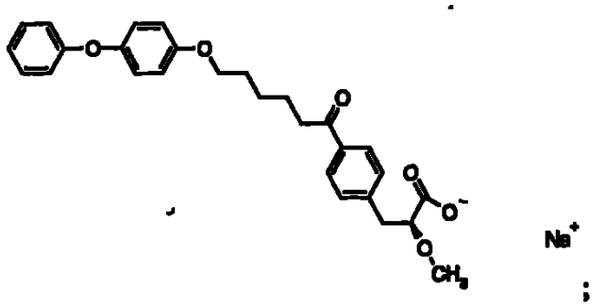
Sodium (S)-3-{4-[6-(biphenyl-4-yloxy)-hex-1-ynyl]-phenyl}-2-methoxy-propionate, represented by the following structural formula:



(S)-3-(4-{3-[4-(4-Hydroxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid, represented by the following structural formula:

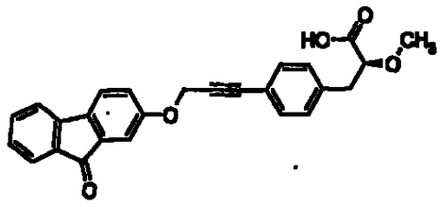


Sodium (S)-2-methoxy-3-{4-[6-(4-phenoxy-phenoxy)-hexanoyl]-phenyl}-propionate, represented by the following structural formula:



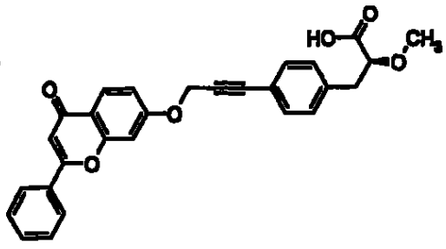
;

(S)-2-Methoxy-3-{4-[3-(9-oxo-9H-fluoren-2-yloxy)-prop-1-ynyl]-phenyl}-propionic acid, represented by the following structural formula:



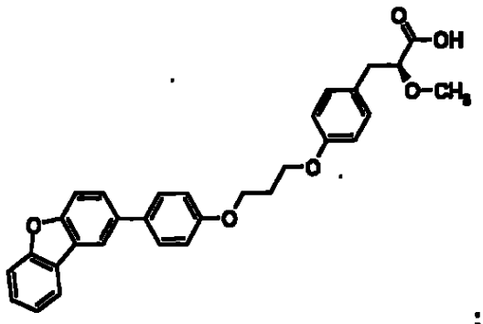
;

(S)-2-Methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-7-yloxy)-prop-1-ynyl]-phenyl}-propionic acid, represented by the following structural formula:



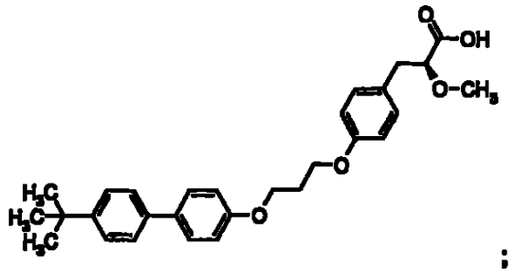
;

(S)-3-{4-[3-(4-Dibenzofuran-2-yl-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



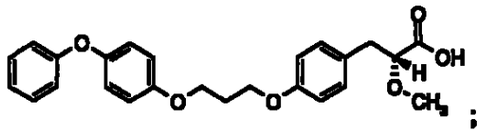
;

(S)-3-{4-[3-(4'-tert-Butyl-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



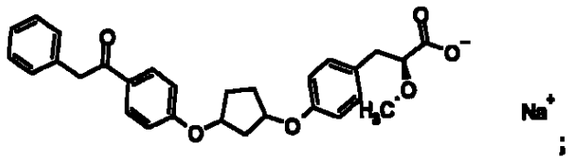
;

(R)-2-Methoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



;

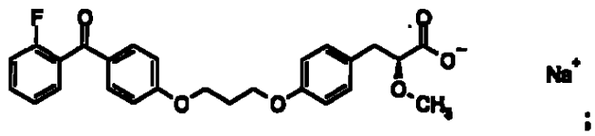
Sodium (S)-2-methoxy-3-{4-[3-(4-phenylacetyl-phenoxy)-cyclopentyloxy]-phenyl}-propionate, represented by the following structural formula:



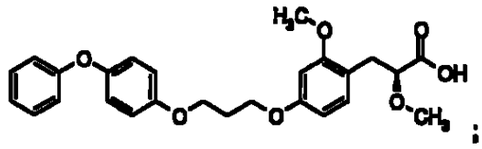
;

Sodium (S)-3-(4-{3-[4-(2-fluoro-benzoyl)-phenoxy]-propoxy}-phenyl)-2-

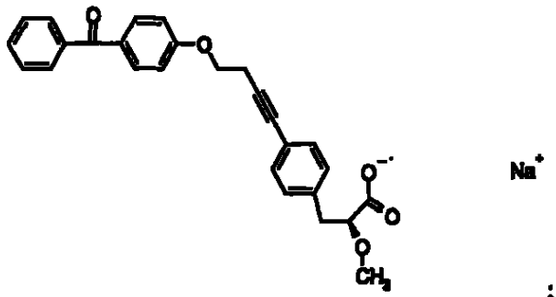
methoxy-propionate, represented by the following structural formula:



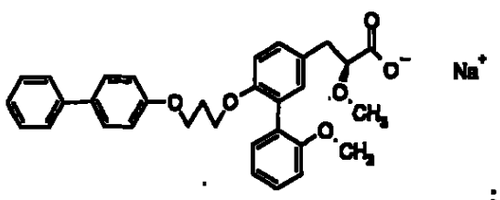
(S)-2-Methoxy-3-{2-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



Sodium (S)-3-{4-[4-(4-benzoyl-phenoxy)-but-1-ynyl]-phenyl}-2-methoxy-propionate, represented by the following structural formula:

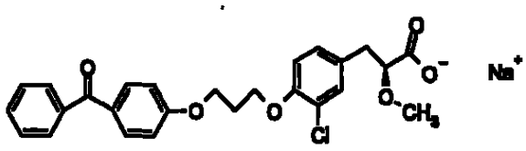


Sodium (S)-3-{6-[3-(biphenyl-4-yloxy)-propoxy]-2'-methoxy-biphenyl-3-yl}-2-methoxy-propionate, represented by the following structural formula:



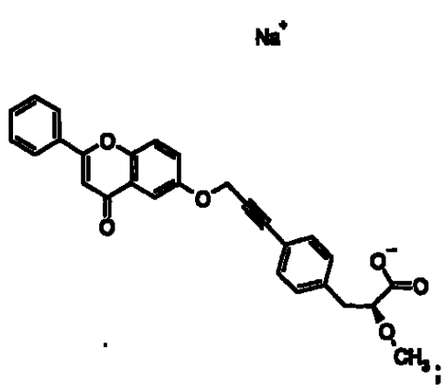
;

Sodium (S)- 3-{4-[3-(4-benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-methoxy-propionate, represented by the following structural formula:



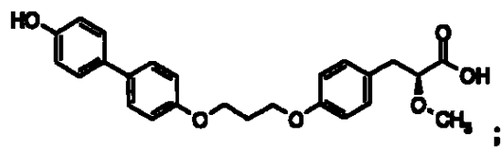
;

Sodium (S)- 2-methoxy-3-{4-[3-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-prop-1-ynyl]-phenyl}-propionate, represented by the following structural formula:



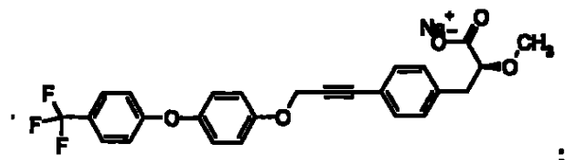
;

(S)-3-{4-[3-(4'-Hydroxy-biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



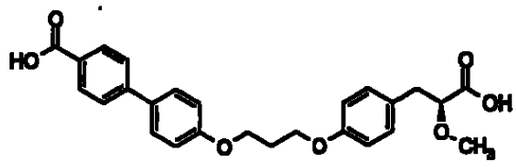
;

Sodium (S)-2-methoxy-3-(4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-prop-1-ynyl}-phenyl)-propionate, represented by the following structural formula:



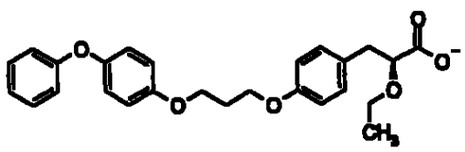
;

(S)-4'-{3-[4-(2-Carboxy-2-methoxy-ethyl)-phenoxy]-propoxy}-biphenyl-4-carboxylic acid, represented by the following structural formula:



;

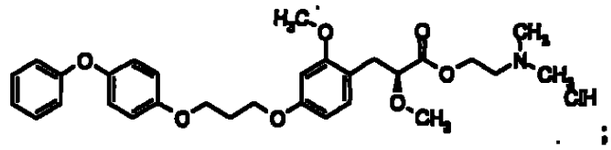
Sodium (S)-2-ethoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionate, represented by the following structural formula:



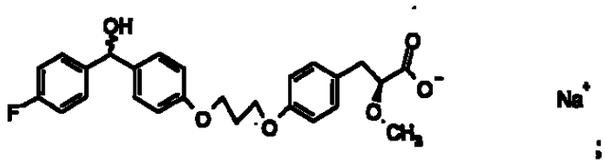
;

(S)-2-Methoxy-3-{2-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-

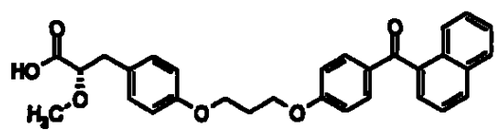
propionic acid 2-dimethylamino-ethyl ester, represented by the following structural formula:



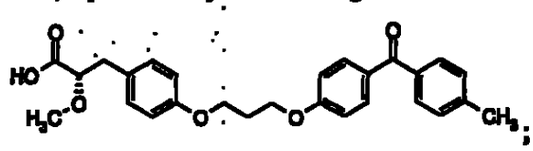
Sodium (S)-3-[4-(3-{4-[(4-fluoro-phenyl)-hydroxy-methyl]-phenoxy}-propoxy)-phenyl]-2-methoxy-propionate, represented by the following structural formula:



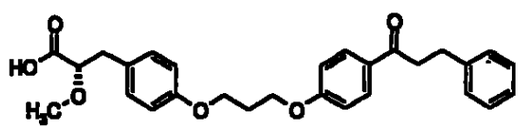
(S)-2-Methoxy-3-(4-{3-[4-(naphthalene-1-carbonyl)-phenoxy]-propoxy}-phenyl)-propionic acid, represented by the following structural formula:



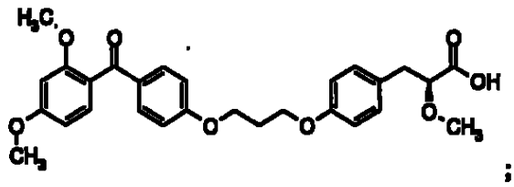
(S)-2-Methoxy-3-(4-{3-[4-(4-methyl-benzoyl)-phenoxy]-propoxy}-phenyl)-propionic acid, represented by the following structural formula:



(S)-2-Methoxy-3-(4-{3-[4-(3-phenyl-propionyl)-phenoxy]-propoxy}-phenyl)-propionic acid, represented by the following structural formula:

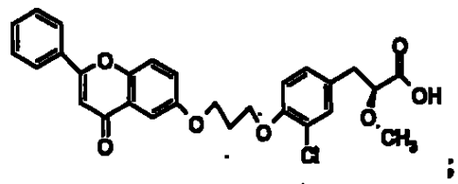


(S)-3-(4-{3-[4-(2,4-Dimethoxy-benzoyl)-phenoxy]-propoxy}-phenyl)-2-methoxy-propionic acid, represented by the following structural formula:



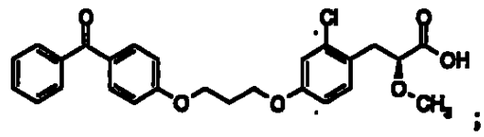
;

(S)-3-{3-Chloro-4-[3-(4-oxo-2-phenyl-4H-chromen-6-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



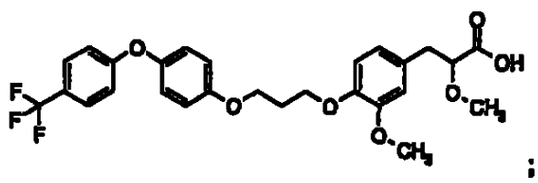
;

(S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



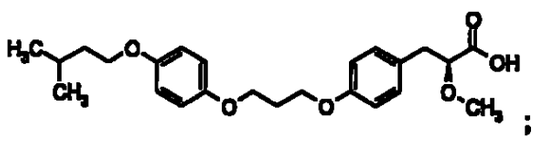
;

(S)-2-Methoxy-3-(3-methoxy-4-{3-[4-(4-trifluoromethyl-phenoxy)-phenoxy]-propoxy}-phenyl)-propionic acid, represented by the following structural formula:



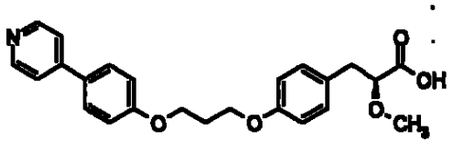
;

(S)-2-Methoxy-3-(4-{3-[4-(3-methyl-butoxy)-phenoxy]-propoxy}-phenyl)-propionic acid, represented by the following structural formula:



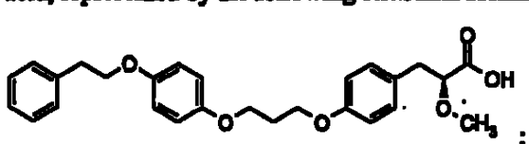
;

(S)-2-Methoxy-3-{4-[3-(4-pyridin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



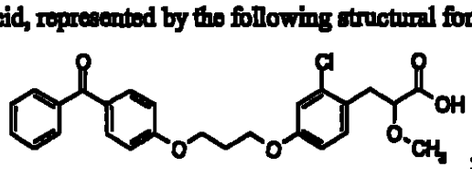
;

(S)-2-Methoxy-3-{4-[3-(4-phenethyloxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



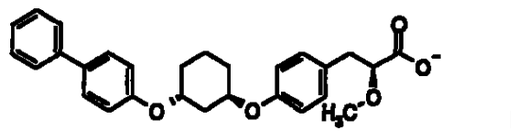
;

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-2-chloro-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



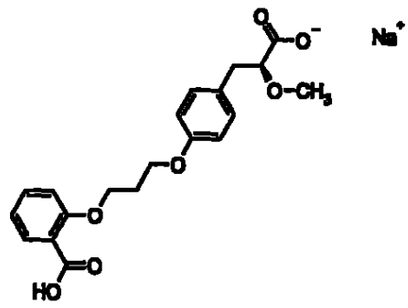
;

Sodium (S)-3-{4-[3-(biphenyl-4-yloxy)-cyclohexyloxy]-phenyl}-2-methoxy-propionate, represented by the following structural formula:



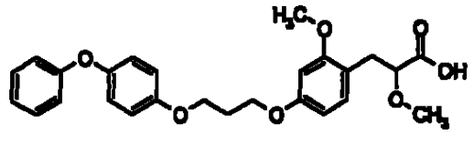
;

Sodium (S)-3-{4-[3-(2-carboxy-phenoxy)-propoxy]-phenyl}-2-methoxy-propionate, represented by the following structural formula:



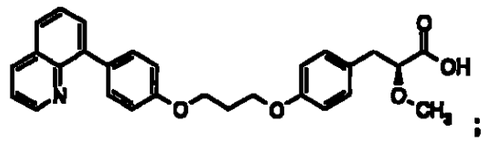
;

2-Methoxy-3-{2-methoxy-4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



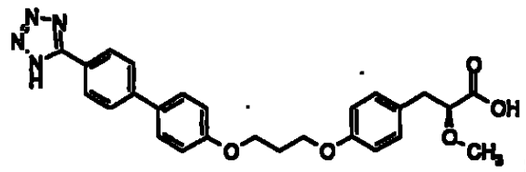
;

(S)-2-Methoxy-3-{4-[3-(4-quinolin-8-yl-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



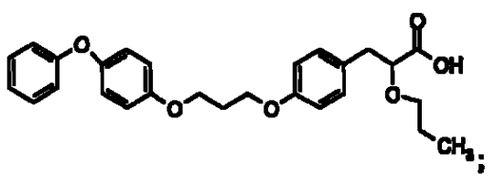
;

(S)-2-Methoxy-3-(4-{3-[4'-(1H-tetrazol-5-yl)-biphenyl-4-yloxy]-propoxy}-phenyl)-propionic acid, represented by the following structural formula:



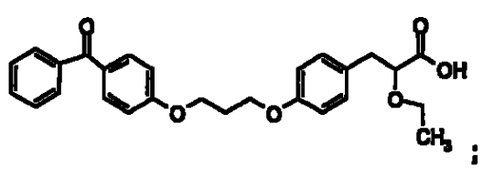
;

3-{4-[3-(4-Phenoxy-phenoxy)-propoxy]-phenyl}-2-propoxy-propionic acid, represented by the following structural formula:



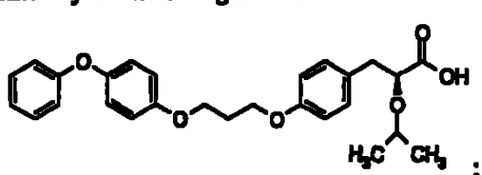
;

3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid, represented by the following structural formula:



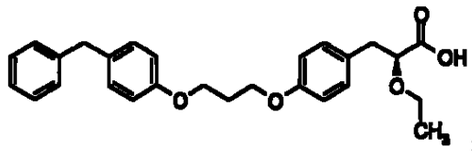
;

(S)-2-Isopropoxy-3-{4-[3-(4-phenoxy-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



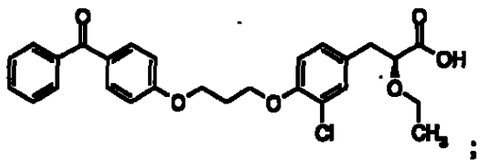
;

(S)-3-{4-[3-(4-Benzyl-phenoxy)-propoxy]-phenyl}-2-ethoxy-propionic acid, represented by the following structural formula:



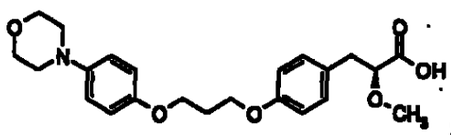
;

(S)-3-{4-[3-(4-Benzoyl-phenoxy)-propoxy]-3-chloro-phenyl}-2-ethoxy-propionic acid, represented by the following structural formula:



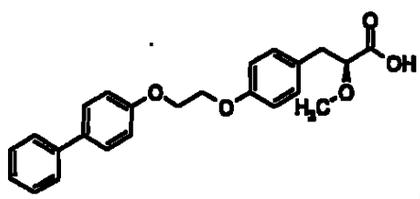
;

(S)-2-Methoxy-3-{4-[3-(4-morpholin-4-yl-phenoxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



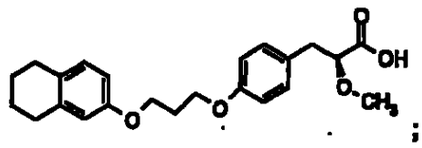
;

(S)-3-{4-[2-(Biphenyl-4-yloxy)-ethoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:

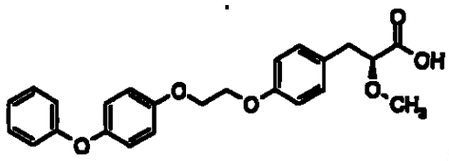


;

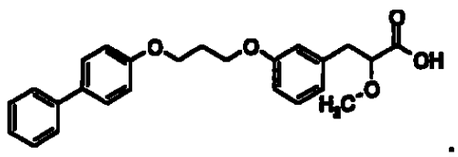
(S)-2-Methoxy-3-{4-[3-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-propoxy]-phenyl}-propionic acid, represented by the following structural formula:



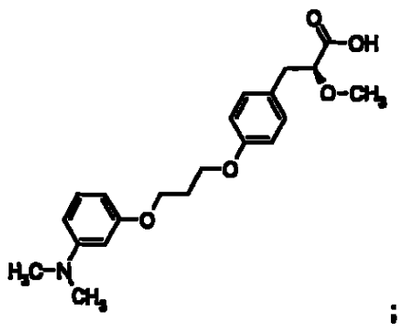
(S)-2-Methoxy-3-{4-[2-(4-phenoxy-phenoxy)-ethoxy]-phenyl}-propionic acid, represented by the following structural formula:



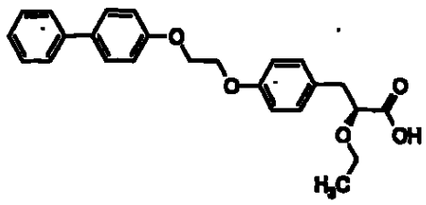
3-{3-[3-(Biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



(S)-3-{4-[3-(3-Dimethylamino-phenoxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:

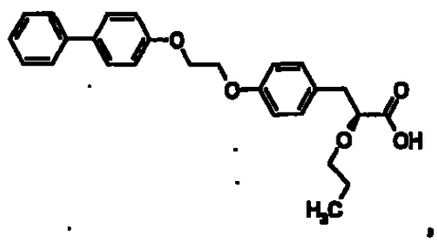


(S)-3-{4-[2-(Biphenyl-4-yloxy)-ethoxy]-phenyl}-2-ethoxy-propionic acid, represented by the following structural formula:



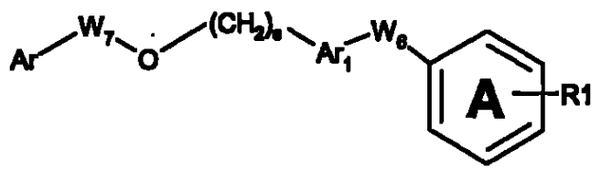
; and

(S)-3-{4-[2-(Biphenyl-4-yloxy)-ethoxy]-phenyl}-2-propoxy-propionic acid, represented by the following structural formula:



or apharmaceutically acceptable salts, hydrates and solvates of the foregoing compounds.

38. A compound represented by the following structural formula:



(XL)

or pharmaceutically acceptable salts, hydrates, stereoisomers and solvates thereof, wherein:

Ar is a substituted or unsubstituted aromatic group;

R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ or $-(CH)=C(Y)-(CH_2)_mE$; wherein E is $COOR_3$, C_1-C_3-alkyinitrile, carboxamide, sulfonamide, acylsulfonamide or tetrazole and wherein sulfonamide, acylsulfonamide and tetrazole are optionally substituted with one or more substituents independently selected from: C1-

C6 alkyl, haloalkyl and aryl-C0-4-alkyl;

R_2 is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ or $-C(S)NR_5R_6$;

Y is –O-, $-CH_2-$, $-CH_2CH_2-$ or –CH=CH- and is bonded to a carbon atom in Phenyl Ring A that is *ortho* to R_1;

R_3-R_6 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group;

n and m are independently 0, 1 or 2;

s is 0, 1 or 2;

Ar_1 is a substituted or unsubstituted arylene group;

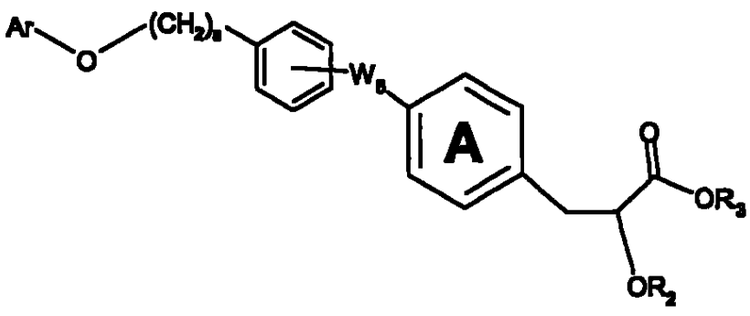
W_6 is a covalent bond, $-W_1-$, $-CH_2W_1-$ or $-W_1CH_2-$;

W_7 is a covalent bond or CH_2-; and

W_1 is -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, $-C(=NOH)-$ or $-CH(NR_7R_8)-$.

39. The compound of Claim 38 wherein R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ or $-(CH)=C(Y)-(CH_2)_mCOOR_3$.

40. The compound of Claim 39 wherein the compound is represented by the following structural formula:



;

wherein s is 0 or 1 and W_6 is a covalent bond, -O-, $-CH_2O-$ or $-OCH_2-$.

41. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

42. The pharmaceutical composition of Claim 41 additionally comprising a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

43. A pharmaceutical composition comprising the compound of any one of Claims 2-17 or 19-40 and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition comprising: 1) the compound of any one of Claims 2-17 or 19-40 or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof; a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and 3) a pharmaceutically acceptable carrier.

45. A pharmaceutical composition comprising the compound of Claim 18 or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

46. The pharmaceutical composition of Claim 45 additionally comprising a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase

inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

47. A method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with at least one compound of Claim 1.

48. The method of Claim 47, wherein the PPAR is an alpha receptor.

49. The method of Claim 47, wherein the PPAR is an gamma receptor.

50. A method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with at least one compound of Claim 2.

51. A method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with the compound of Claim 18.

52. A method for treating a PPAR-gamma mediated disease or condition in a subject comprising the step of administering to the subject an effective amount of the compound Claim 1.

53. A method for treating a PPAR-gamma mediated disease or condition in a subject comprising the step of administering to the subject an effective amount of the compound Claim 2.

54. A method for treating a PPAR-gamma mediated disease or condition in a subject comprising the step of administering to the subject an effective

amount of the compound Claim 18.

55. A method for lowering blood-glucose in a subject comprising the step of administering to the subject an effective amount of the compound of Claim 1.

56. A method for lowering blood-glucose in a subject comprising the step of administering to the subject an effective amount of the compound of Claim 2.

57. A method for lowering blood-glucose in a subject comprising the step of administering to the subject an effective amount of the compound of Claim 18.

58. A method of treating a subject with hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease or other diseases where insulin resistance is a component, said method comprising the step of administering to the subject an effective amount of the compound of Claim 1.

59. A method of treating a subject with hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease or other diseases where insulin resistance is a component, said method comprising the step of administering to the subject an effective amount of the compound of Claim 2.

60. A method of treating a subject with hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, polycystic ovarian syndrome, anorexia nervosa, cardiovascular disease or other diseases where insulin resistance is a component, said method comprising the step of administering to the subject an effective amount of the compound of Claim 18.

61. The method of Claim 58 additionally comprising the step of administering to the subject an effective amount of second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

62. The method of Claim 59 additionally comprising the step of administering to the subject an effective amount of second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

63. The method of Claim 60 additionally comprising the step of administering to the subject an effective amount of second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase

inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

64. A method of treating a subject with diabetes mellitus, said method comprising the step of administering to the subject an effective amount of the compound of Claim 1.

65. A method of treating a subject with diabetes mellitus, said method comprising the step of administering to the subject an effective amount of the compound of Claim 2.

66. A method of treating a subject with diabetes mellitus, said method comprising the step of administering to the subject an effective amount of the compound of Claim 18.

67. A method of treating a subject with cardiovascular disease, said method comprising the step of administering to the subject an effective amount of the compound of Claim 1.

68. A method of treating a subject with cardiovascular disease, said method comprising the step of administering to the subject an effective amount of the compound of Claim 2.

69. A method of treating a subject with cardiovascular disease, said method comprising the step of administering to the subject an effective amount of the compound of Claim 18.

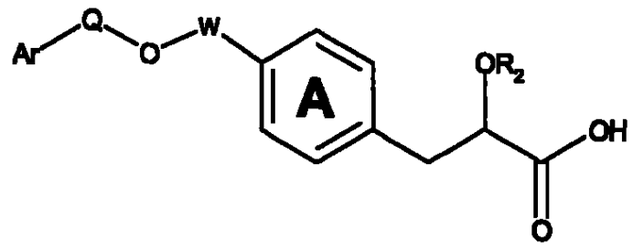
70. A method of treating a subject with Syndrome X, said method comprising the step of administering to the subject an effective amount of the compound of Claim 1.

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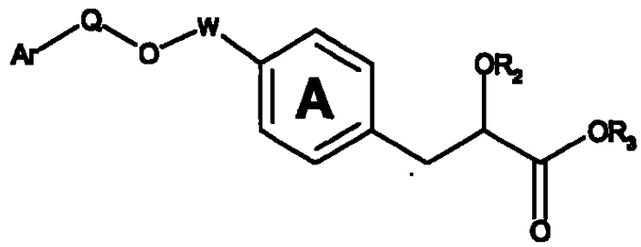
71. A method of treating a subject with Syndrom X, said method comprising the step of administering to the subject an effective amount of the compound of Claim 2.

72. A method of treating a subject with Syndrome X, said method comprising the step of administering to the subject an effective amount of the compound of Claim 18.

73. A method of preparing a compound represented by the following structural formula:



from a starting compound represented by the following structural formula:



;

said method comprising the step of hydrolyzing the ester group in the starting compound, wherein:

Ar is a substituted or unsubstituted aromatic group;

Q is a covalent bond, $-CH_2-$ or $-CH_2CH_2-$;

W is a substituted or unsubstituted alkylene or heteroalkylene linking group from two to ten atoms in length;

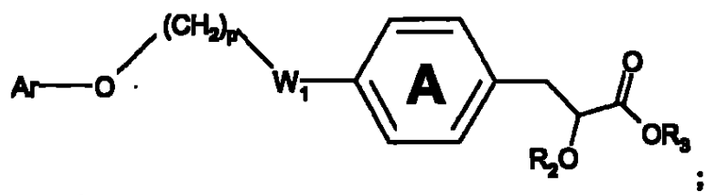
phenyl Ring A is optionally substituted with up to four substituents in addition to W and $-CH_2CHOR_2C(O)OR_3$;

R_2 is –H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group;

R_3 an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group.

74. The method of Claim 73 wherein Q is a covalent bond.

75. The method of Claim 74 wherein the starting compound is represented by the following structural formula:



;

i. p is an integer from one to four;

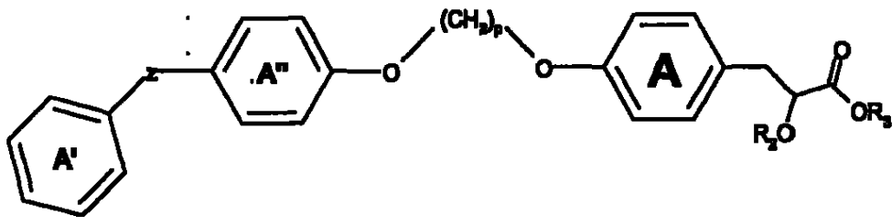
W_1 is -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- or $-CH(NR_7R_8)-$;

R_2 is a C1-C6 alkyl group, phenyl, benzyl or benzoyl;

R_3 –H or a C1-C3 alkyl group; and

R_7 and R_8 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group.

76. The method of Claim 75 wherein the compound is represented by the following structural formula:



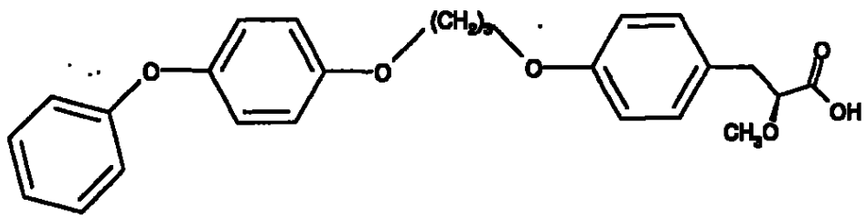
;

wherein:

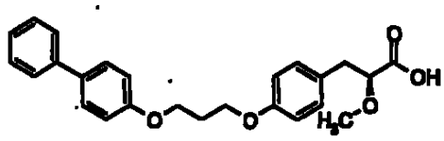
Phenyl Rings A' and A'' independently substituted or unsubstituted

and Z is –O- or –CO-.

77. The method of Claim 76 wherein the compound is represented by the following structural formula:



78. A compound, wherein the compound is radiolabeled (S)-3-{4-[3-(Biphenyl-4-yloxy)-propoxy]-phenyl}-2-methoxy-propionic acid, represented by the following structural formula:



79. The compound of Claim 78 wherein the radiolabel is a tritium atom.

80. A method for determining whether a compound does or does not interact directly with peroxisome proliferator-activated receptor, comprising the step of specifically binding the radiolabeled compound of Claim 78 to the ligand binding domain of the peroxisome proliferator-activated receptor.

81. The method of Claim 80 wherein the peroxisome proliferator-activated receptor is PPARγ.

82. The method of Claim 81 additionally comprising the step of contacting the receptor with a test compound and assessing the amount of specific binding

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of the radiolabeled compound to the receptor, wherein a decrease in the binding of the radiolabeled compound indicates that the test compound interacts directly with the peroxisome proliferator-activated receptor.

83. The method of Claim 82 wherein the radiolabeled compound is tritiated.

MODULADORES DE LOS RECEPTORES ACTIVADOS POR PROLIFERADORES DE PEROXISOMAS

ANTECEDENTES DE LA INVENCION

Los receptores activados por proliferadores de peroxisomas (PPAR) son miembros de la familia de los genes de los receptores nucleares que son activados por los ácidos grasos y los metabolitos de ácidos grasos. Los PPAR pertenecen al subgrupo de receptores nucleares que funcionan como heterodímeros con el receptor del ácido 9-*cis*-retinóico (RXR). Tres subtipos, denominados PPARα, PPARγ y PPARδ, se encuentran en especies que abarcan de *Xenopus* a humanos.

El PPARα es el subtipo principal en el hígado y ha facilitado el análisis del mecanismo por el cual los proliferadores de peroxisomas ejercen sus efectos pleiotrópicos. El PPARα es activado por varios ácidos grasos de cadena media y larga, y está implicado en la estimulación de la β-oxidación de ácidos grasos. El PPARα está implicado también en la actividad de los fibratos y los ácidos grasos en roedores y humanos. Los derivados de ácido fíbrico tales como clofibrato, fenofibrato, bezafibrato, ciprofibrato, beclofibrato y etofibrato, así como el gemfibrozil, producen una reducción sustancial de triglicéridos en plasma junto con una reducción moderada del colesterol con lipoproteínas de baja densidad (LDL), y se utilizan concretamente para el tratamiento de la hipertrigliceridemia.

El PPARγ es el subtipo principal en el tejido adiposo y está implicado en la activación del programa de diferenciación de los adipocitos. El PPARγ no está implicado en la estimulación de la proliferación de peroxisomas en el hígado. Existen dos isómeros del PPARγ: PPARγ1 y PPARγ2, que difieren únicamente en que PPARγ2

contiene 28 aminoácidos adicionales presentes en el extremo amino. Las secuencias de ADN para los receptores PPARγ son descritas por Elbrecht, y col., BBRC 224;431-437 (1996). Aunque los proliferadores de peroxisomas, incluyendo los fibratos y los ácidos grasos, activan la actividad transcripcional de los PPAR, únicamente los derivados J_2 de prostaglandinas han sido identificados como ligandos naturales para los PPARγ, que también se unen a las tiazolidinodionas de los agentes antidiabéticos con elevada afinidad. Las funciones fisiológicas del PPARα y PPARγ en el metabolismo de los lípidos y de los hidratos de carbono fueron descubiertas una vez que se advirtió que eran los receptores para los fármacos con fibrato y glitazona, respectivamente.

Los receptores PPARα y PPARγ han sido implicados en la diabetes sacarina, las enfermedades cardiovasculares, la obesidad, y las enfermedades gastrointestinales, tales como la enfermedad inflamatoria del intestino y otros trastornos relacionados con la inflamación. Entre tales trastornos relacionados con la inflamación se incluyen, pero no están limitados a la enfermedad de Alzheimer, la enfermedad de Crohn, la artritis reumatoide, la psoriasis, y la lesión isquémica por reperfusión.

En contraste, no se ha informado que el PPARδ (también referido como PPARβ y NUC1) sea receptor de ninguna clase conocida de moléculas de fármaco, y su papel en la fisiología de mamíferos ha permanecido indefinido. El gen del receptor nuclear humano PPARδ (hPPARδ) ha sido clonado a partir de una genoteca de ADNc de células de osteosarcoma humano y lo describen completamente A. Schmidt y col., en *Molecular Endocrinology*, 6:1634-1641 (1992).

La diabetes es una enfermedad en la que la capacidad de los mamíferos para regular los niveles de glucosa en sangre resulta deteriorada debido a que el mamífero tiene

reducida su capacidad para convertir la glucosa en glucógeno para el almacenamiento en las células del músculo y el hígado. En la diabetes de Tipo I, esta reducción de la capacidad para almacenar glucosa está causada por la reducción de la producción de insulina. La "Diabetes de Tipo II" o "diabetes sacarina no dependiente de insulina" (NIDDM en sus siglas en inglés) es la forma de diabetes, que está debida a una profunda resistencia al efecto estimulador o regulador de la insulina sobre el metabolismo de glucosa y de lípidos en los tejidos sensibles a la insulina principales, músculo, hígado y tejido adiposo. Esta resistencia al grado de reacción de la insulina ocasiona una activación insuficiente por la insulina de la absorción, la oxidación y el almacenamiento de glucosa en el músculo y una represión inadecuada por la insulina de la lipólisis en el tejido adiposo y de la producción y secreción de glucosa en el hígado. Cuando estas células comienzan a desensibilizarse a la insulina, el organismo trata de compensar produciendo niveles anormalmente altos de insulina y se produce hiperinsulinemia. La hiperinsulinemia está asociada con la hipertensión y el peso corporal elevado. Puesto que la insulina está implicada en la promoción de la absorción celular de glucosa, aminoácidos y triglicéridos de la sangre por las células sensibles a la insulina, la insensibilidad a la insulina puede ocasionar elevados niveles de triglicéridos y de LDL (conocido como colesterol "malo") que son factores de riesgo en las enfermedades cardiovasculares. La constelación de síntomas entre los que se incluyen la hiperinsulemia combinada con hipertensión, peso corporal elevado, elevados triglicéridos y elevadas LDL es conocida como Síndrome X.

La hiperlipidemia es una afección que está caracterizada por un incremento anormal de lípidos en

suero, tales como el colesterol, los triglicéridos y los fosfolípidos. Estos lípidos no circulan libremente en solución en plasma, pero se unen a proteínas y son transportados por complejos macromoleculares denominados lipoproteínas. Una forma de hiperlipidemia es la hipercolesterolemia, caracterizada por la existencia de elevados niveles de colesterol LDL. El tratamiento inicial para la hipercolesterolemia es a menudo una dieta con bajo contenido de grasas y colesterol unida a ejercicio físico apropiado. La intervención del fármaco se inicia si los objetivos de disminución de LDL no son cumplidos sólo por la dieta y el ejercicio. Es deseable disminuir los elevados niveles de colesterol LDL y aumentar los niveles de colesterol HDL. Generalmente, se ha encontrado que niveles elevados de HDL están asociados con un menor riesgo de enfermedad cardíaca coronaria (CHD). Ver Gordon, y col., *Am. J. Med.*, 325, 373-381 (1991); y Kannel, y col., *Ann. Internal Med*, 90, 85-91 (1979). Un ejemplo de un agente elevador de las HDL es el ácido nicotínico, pero las cantidades necesarias para lograr la elevación de las HDL están asociadas con efectos no deseables, tales como la ruborización.

Existen varios tratamientos disponibles en la actualidad para tratar la diabetes sacarina pero estos tratamientos son todavía insatisfactorios y tienen limitaciones. Si bien el ejercicio físico y la reducción de la toma de calorías en la dieta mejorará la afección diabética, la conformidad con este enfoque puede ser escasa debido al estilo de vida sedentario y al exceso de consumo de alimentos, en concreto de alimentos con alto contenido de grasas. Por consiguiente, el tratamiento con hipoglicémicos, tales como sulfonilureas (v.g., clorpropamida, tolbutamida, tolazamida y acetohexamida) y biguanidas (v.g. fenformin y metformin) es a menudo necesario según progresa la enfermedad. Las sulfonilureas

estimulan las células β del páncreas para que secreten más insulina según progresa la enfermedad. No obstante, la respuesta de las células β eventualmente falla y es necesario el tratamiento con inyecciones de insulina. Además, tanto el tratamiento con sulfonilurea como con la inyección de insulina tienen el efecto secundario amenazador para la vida del coma hipoglicémico, y de este modo los pacientes que utilizan estos tratamientos deben controlar cuidadosamente la dosificación.

Ha quedado bien establecido que la mejora del control glicémico en pacientes con diabetes (de Tipo I y Tipo II) está acompañada del descenso de las complicaciones microvasculares (DCCT y UKPDS). Debido a la dificultad para mantener el control glicémico adecuado a lo largo del tiempo en pacientes con diabetes de Tipo II, está creciendo el uso de sensibilizadores a la insulina en la terapia de la diabetes de Tipo II. También hay un conjunto creciente de evidencias de que el agonista del PPARγ, un sensibilizador a la insulina, puede tener beneficios en el tratamiento de la diabetes de Tipo II por encima de sus efectos en la mejora del control glicémico.

En la última década ha emergido una clase de compuestos conocidos como tiazolidinodionas (v.g. Patentes de los Estados Unidos Núms. 5.089.514, 4.342.771, 4.367.234, 4.340.605; y 5.306.726) como agentes antidiabéticos eficaces que se ha demostrado que aumentan la sensibilidad de los tejidos sensibles a la insulina, tales como el músculo esquelético, el hígado y el adiposo, a la insulina. El incremento de la sensibilidad a la insulina en lugar de la cantidad de insulina en sangre reduce la probabilidad de coma hipoglicémico. Si bien se ha demostrado que las tiazolidinodionas aumentan la sensibilidad a la insulina uniéndose a los receptores PPARγ, este tratamiento

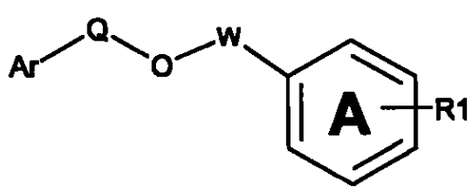
también produce efectos secundarios no buscados tales como la ganancia de peso y, para la troglitazona, toxicidad para el hígado.

En vista de lo anterior, existe la necesidad de nuevos agentes farmacéuticos que modulen estos receptores para prevenir, tratar y/o aliviar estas enfermedades o afecciones a la vez que se mejoran los efectos secundarios de los tratamientos actuales.

COMPENDIO DE LA INVENCION

Aquí se describen α-metoxicinamatos novedosos que son moduladores de los receptores activados por proliferadores de peroxisomas (PPAR). Muchos de estos α-metoxicinamatos novedosos tienen la ventaja sobre los moduladores de los PPAR previamente conocidos de que se unen selectivamente a los moduladores de los receptores activados por proliferadores de peroxisomas. Basándose en este descubrimiento, se describen aquí los métodos para modular un receptor activado por proliferadores de peroxisomas en un sujeto que necesite semejante modulación, los métodos para tratar un sujeto con diabetes de Tipo II, los métodos para tratar un sujeto con enfermedades cardiovasculares, los métodos para tratar un sujeto con Síndrome X y los métodos para tratar un sujeto con otras enfermedades y afecciones mediadas por los PPAR.

Una realización de la presente invención es un compuesto representado mediante la Fórmula Estructural (I):



(I).

Las variables en la Fórmula Estructural (I) se definen más abajo.

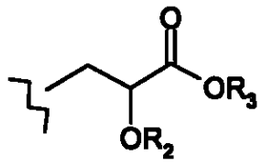
Ar es un grupo aromático sustituido o no sustituido. Preferiblemente, Ar es un grupo aromático no sustituido, monosustituido o disustituido.

Q es a enlace covalente, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ o $-CH_2CH_2CH_2CH_2-$. Preferiblemente, Q es un enlace covalente.

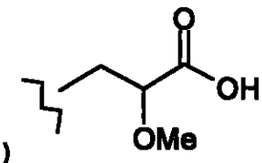
W es un grupo alquileno sustituido o no sustituido de dos a diez átomos de longitud o un grupo heteroalquileno sustituido o no sustituido, donde el grupo heteroalquileno es un grupo alquileno de dos a diez átomos de longitud en el que uno o más grupos metileno han sido reemplazados por un grupo funcional seleccionado entre $-CH=CH-$, $-C\equiv C-$, $-O-$, $-CO-$, $-NR_7-$, $-NR_7CO-$, $-C(=NOH)-$, $-S-$, $-S(O)-$, $-S(O)_2-$ o $-CH(NR_7R_8)-$.

El Anillo de Fenilo **A** está sustituido opcionalmente con hasta cuatro sustituyentes además de R_1 y W.

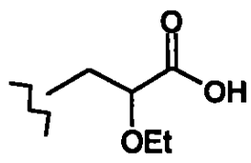
R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ o $-(CH)=C(Y)-(CH_2)_mE$. E es $COOR_3$, alquil(C1-C3)nitrilo, carboxamida, sulfonamida, acilsulfonamida o tetrazol y donde sulfonamida, acilsulfonamida y tetrazol están sustituidos opcionalmente con uno o más sustituyentes seleccionados independientemente entre: alquilo C1-C6, haloalquilo C1-C6 y arilalquilo C0-C4. Preferiblemente R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ o $-(CH)=C(Y)-(CH_2)_mCOOR_3$. Más preferiblemente R_1 está en *meta* o *para* respecto a W y está representado mediante la Fórmula Estructural (II), incluso más preferiblemente mediante las Fórmulas Estructurales (III) o (IV) e incluso más preferiblemente mediante la Fórmula Estructural (V):



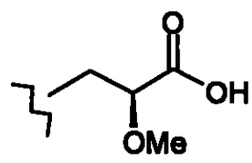
(II)



(III)



(IV)



(V).

R_2 es -H, un grupo alifático, un grupo alifático sustituido, haloalquilo, un grupo aralquilo, un grupo aralquilo sustituido, un grupo aromático, un grupo aromático sustituido, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ o $-C(S)NR_5R_6$.

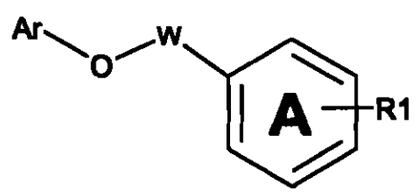
Y es -O-, $-CH_2-$, $-CH_2CH_2-$ o un grupo -CH=CH- que está unido a un átomo de carbono en el Anillo de Fenilo **A** que está en *orto* respecto a R_1. De ese modo, Y, junto con los dos átomos de carbono a los que Y está unido y los átomos de carbono intermedios, forman un anillo que está fusionado al Anillo de Fenilo **A**.

R_3-R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

n y m son independientemente 0, 1 o 2.

En la Fórmula Estructural (I), preferiblemente, R_2 es un grupo alquilo inferior C1-C6, fenilo, bencilo o benzoílo; y R_3 es -H o un grupo alquilo C1-C6 (más preferiblemente grupo alquilo C1-C3).

En otra realización, el compuesto de la presente invención está representado mediante la Fórmula Estructural (VI):



(VI).

Las variables en la Fórmula Estructural (VI) se definen más abajo.

Ar es un grupo aromático sustituido o no sustituido. Preferiblemente, Ar es un grupo aromático no sustituido, monosustituido o disustituido.

W es un grupo conector alquileno sustituido o no sustituido o un grupo conector heteroalquileno sustituido o no sustituido de dos a diez átomos de longitud, preferiblemente de dos a siete átomos de longitud.

El Anillo de Fenilo **A** está sustituido opcionalmente con hasta cuatro sustituyentes además de R_1.

R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ o $-(CH)=C(Y)-(CH_2)_mCOOR_3$. Preferiblemente R_1 está en *meta* o *para* respecto W y está representado mediante la Fórmula Estructural (II), más preferiblemente mediante la Fórmula Estructural (III) e incluso más preferiblemente mediante la Fórmula Estructural (IV). La Fórmulas Estructurales (II)-(V) se han mostrado antes.

R_2 es -H, un grupo alifático, un grupo alifático sustituido, un grupo arilo, un grupo arilo sustituido, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ o $-C(S)NR_5R_6$.

Y es -O-, $-CH_2-$, $-CH_2CH_2-$ o -CH=CH- y está unido a un átomo de carbono en el Anillo de Fenilo **A** que está en *orto* respecto R_1.

R_3-R_6 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo arilo o un grupo arilo sustituido.

n y m son independientemente 0, 1 o 2.

En la Fórmula Estructural (VI), preferiblemente, R_2 es un grupo alquilo inferior C1-C6, fenilo, bencilo o benzoílo; y R_3 es -H o un grupo alquilo inferior C1-C3.

Otra realización de la presente invención es un método para modular un receptor activado por proliferadores de peroxisomas (PPAR). El método comprende

la etapa de poner en contacto el receptor con al menos uno de los compuestos de la presente invención.

Otra realización de la presente invención es un método para modular un receptor activado por proliferadores de peroxisomas gamma en un sujeto que necesite la modulación del receptor activado por proliferadores de peroxisomas gamma, esto es, tratando una enfermedad mediada por PPAR-gamma en un sujeto. El método comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto de la presente invención.

Otra realización de la presente invención es un método para disminuir la glucosa en sangre en un sujeto que necesite semejante tratamiento. El método comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto de la presente invención.

Otra realización de la presente invención es un método para tratar a un sujeto con hiperglicemia, dislipidemia, diabetes de Tipo II, diabetes de Tipo I, hipertrigliceridemia, síndrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesteremia, hipertensión, obesidad, anorexia-bulimia, síndrome del ovario poliquístico, anorexia nerviosa, enfermedades cardiovasculares u otras enfermedades en las que la resistencia a la insulina es un componente. El método comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto de la presente invención.

Otra realización de la presente invención es un método para tratar a un sujeto con diabetes sacarina. El método comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto de la presente invención.

Otra realización de la presente invención es un método para tratar a un sujeto de una enfermedad cardiovascular. El método comprende la etapa de

administrar al sujeto una cantidad eficaz de un compuesto de la presente invención.

Otra realización de la presente invención es un método para tratar a un sujeto de Síndrome X. El método comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto de la presente invención.

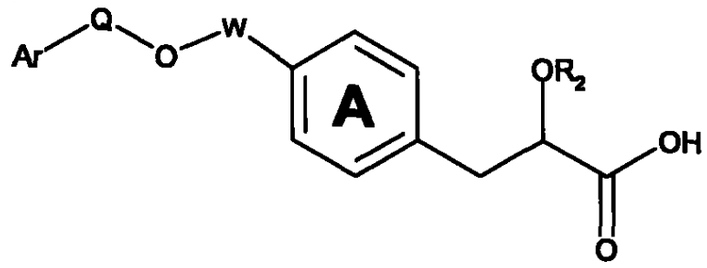
Otra realización de la presente invención es un compuesto de la presente invención para el uso en terapia. La terapia puede ser, por ejemplo, para tratar la diabetes de Tipo II, las enfermedades cardiovasculares, el Síndrome X o una alteración modulada por un receptor activado por proliferadores de peroxisomas.

Otra realización de la presente invención es el uso de un compuesto de la presente invención para la fabricación de un medicamento para el tratamiento de la hiperglicemia, la dislipidemia, la diabetes de Tipo II, la diabetes de Tipo I, hipertrigliceridemia, el síndrome X, la resistencia a la insulina, la insuficiencia cardíaca, la dislipidemia diabética, la hiperlipidemia, la hipercolesteremia, la hipertensión, la obesidad, la anorexia, la bulimia, el síndrome del ovario poliquístico, la anorexia nerviosa, las enfermedades cardiovasculares u otras enfermedades en las que la resistencia a la insulina es un componente u otras alteraciones moduladas por un receptor activado por proliferadores de peroxisomas.

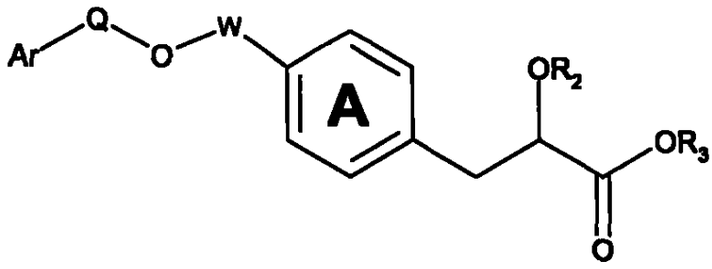
Otra realización más de la presente invención es una composición farmacéutica que comprende un portador farmacéuticamente aceptable y al menos un compuesto de la presente invención.

Otra realización más de la presente invención es un método para preparar un compuesto representado mediante la Fórmula Estructural (VII) a partir de un compuesto de partida representado mediante la Fórmula Estructural

(VIII):



(VII)



(VIII).

El método comprende la etapa de hidrolizar el grupo éster en el compuesto de partida. El Anillo de Fenilo **A**, Ar, Q, W, R_2 y R_3 se describen como para las Fórmulas Estructurales (I) o (VI). Q en las Fórmulas Estructurales (VII) y (VIII) es preferiblemente un enlace covalente.

Otra realización más de la presente invención es uno de los compuestos novedosos descritos aquí, donde el compuesto es marcado radiactivamente, esto es, comprende un isótopo radiactivo (v.g., H^3 o C^{14}) en un sitio específico del compuesto a un nivel significativamente más alto que la abundancia natural del isótopo. "Significativamente más alto que la abundancia natural" significa que la cantidad de isótopo más alta que la abundancia natural puede ser evaluada mediante medios adecuados (v.g., recuento de centelleo). El ácido (S)-3-{4-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico radiomarcado, preferiblemente tritiado, es un ejemplo de compuesto de la invención radiomarcado. Los compuestos radiomarcados, pueden ser utilizados

ventajosamente para evaluar la unión del compuesto de ensayo a PPARγ.

Otra realización más de la presente invención es un método para determinar si un compuesto interacciona o no interacciona directamente (v.g., se une) con PPARγ. El método comprende la etapa de unir específicamente un compuesto marcado radiactivamente descrito aquí al dominio de unión al ligando de un receptor PPARγ. El receptor es combinado después con un compuesto de ensayo y se evalúa la cantidad de unión específica de compuesto marcado radiactivamente. Cualquier descenso de la unión del compuesto radiomarcado indica que el compuesto de ensayo interacciona directamente con el receptor activado por proliferadores de peroxisomas.

Los compuestos de la presente invención y las sales, solvatos e hidratos, estereoisómeros farmacéuticamente aceptables de los mismos disminuyen uno o más de los siguientes en mamíferos: glucosa, insulina, triglicéridos, ácidos grasos y/o colesterol. Por consiguiente se cree que son eficaces para tratar la hiperglicemia, la dislipidemia, la diabetes de Tipo II, la diabetes de Tipo I, hipertrigliceridemia, el síndrome X, la resistencia a la insulina, la insuficiencia cardíaca, la dislipidemia diabética, la hiperlipidemia, la hipercolesteremia, la hipertensión, la obesidad, la anorexia-bulimia, el síndrome del ovario poliquístico, la anorexia nerviosa, las enfermedades cardiovasculares u otras enfermedades en las que la resistencia a la insulina es un componente u otras alteraciones moduladas por un receptor activado por proliferadores de peroxisomas.

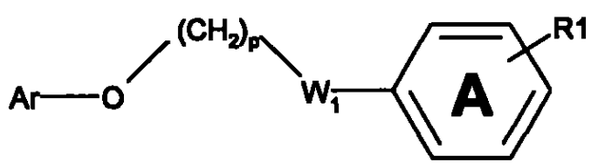
DESCRIPCION DETALLADA DE LA INVENCION

En los Esquemas, Preparaciones y Ejemplos de más abajo, los diferentes símbolos de reactivos y abreviaturas tienen los siguientes significados:

BINAP	2,2'-Bis(difenilfosfino)-1,1'-binaftilo
Boc	t-butoxicarbonilo
CBZ	benciloxicarbonilo
DCM	diclorometano
DEAD	azodicarboxilato de dietilo
DIAD	azodicarboxilato de diisopropilo
DIPEA	diisopropiletilamina
DMAP	4-dimetilaminopiridina
DMF	N,N-dimetilformamida
DMSO	dimetilsulfoxido
eq.	equivalente(s)
EDC	1-(3-dimetilaminopropil)-3-etilcarbodiimida HCl
ESI-MS	espectroscopía de masas por electropulverización de iones
Et	etilo
EtOAc	acetato de etilo
FMOC	carbamato de 9-flurorenilmeti
HATU	hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio
HOAT:	1-hidroxi-7-azabenzotriazol
HOBT	hidrato de 1-hidroxibenzotriazol
HPLC	cromatografía de líquidos de alta resolución
HRMS	espectro de masas de alta resolución
LRMS	espectro de masas de baja resolución
Me	metilo
Ms	metanosulfonilo
$Pd_2(dba)_3$	tris(dibencilidenacetona) dipaladio(0)
Ph	fenilo

Phe	fenilalanina
Pr	propilo
t.a.	temperatura ambiente
TBAF	fluoruro de tetrabutilamonio
TBS	t-butildimetilsililo
TFA	ácido trifluoroacético
TEA	trietilamina
THF	tetrahidrofurano
Tic	ácido 1,2,3,4-tetrahidroiso-quinolino-3-carboxílico
TLC	cromatografía en capa fina

En una realización preferida, el compuesto de la presente invención está representado mediante la Fórmula Estructural (IX):



(IX).

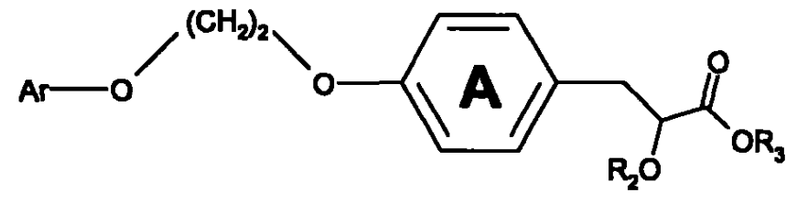
Ar, el Anillo de Fenilo **A** y R_1 en la Fórmula Estructural (IX) se definen como en las Fórmulas Estructurales (I) o (VI). R_1 está preferiblemente en *para* respecto a W_1 y está representado mediante la Fórmula Estructural (II), más preferiblemente las Fórmulas Estructurales (III) o (IV) e incluso más preferiblemente, la Fórmula Estructural (V).

p es un entero de uno a nueve, preferiblemente de uno a cuatro.

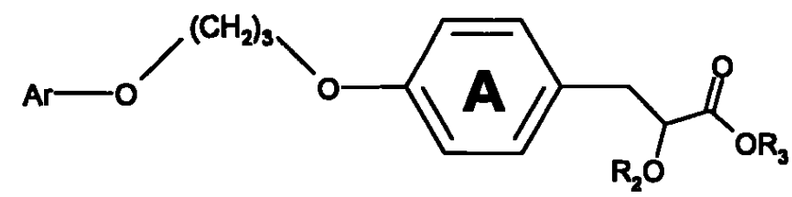
W_1 es $-O-$, $-C(O)-$, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, $-C(=NOH)-$ o $-CH(NR_7R_8)-$.

R_7 y R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

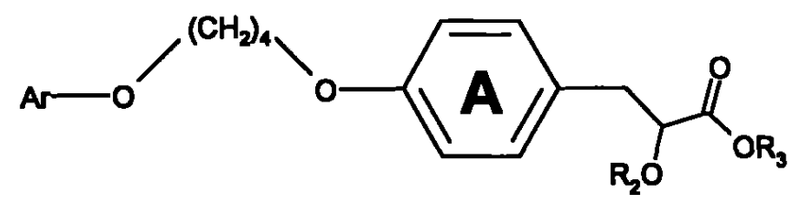
En una realización más preferida, el compuesto de la presente invención está representado mediante una fórmula estructural seleccionada entre las Fórmulas Estructurales (X)-(XVIII):



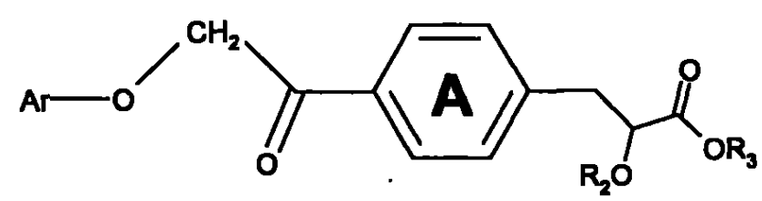
(X)



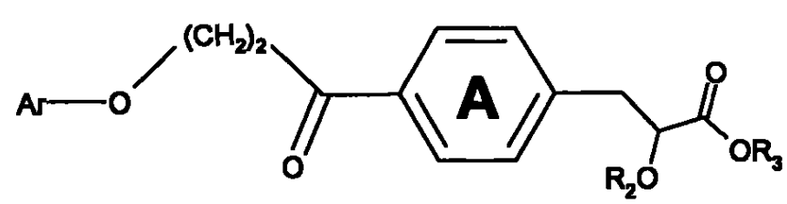
(XI)



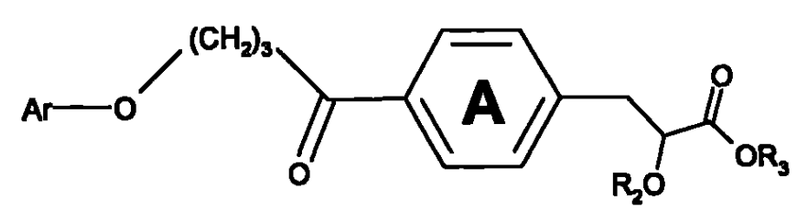
(XII)



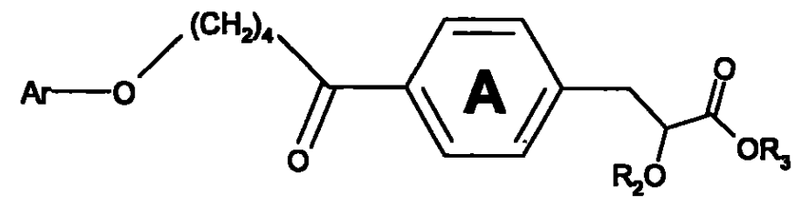
(XIII)



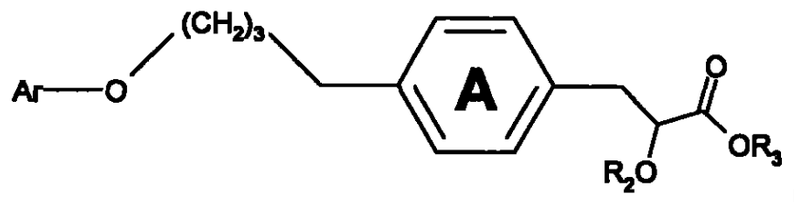
(XIV)



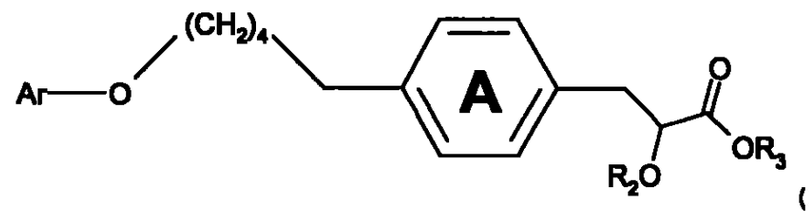
(XV)



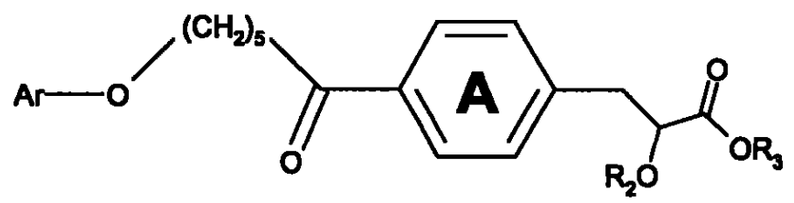
(XVI)



(XVII)



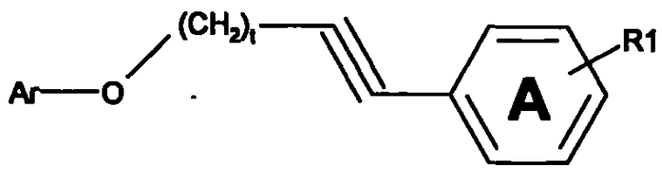
(XVIII)



(XIX).

Ar, Anillo de Fenilo **A**, R_2 y R_3 en las Fórmulas Estructurales (X)-(XIX) se describen como para la Fórmula Estructural (IX). Preferiblemente, R_2 y R_3 se describen como para la Fórmula Estructural (II). Más preferiblemente, $-CH_2CH(OR_2)COOR_3$ en las Fórmulas Estructurales (X)-(XIX) está representado mediante las Fórmulas Estructurales (III) o (IV) en incluso más preferiblemente mediante la Fórmula Estructural (V).

En otra realización preferida, el compuesto de la presente invención está representado mediante la Fórmula Estructural (XX):

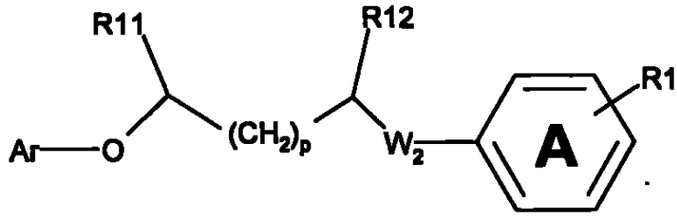


(XX).

Ar y Anillo de Fenilo **A** en la Fórmula Estructural (XX) se describen como para las Fórmulas Estructurales (I) o (VI) y t es un entero de 1 a aproximadamente 5.

En una realización más preferida, R_1 en la Fórmula estructural (XX) está en *para* respecto al carbono unido al grupo alquino y está representado mediante la Fórmula Estructural (II), más preferiblemente mediante las Fórmulas Estructurales (III) o (IV) en incluso más preferiblemente mediante la Fórmula Estructural (V). Preferiblemente, t es 1, 2 o 3.

En otra realización preferida, el compuesto de la presente invención está representado mediante la Fórmula Estructural (XXI):



(XXI).

Ar y Anillo de Fenilo **A** en la Fórmula Estructural (XXI) se describen como para las Fórmulas Estructurales (I) o (VI).

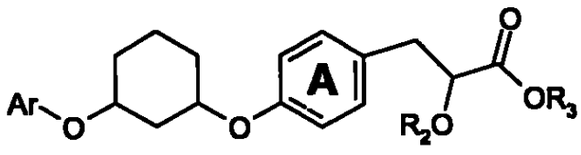
p es cero, uno o dos.

W_2 es -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- o $-CH(NR_7R_8)-$. W_2 es preferiblemente -O-.

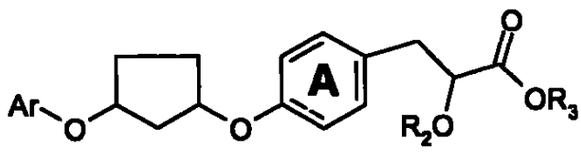
R_7 y R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

R_{11} y R_{12} son independientemente un grupo alquilo C1-C6 (preferiblemente grupo alquilo C1-C3), o, tomados juntos son un grupo etileno, propileno o butileno sustituido o no sustituido.

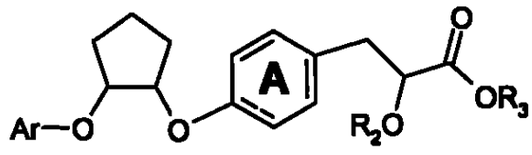
En una realización más preferida, el compuesto de la presente invención está representado mediante una fórmula estructural seleccionada entre las Fórmulas Estructurales (XXII) - (XXVI):



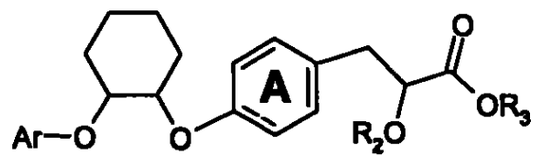
(XXII)



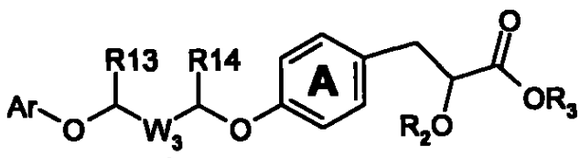
(XXIII)



(XXIV)



(XXV)

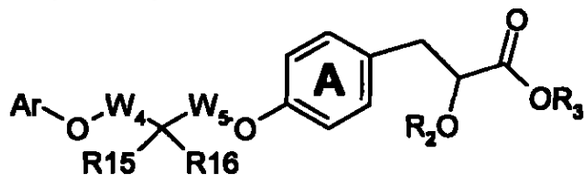


(XXVI).

Ar y el Anillo de Fenilo **A** en las Fórmulas Estructurales (XXII) - (XXVI) se describen como para la Fórmula Estructural (XXI) y R_2 y R_3 en las Fórmulas Estructurales (XXII) - (XXVI) se describen como en la Fórmula Estructural (II). En la Fórmula Estructural (XXVI), W_3 es un enlace covalente, metileno o etileno y R_{13} y R_{14} son metilo, etilo o propilo y son iguales o

diferentes, preferiblemente iguales. Preferiblemente, $-CH_2CH(OR_2)COOR_3$ en las Fórmulas Estructurales (XXII)-(XXVI) está representado mediante las Fórmulas Estructurales (III) o (IV), más preferiblemente mediante la Fórmula Estructural (V).

En otra realización preferida, el compuesto de la presente invención está representado mediante la Fórmula Estructural (XXVII):



(XXVII).

Ar, el Anillo de Fenilo **A**, R_2 y R_3 en las Fórmulas Estructurales (XXVII) se describen como para las Fórmulas Estructurales (I) o (VI); W_4 y W_5 son independientemente metileno o etileno; y R_{15} es -H y R_{16} es un grupo alquilo C1-C6 (preferiblemente metilo, etilo o propilo), o R_{15} y R_{16}, tomados juntos, son =O o $=CH_2$. Preferiblemente, $-CH_2CH(OR_2)COOR_3$ en la Fórmula Estructural (XXVII) está representado mediante las Fórmulas Estructurales (III) o (IV), más preferiblemente mediante la Fórmula Estructural (V).

Un "grupo alifático" es no aromático, consta únicamente de carbono e hidrógeno y puede contener opcionalmente una o más unidades de insaturación, v.g., enlaces dobles y/o triples. Un grupo alifático puede ser de cadena lineal, ramificado o cíclico. Cuando es de cadena lineal o ramificado, un grupo alifático típicamente contiene entre aproximadamente 1 y aproximadamente 10 átomos de carbono, más típicamente entre aproximadamente 1 y aproximadamente 6 átomos de carbono. Cuando es cíclico, un grupo alifático típicamente contiene entre aproximadamente 3 y aproximadamente 10 átomos de carbono, más típicamente

entre aproximadamente 3 y aproximadamente 7 átomos de carbono. Los grupos alifáticos son preferiblemente grupos alquilo C1-C10 de cadena lineal o ramificada (esto es, grupos alifáticos completamente saturados), más preferiblemente grupos alquilo C1-C6 de cadena lineal o ramificada. Entre los ejemplos se incluyen metilo, etilo, *n*-propilo, *iso*-propilo, *n*-butilo, *sec*-butilo y *t*-butilo.

Un "grupo haloalifático" es un grupo alifático, como se ha definido antes, sustituido con uno o más átomos de halógeno.

Un "grupo haloalquilo" es un grupo alquilo (esto es, un grupo alifático saturado), como se ha definido antes, sustituido con uno o más átomos de halógeno. Entre los ejemplos se incluyen $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$ y similares.

Un "grupo aralquilo" es un grupo alquilo sustituido con un grupo aromático, preferiblemente un grupo fenilo. Un grupo aralquilo preferido es un grupo bencilo. Los grupos aromáticos adecuados se describen más abajo y los grupos alquilo adecuados se han descrito antes. Los sustituyentes adecuados para un grupo aralquilo se describen más abajo.

Un "grupo aralquenilo" es un grupo alquenilo sustituido con un grupo aromático. Un "grupo alquenilo" es un grupo alifático con uno o más enlaces dobles carbono- carbono. Los grupos aromáticos adecuados se describen más abajo. Los grupos alifáticos adecuados se han definido antes. Los sustituyentes adecuados para un grupo aralquenilo se describen más abajo.

Un "grupo alilo" tiene la fórmula "$-CH_2CH=CH_2$. Los sustituyentes adecuados para un grupo alilo se describen más abajo.

Un "grupo alquileno" es un grupo polimetileno, esto es, $-(CH_2)_n-$, donde n es un entero positivo. Preferiblemente, n es un entero de aproximadamente 2 a

aproximadamente 10, más preferiblemente de aproximadamente 2 a aproximadamente 7. Un "grupo alquileno sustituido" es un grupo alquileno en el que uno o más átomos de hidrógeno metilénicos se reemplazan por un sustituyente. Los sustituyentes adecuados se describen más abajo.

Un "arileno" es un grupo aromático en el que al menos dos átomos de carbono están unidos a radicales diferentes de hidrógeno. Los grupos arileno adecuados son aquellos correspondientes a los grupos aromáticos descritos aquí.

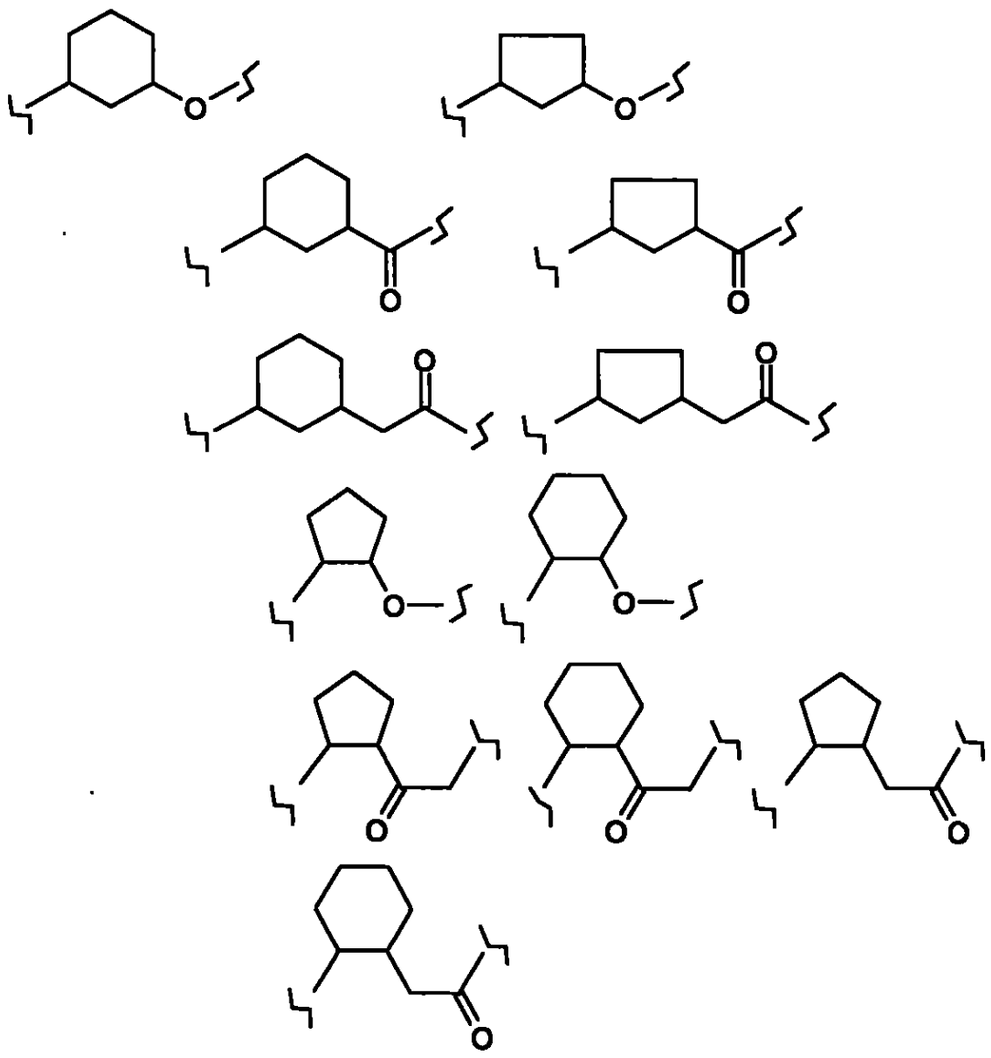
Un "grupo sulfonamida" está representado por $-S(O)_2NH_2$. Un "grupo sulfonamida sustituido" está representado por $-S(O)_2N(R)_2$, donde cada R es independientemente -H, alquilo C1-C6, haloalquilo C1-C6 o arilalquilo C0-C4 y al menos un R no es -H.

Un "grupo acilsulfonamida" está representado por $-S(O)_2NH-C(O)-R$ donde R es -H o un grupo alquilo C1-C6 o un grupo haloalquilo C1-C6. Un "grupo acilsulfonamida sustituido" está representado por $-S(O)_2NR'-C(O)R$, donde R es -H o un grupo alquilo C1-C6 o grupo haloalquilo C1-C6 y R' es alquilo C1-C6, haloalquilo C1-C6 o arilalquilo C0-C4.

El término "grupo heteroalquileno" hace referencia a un grupo alquileno en el que uno o más grupos metileno han sido reemplazados por un grupo funcional, v.g., $-(CH_2)_p-Z-(CH_2)_q-$ donde p es un entero positivo y q es cero o un entero positivo tal que p + q es menor que 10 y Z es un grupo funcional. Entre los ejemplos de los grupos funcionales adecuados se incluyen -CH=CH-, -C≡C-, -O-, -CO-, $-NR_8-$, $-NR_8CO-$, $-C(=NOH)-$, $-S(O)_k-$ y $-CH(NR_7R_8)-$ donde cada R_7 y cada R_8 es independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido; y k es 0, 1 o 2. Preferiblemente, un grupo heteroalquileno tiene entre

aproximadamente 2 y 10 átomos de longitud. Con el propósito de determinar la longitud de un grupo heteroalquileno, en esta solicitud se considera que un grupo funcional tiene un átomo. De este modo, por ejemplo, $-(CH_2)_3-CO-NH-(CH_2)_2-$ tiene seis átomos de longitud (cinco carbonos metilénicos y un grupo funcional); y $-(CH_2)_3-C(=NOH)-(CH_2)_2-$ tiene también seis átomos de longitud (cinco carbonos metilénicos y un carbono de oxima). Entre los ejemplos de los grupos heteroalquileno preferidos se incluyen $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-(CH_2)_4-O-$, $-CH_2-C\equiv CH-$, $-(CH_2)_2-C\equiv CH-$, $-(CH_2)_3-C\equiv CH-$, $-(CH_2)_4-C\equiv CH-$, $-(CH_2)_5-C\equiv CH-$, $-(CH_2)CO-$, $-(CH_2)_2CO-$, $-(CH_2)_3CO-$, $-(CH_2)_4CO-$, $-(CH_2)_2-C(=NOH)-$, $-(CH_2)_3-C(=NOH)-$, $-(CH_2)_4-C(=NOH)-$, $-(CH_2)_2-NR_8-$, $-(CH_2)_3-NR_8-$, $-(CH_2)_4-NR_8-$, $-(CH_2)_2-NR_8CO-$, $-(CH_2)_3-NR_8CO-$, $-(CH_2)_4-NR_8CO-$, $-(CH_2)_2-OCH_2-$, $-(CH_2)_3-OCH_2-$, $-(CH_2)_4-OCH_2-$, $-(CH_2)_2-NR_8CH_2-$, $-(CH_2)_3-NR_8CH_2-$, $-(CH_2)_4-NR_8CH_2-$, $-(CH_2)_2CH(NR_7R_8)-$, $-(CH_2)_3CH(NR_7R_8)-$ y $-(CH_2)_4-CH(NR_7R_8)-$.

Un "grupo heteroalquileno sustituido" es un grupo heteroalquileno en el que uno o más átomos de hidrógeno metilénicos se reemplazan por un sustituyente. Entre los sustituyentes preferidos se incluyen =O, $=CH_2$, alquilo C1-C6 y alquileno C2-C4. Cuando un grupo heteroalquileno está sustituido con un grupo alquileno C2-C4, el grupo alquileno C2-C4 junto con los átomos de carbono del grupo heteroalquileno al que están unidos los dos extremos grupo alquileno C2-C4 y cualquier átomo de carbono intermedio forma un anillo de cicloalquilo. La Fórmula Estructural (XX) proporciona un ejemplo de un grupo heteroalquileno sustituido con un grupo alquileno C2-C4, que está representado por R_{11} y R_{12} tomados juntos. Específicamente, R_{11} y R_{12}, tomados junto con $-CH-(CH_2)_pCH-$ pueden formar un anillo de cicloalquilo. Otros ejemplos de grupos heteroalquileno sustituidos con alquileno se muestran en la siguiente fórmulas estructurales:



Otros sustituyentes adecuados para un grupo heteroalquileno se describen más abajo.

Un "anillo heterocíclico no aromático" (o también referido como un "anillo heterocíclico") es un anillo monocíclico, bicíclico, o tricíclico no aromático de 3 a 14 átomos anulares que está saturado o parcialmente saturado conteniendo carbono y de uno a cuatro heteroátomos seleccionados entre N, O o S. El término "anillo heterocíclico no aromático" incluye los anillos

heterocíclicos que contienen nitrógeno, que contienen de uno a tres átomos de nitrógeno y opcionalmente contiene adicionalmente un heteroátomo diferente seleccionado entre O o S. Entre los ejemplos se incluyen morfolinilo, tiomorfolinilo, pirrolidinilo, piperazinilo, piperidinilo, azetidinilo, azacicloheptilo, o N-fenilpiperazinilo. En el término "anillo heterocíclico no aromático" también se incluyen los anillos heterocíclicos no aromáticos fusionados a un grupo aromático, v.g., 1,3-benzodioxol, 4-cromanona, y ftalimida. Un "anillo heterocíclico no aromáticos" puede estar sustituido opcionalmente con un número designado de sustituyentes, como se describe más abajo.

Un "grupo aromático" (también referido como un "grupo arilo") según se utiliza aquí incluye los grupos aromáticos carbocíclicos, los grupos aromáticos heterocíclicos (también referidos como "heteroarilo") y los sistemas anulares aromáticos policíclicos fusionados como se ha definido aquí.

Un "grupo aromático carbocíclico" es un grupo anular aromático de 5 a 14 átomos de carbono, y se incluye un grupo aromático carbocíclico fusionado con un grupo cicloalquilo de 5 o 6 miembros tal como indano. Entre los ejemplos de los grupos aromáticos carbocíclicos se incluye, pero no están limitados a, fenilo, 1-naftilo, 2-naftilo, 1-antracenilo, 2-antracenilo, fenantrenilo, fluoreno, 9-fluorenono, indano y similares. El grupo aromático carbocíclico está sustituido opcionalmente con un número designado de sustituyentes, descritos más abajo para los grupos aromáticos.

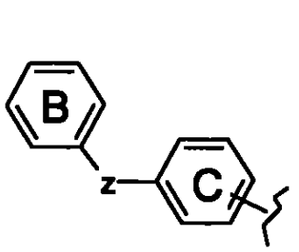
Un "grupo aromático heterocíclico" (o "heteroarilo") es un anillo aromático monocíclico, bicíclico o tricíclico de 5- a 14 átomos de carbono anulares y de uno a cuatro heteroátomos seleccionados entre O, N, o S. Entre los ejemplos de heteroarilo se incluyen, pero no

están limitados a N-imidazolilo, 2-imidazol, 2-tienilo, 3-tienilo, 2-furanilo, 3-furanilo, 2-piridilo, 3-piridilo, 4-piridilo, 2-pirimidilo, 4-pirimidilo, 2-piranilo, 3-piranilo, 4-pirazolilo, 5-pirazolilo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo, 2-oxazoilo, 4-oxazoilo, 5-oxazoilo, 2-imidazolilo, isoxazoilo, pirrolilo, pirazinilo, y purinilo y similares. El aromático heterocíclico (o heteroarilo) como se ha definido antes puede estar sustituido opcionalmente con un número designado de sustituyentes, como se describe más abajo para los grupos aromáticos.

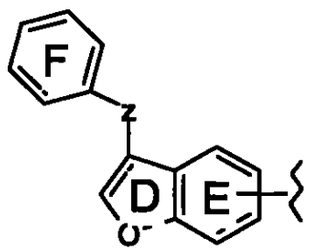
Un sistema anular "aromático policíclico fusionado" es un grupo aromático carbocíclico o heteroarilo fusionado con uno o más anillos heteroarílicos o heterocíclicos no aromáticos. Entre los ejemplos se incluyen 2,3-dihidrobenzofurano, dibenzotiofeno, dibenzofurano, 2-benzotienilo, 3-benzotienilo, 2-benzofuranilo, 3-benzofuranilo, 2-indolilo, 3-indolilo, 2-quinolinilo, 3-quinolinilo, 2-benzotiazolilo, 2-benzoxazolilo, 2-benzimidazolilo, 2-quinolinilo, 3-quinolinilo, 1-isoquinolinilo, 3-quinolinilo, 1-isoindolilo, 3-isoindolilo, benzotriazolilo y similares. Los sistemas anulares policíclicos aromáticos fusionados pueden estar sustituidos opcionalmente con un número designado de sustituyentes, como se describe más abajo para los grupos aromáticos.

"Halo" hace referencia a fluoro, cloro, bromo y yodo.

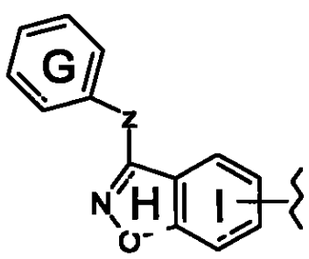
Los ejemplos preferidos de los valores adecuados para Ar en las Fórmulas Estructurales (I), y (VI)-(XXVII) se muestran más abajo:



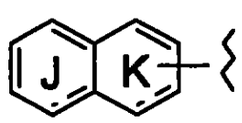
(XXVIII)



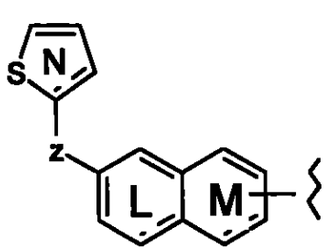
(XXIX)



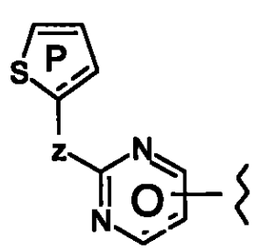
(XXX)



(XXXI)



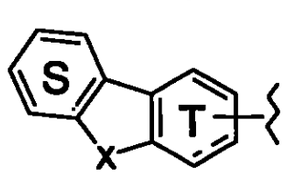
(XXXII)



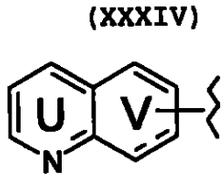
(XXXIII)



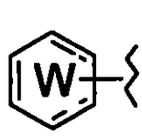
(XXXIV)



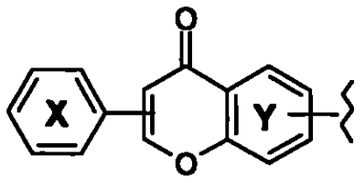
(XXXV)



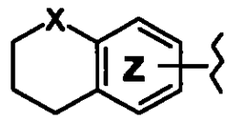
(XXXVI)



(XXXVII)



(XXXVIII)



(XXXIX)

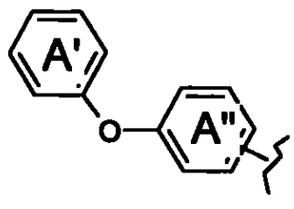
Los anillos **B-Z** están independientemente sustituidos o no sustituidos. Entre otros ejemplos de grupos adecuados para Ar se incluyen benzoilnaftilo, tienilfenilo y naftoilfenilo sustituidos o no sustituidos. Otros ejemplos de valores adecuados para Ar se encuentran en los Ejemplos 1-379. Estos grupos aromáticos, cuando se utilizan como valores para Ar, pueden estar sustituidos o no sustituidos, como se muestra en los Ejemplos 1-379, o, alternativamente, pueden contener uno o más grupos aromáticos sustituyentes diferentes que se describen aquí.

X es -O-, -S-, $-CH_2-$ o -C(O).

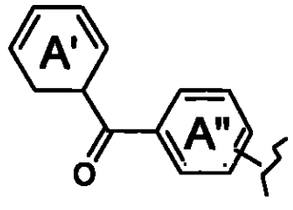
Z es un enlace covalente, -O-, $(-CH_2)_q-$, $-CH(CH_3)(CH_2)_q-$, $-C(CH_3)_2(CH_2)_q-$, $-(CH_2)_qCH(CH_3)-$, $-(CH_2)_qC(CH_3)_2-$, $-O(CH_2)_q-$, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, $-(CH_2)_qNH-$, $-(CH_2)_qCHR_{20}-$, $-CHR_{20}(CH_2)_q-$, $-(CH_2)_qCR_{20}R_{20}-$, $-(CH_2)_qCR_{20}R_{20}-$, $-(CH_2)_qNR_{20}-$, $-NR_{20}(CH_2)_q-$, $-(CH_2)_qC(=NOH)-$, $-C(=NOH)(CH_2)_q-$, $-CH(OH)-(CH_2)_q-$, $-(CH_2)_q-CH(OH)-$, $-CO-(CH_2)_q-$, $-(CH_2)_q-CO-$, $-COO-(CH_2)_q-$, $-OCO-(CH_2)_q-$, $-(CH_2)_q-OCO-$, $-(CH_2)_q-COO-$, $-(CH_2)_qCO-NH-$, $-(CH_2)_qNH-CO-$, $-(CH_2)_qCONR_{20}-$, $-CONR_{20}(CH_2)_q-$, $-(CH_2)_qNR_{20}CO-$ o $-NR_{20}CO(CH_2)_q-$. Z es preferiblemente un enlace covalente, -C(=NOH), -O- o -C(O)- (más preferiblemente -O- o -C(O)-); y q es 0, 1, 2 o 3, preferiblemente 0 o 1.

Cada R_{20} es independientemente un grupo alquilo C1-C5 o un grupo alquilo halogenado C1-C5.

Los grupos de valores especialmente preferidos para Ar en las Fórmulas Estructurales (I) y (VI)-(XXVII) se muestran más abajo:



(XL)



(XLI).

Los anillos de Fenilo **A'** y **A"** están sustituidos o no sustituidos.

Los sustituyentes adecuados para un grupo aromático, incluyendo el grupo aromático representado por Ar (v.g., los Anillos de Fenilo **A'** y **A"** y los Anillos **B-Z**) y el Anillo de Fenilo **A**, un grupo alifático, un grupo alquilo, un grupo alquileno, un grupo heteroalquileno, un grupo heterocíclico no aromático, un grupo aralquilo, un grupo aralquenilo y un grupo alilo son aquellos que no disminuyen significativamente la actividad del compuesto en los Receptores Activados por Proliferadores de Peroxisomas (PPAR), v.g., disminuyen la actividad en más de un factor de cinco (preferiblemente no más de un factor de dos) en comparación con el compuesto correspondiente sin el sustituyente. Entre los ejemplos de los sustituyentes se incluyen halógeno (-Br, -Cl, -I y -F) -R, -OR, -CN, $-NO_2$, $-N(R)_2$, -COR, -COOR, $-CON(R)_2$, $-SO_kR$ (k es 0, 1 o 2) y $-NH-C(=NH)-NH_2$. Entre otros ejemplos se incluyen sulfonamida, acilsulfonamida, -NR-CO-R, $-OS(O)R$, $-OS(O)_2R$, grupos cicloalquilo, grupos heterocíclicos no aromáticos sustituidos ó no sustituidos, $-O(CH_2)_rCOOH$, $-O-O(CH_2)_r-N(R)_2$, $-O(CH_2)_r-$(cicloalquilo), $-O(CH_2)_rOH$, $-O(CH_2)_r-OSi(R)_3$, y $-(CH_2)_aCH(OR_{30})(CH_2)_bCOOR_{31}$. Cada R es independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo alifático halogenado, un grupo bencilo, un grupo

bencilo sustituido, un grupo aromático o un grupo aromático sustituido, y preferiblemente -H, un grupo alquilo (v.g., a grupo alquilo C1-C10), un grupo alquilo halogenado (v.g., un grupo alquilo C1-C10 halogenado), un grupo fenilo o un grupo fenilo sustituido; R_{30} es un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado, R_{31} es -H, un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado; r es un entero de 1 a 6; a y b son independientemente 0, 1 o 2. Un grupo aromático, un grupo bencílico, un grupo alifático, un grupo alquilo, un grupo alquileno, un grupo heteroalquileno, un grupo heterocíclico no aromático, un grupo aralquilo y un grupo aralquenilo pueden tener más de un sustituyente. Otros ejemplos de sustituyentes adecuados para un grupo aromático representado por Ar son aquellos encontrados en la posición correspondiente de los compuestos descritos in la Sección de Ejemplificación.

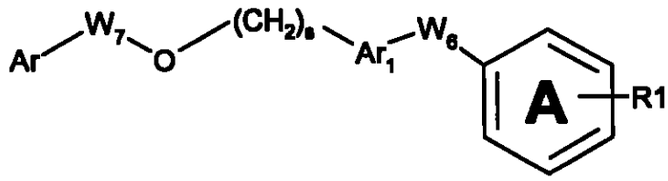
Entre los sustituyentes preferidos para los Anillos **B-Z** se incluyen halógeno, $-R_9$, $-OR_9$, $-COR_9$, $-COOR_9$, -CN, un grupo heterocíclico no aromático, un grupo alílico, $-(CH_2)_aCH(OR_{30})(CH_2)_bCOOR_{31}$ o $-NR_9C(O)R_9$. R_9 es -H, un grupo alquilo (v.g., un grupo alquilo C1-C10), cicloalquilo, un grupo alquilo halogenado (v.g., un grupo alquilo C1-C10 halogenado) o un grupo aromático. R_{30}, R_{31}, a y b se describen como antes; preferiblemente R_{30} es metilo o etilo, R_{31} es $-H_3$ y a y b son uno.

Más preferiblemente, entre los sustituyentes adecuados para los Anillos **B-Z** se incluyen uno o más grupos seleccionados entre halógeno, alquilo C1-C8 de cadena lineal o ramificado, alquilo C1-C8 halogenado de cadena lineal o ramificado (v.g., $-CF_3$), cicloalquilo C3-C8, alcanoílo C1-C8 de cadena lineal o ramificado, alcoxi C1-C8 de cadena lineal o ramificado (v.g., metoxi), -Br, -F, *N*-morfolino, -COOH, -OH, -CN, o alcoxi C1-C8 halogenado de cadena lineal o ramificado (v.g., $-OCF_3$).

Los sustituyentes adecuados para los Anillos de Fenilo **A'** y **A"** se describen como antes para los Anillos **B-Z**.

Entre los sustituyentes preferidos para el Anillo de Fenilo **A** se incluyen halógeno, $-OR_{10}$, $-R_{10}$, un grupo aromático, un grupo aromático sustituido, aralquilo, aralquilo sustituido, aralquenilo, aralquenilo sustituido, alilo y alilo sustituido y R_{10} es -H, un grupo alquilo (v.g., un grupo alquilo C1-C10) o un grupo alquilo halogenado (v.g., un grupo alquilo C1-C10 halogenado). Entre los Ejemplos específicos de los sustituyentes adecuados para el Anillo de Fenilo **A** se incluyen -F, -Cl, $-OCH_3$, $-OCF_3$, $-CH_3$, etilo, *n*-propilo, *iso*-propilo, alilo, 2-feniletenilo, 2-feniletilo, fenilo, -*o*-bifenilo, -*m*-bifenilo, -*p*-bifenilo, $-o-C_6H_4OCH_3$, $-m-C_6H_4OCH_3$, $-p-C_6H_4OCH_3$, $-o-C_6H_4F$, $-m-C_6H_4F$ y $-p-C_6H_4F$.

Otra realización de la presente invención es un compuesto representado mediante la Fórmula Estructural (XLII):



(XLII).

Ar y R_1 en la Fórmula Estructural (XLI) se definen como antes en las Fórmulas Estructurales (I) y (VI); s es 0, 1 o 2; Ar_1 es un grupo arileno sustituido o no sustituido; W_6 es un enlace covalente, $-W_1-$, $-CH_2W_1-$ o $-W_1CH_2-$; W_7 es un enlace covalente o $-CH_2-$ y W_1 se define como antes. Preferiblemente R_1 está representado mediante la Fórmula Estructural (II), s es 0 o 1, Ar_1 es fenileno (sustituido en *orto*, *meta* o *para*), W_7 es un enlace covalente y W_1 es -O-. Más preferiblemente, Ar está representado una cualquiera de las Fórmulas Estructurales (XXVIII)-(XXXIX) y R_1 está representado mediante las

Fórmulas Estructurales (III) o (IV). Incluso más preferiblemente, Ar está representado mediante las Fórmulas Estructurales (XL) o (XLI) y R_1 está representado mediante la Fórmula Estructural (V).

También están incluidos en la presente invención los métodos de tratamiento descrito antes, donde el compuesto representado mediante la Fórmula Estructural (XLI) se administra como agente terapéutico y el uso del compuesto para la fabricación de un medicamento para el tratamiento de las alteraciones mediadas por los PPAR descritas aquí.

Los siguientes son ejemplos específicos de los compuestos de la presente invención:

Acido (2S)-3-{4-[3-(bifenil-4-iloxi)-prop-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 1);

Acido (2S)-3-{4-[3-(4-benzoil-fenoxi)-prop-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 2);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-prop-1-inil]-fenil}-propiónico (Compuesto 3);

Acido (2S)-3-{4-[3-(4-fluoro-fenoxi)-prop-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 4);

Acido (2S)-2-metoxi-3-{4-[3-(3-fenil-benzofuran-6-iloxi)-prop-1-inil]-fenil}-propiónico (Compuesto 5);

Acido (2S)-3-{4-[3-(4-butil-fenoxi)-prop-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 6);

Acido (2S)-2-metoxi-3-(4-{3-[4-(4-trifluorometil-fenoxi)-fenoxi]-prop-1-inil}-fenil)-propiónico (Compuesto 7);

Acido (2S)-2-metoxi-3-{4-[3-(9-oxo-9H-fluoren-2-iloxi)-prop-1-inil]-fenil}-propiónico (Compuesto 8);

Acido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-7-iloxi)-prop-1-inil]-fenil}-propiónico (Compuesto 9);

Acido (2S)-3-(4-{3-[4-(2-fluoro-benzoil)-fenoxi]-prop-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 10);

Acido (2S)-2-metoxi-3-{4-[3-(3-fenilamino-fenoxi)-prop-1-inil]-fenil}-propiónico (Compuesto 11);

Acido (2S)-3-(4-{3-[4-(4-fluoro-benzoil)-fenoxi]-prop-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 12);

Acido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-6-iloxi)-prop-1-inil]-fenil}-propiónico (Compuesto 13);

Acido (2S)-3-(4-{3-[3-(4-fluoro-fenil)-benzofuran-6-iloxi]-prop-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 14);

Acido (2S)-2-metoxi-3-(4-{3-[4-(1-metil-1-fenil-etil)-fenoxi]-prop-1-inil}-fenil)-propiónico (Compuesto 15);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenilacetil-fenoxi)-prop-1-inil]-fenil}-propiónico (Compuesto 16);

Acido (2S)-3-{4-[3-(4-bencil-fenoxi)-prop-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 17);

Acido (2S)-3-[4-(3-{4-[(2-fluoro-fenil)-hidroxiimino-metil]-fenoxi}-prop-1-inil)-fenil]-2-metoxi-propiónico (Compuesto 18);

Acido (2S)-3-(4-{3-[4-(hidroxiimino-fenil-metil)-fenoxi]-prop-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 19);

Acido (2S)-3-[4-(3-{4-[(4-fluoro-fenil)-hidroxiimino-metil]-fenoxi}-prop-1-inil)-fenil]-2-metoxi-propiónico (Compuesto 20);

Acido (2S)-3-{4-[5-(bifenil-4-iloxi)-pent-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 21);

Acido (2S)-2-metoxi-3-{4-[5-(4-fenoxi-fenoxi)-pent-1-inil]-fenil}-propiónico (Compuesto 22);

Acido (2S)-3-{4-[5-(4-benzoil-fenoxi)-pent-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 23);

Acido (2S)-3-{4-[5-(4-bencil-fenoxi)-pent-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 24);

Acido (2S)-3-(4-{5-[4-(4-fluoro-benzoil)-fenoxi]-pent-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 25);

Acido (2S)-2-metoxi-3-(4-{5-[4-(4-trifluorometil-fenoxi)-fenoxi]-pent-1-inil}-fenil)-propiónico (Compuesto 26);

Acido (2S)-2-metoxi-3-{4-[5-(4-oxo-2-fenil-4H-cromen-7-iloxi)-pent-1-inil]-fenil}-propiónico (Compuesto 27);

Acido (2S)-2-metoxi-3-{4-[5-(4-oxo-2-fenil-4H-cromen-6-iloxi)-pent-1-inil]-fenil}-propiónico (Compuesto 28);

Acido (2S)-2-metoxi-3-(4-{5-[4-(1-metil-1-fenil-etil)-fenoxi]-pent-1-inil}-fenil)-propiónico (Compuesto 29);

Acido (2S)-2-metoxi-3-{4-[5-(9-oxo-9H-fluoren-2-iloxi)-pent-1-inil]-fenil}-propiónico (Compuesto 30);

Acido (2S)-2-metoxi-3-{4-[5-(3-fenilamino-fenoxi)-pent-1-inil]-fenil}-propiónico (Compuesto 31);

Acido (2S)-3-(4-{5-[4-(2-fluoro-benzoil)-fenoxi]-pent-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 32);

Acido (2S)-2-metoxi-3-{4-[5-(3-fenil-benzofuran-6-iloxi)-pent-1-inil]-fenil}-propiónico (Compuesto 33);

Acido (2S)-3-(4-{5-[3-(4-fluoro-fenil)-benzofuran-6-iloxi]-pent-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 34);

Acido (2S)-2-metoxi-3-(4-[5-(4-fenilacetil-fenoxi)-pent-1-inil]-fenil)-propiónico (Compuesto 35);

Acido (2S)-3-{4-[5-(4-butil-fenoxi)-pent-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 36);

Acido (2S)-3-[4-(5-{4-[(2-fluoro-fenil)-hidroxiimino-metil]-fenoxi}-pent-1-inil)-fenil]-2-metoxi-propiónico (Compuesto 37);

Acido (2S)-3-[4-(5-{4-[(4-fluoro-fenil)-hidroxiimino-metil]-fenoxi}-pent-1-inil)-fenil]-2-metoxi-propiónico (Compuesto 38);

Acido (2S)-3-(4-{5-[4-(hidroxiimino-fenil-metil)-fenoxi]-pent-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 39);

Acido (2S)-3-{4-[4-(bifenil-4-iloxi)-but-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 40);

Acido (2S)-2-metoxi-3-{4-[4-(4-fenoxi-fenoxi)-but-1-inil]-fenil}-propiónico (Compuesto 41);

Acido (2S)-3-{4-[4-(4-benzoil-fenoxi)-but-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 42);

Acido (2S)-3-(4-{4-[4-(hidroxiimino-fenil-metil)-fenoxi]-but-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 43);

Acido (2S)-3-(4-{4-[4-(4-fluoro-benzoil)-fenoxi]-but-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 44);

Acido (2S)-3-(4-{4-[3-(4-fluoro-fenil)-benzofuran-6-iloxi]-but-1-inil}-fenil)-2-metoxi-propiónico (Compuesto 45);

Acido (2S)-2-metoxi-3-(4-{4-[4-(4-trifluorometil-fenoxi)-fenoxi]-but-1-inil}-fenil)-propiónico (Compuesto 46);

Acido (2S)-2-metoxi-3-{4-[4-(4-oxo-2-fenil-4H-cromen-7-iloxi)-but-1-inil]-fenil}-propiónico (Compuesto 47);

Acido (2S)-2-metoxi-3-{4-[4-(4-oxo-2-fenil-4H-cromen-6-iloxi)-but-1-inil]-fenil}-propiónico (Compuesto 48);

Acido (2S)-2-metoxi-3-{4-[6-(4-fenoxi-fenoxi)-hex-1-inil]-fenil}-propiónico (Compuesto 49);

Acido (2S)-3-{4-[6-(4-benzoil-fenoxi)-hex-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 50);

Acido (2S)-3-{4-[6-(bifenil-4-iloxi)-hex-1-inil]-fenil}-2-metoxi-propiónico (Compuesto 51);

Acido (2S)-3-{4-[5-(bifenil-4-iloxi)-pentanoil]-fenil}-2-metoxi-propiónico (Compuesto 52);

Acido (2S)-3-{4-[5-(4-benzoil-fenoxi)-pentanoil]-fenil}-2-metoxi-propiónico (Compuesto 53);

Acido (2S)-2-metoxi-3-{4-[5-(4-fenoxi-fenoxi)-pentanoil]-fenil}-propiónico (Compuesto 54);

Acido 3-{4-[4-(4-benzoil-fenoxi)-butiril]-fenil}-2-metoxi-propiónico (Compuesto 55);

Acido (2S)-2-metoxi-3-{4-[4-(4-fenoxi-fenoxi)-butiril]-fenil}-propiónico (Compuesto 56);

Acido (2S)-3-[4-(bifenil-4-iloxi)-butiril-fenil]-2-metoxi-propiónico (Compuesto 57);

Acido (2S)-3-{4-[6-(bifenil-4-iloxi)-hexanoil]-fenil}-2-metoxi-propiónico (Compuesto 58);

Acido (2S)-2-metoxi-3-{4-[6-(4-fenoxi-fenoxi)-hexanoil]-fenil}-propiónico (Compuesto 59);

Acido (2S)-3-{4-[6-(4-benzoil-fenoxi)-hexanoil]-fenil}-2-metoxi-propiónico (Compuesto 60);

Acido (2S)-3-{4-[5-(bifenil-4-iloxi)-1-hidroxiimino-pentil]-fenil}-2-metoxi-propiónico (Compuesto 61);

Acido (2*S*, 1'*R**, 2'*S**)-3-(4-{2'-[4-(4-fluoro-benzoil)-fenoxi]-ciclopentiloxi}-fenil)-2-metoxi-propiónico (Compuesto 62);

Acido (2S)-(1'R,3'R)-2-metoxi-3-{4-[1',3'-dimetil-3-(4-fenoxi-fenoxi)-propoxil]-fenil}-propiónico (Compuesto 63);

Acido (2S)-(1'*R*,3'*R*)-3-{4-[3-(4-benzoilfenoxi)-1',3'-dimetilpropoxil]-fenil}2-metoxi-propiónico (Compuesto 64);

Acido (2S)-(1'*S*,3'*S*)-2-metoxi-3-{4-[1',3'-dimetil-3-(4-fenoxi-fenoxi)-propoxil]-fenil}-propiónico (Compuesto 65);

Acido (2S)-(1'*S*,3'*S*)-3-{4-[3-(4-benzoilfenoxi)-1',3'-dimetilpropoxil]-fenil}2-metoxi-propiónico (Compuesto 66);

Acido (2S)-(1'*R*,2'*R*)-2-metoxi-3-{4-[1',2'-dimetil-(4-fenoxi-fenoxi)-etoxil]-fenil}-propiónico (Compuesto 67);

Acido (2S)-(1'*R*,2'*R*)-3-{4-[1-(4-benzoilfenoxi)-1',2'-dimetil-etoxil]-fenil}-2-metoxipropiónico (Compuesto 68);

Acido (2S)-(1'*S*,4'*S*)-2-metoxi-3-{4-[1'-metil-4'-(4-fenoxi-fenoxi)-pentiloxi]-fenil}-propiónico (Compuesto 69);

Acido (2S)-(1'S,4'S)-3-{4-[4-(4-benzoil-fenoxi)-1-metil-pentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 70);

Acido (2S)-(1'*R*,4'*R*)-2-metoxi-3-{4-[1'-metil-4'-(4-fenoxi-fenoxi)-pentiloxi]-fenil}-propiónico (Compuesto 71);

Acido (2S)-(1'*R*,4'*R*)-3-{4-[4-(4-benzoil-fenoxi)-1-metil-pentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 72);

Acido (2S)-(1'*S*,2'*S*)-2-metoxi-3-{4-[1',2'-dimetil-(4-fenoxi-fenoxi)-etoxil]-fenil}-propiónico (Compuesto 73);

Acido (2S)-2-metoxi-{4-[2-metilen-3-(4-fenoxi-fenoxi)-propoxil]-fenil}-propiónico (Compuesto 74);

Acido (2S)-2-metoxi-{4-[2-oxo-3-(4-fenoxi-fenoxi)-propoxil]-fenil}-propiónico (Compuesto 75);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenoxi-fenoximetil)-benciloxi]-fenil}-propiónico (Compuesto 76);

Acido (2S)-2-metoxi-3-{4-[2-(4-fenoxi-fenoximetil)-benciloxi]-fenil}-propiónico (Compuesto 77);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-fenoxi]-fenil}-propiónico (Compuesto 78);

Acido (2S)3-[3'-(3-benzoil-fenoximetil)-bifenil-4-il]-2-metoxi-propiónico (Compuesto 79);

Acido (2S)-3-[4'-(4-benzoil-fenoximetil)-bifenil-4-il]-2-metoxi-propiónico (Compuesto 80);

Acido (2S)-(1'*R**,3'*R**)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 81);

Acido (2S)-(1'*R**,3'*S**)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 82);

Acido (2S)-(1'*R**,3'*R**)-2-metoxi-3-{4-[3'-(4-fenoxi-fenoxi)-1'-ciclopentiloxi]-fenil}-propiónico (Compuesto 83);

Acido (2S)-(1'*R**,3'*R**)-3-{4-[3-(4-benzoil-fenoxi)-ciclopentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 84);

Acido (2S)-(1'R*,3'R*)-2-metoxi-3-{4-[3-(4-fenilacetil-fenoxi)-ciclopentiloxi]-fenil}-propiónico (Compuesto 85);

Acido (2S)-(1'*R*,3'*S*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 86);

Acido (2S)-(1'*S*,3'*R*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 87);

Acido (2S)-(1'*S*,3'*S*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 88);

Acido (2S)-(1'*R*,3'*R*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]-fenil}-2-metoxi-propiónico (Compuesto 89);

Acido (2S)-(1'*R*,3'*S*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]-fenil}-2-metoxi-propiónico (Compuesto 90);

Acido (2S)-(1'*S*,3'*R*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]-fenil}-2-metoxi-propiónico (Compuesto 91);

Acido (2S)-(1'*R*,3'*R*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]-fenil}-2-metoxi-propiónico (Compuesto 92);

Acido (2S)-(1'S,3'*S*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]-fenil}-2-metoxi-propiónico (Compuesto 93);

Acido (2S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 94);

Acido (2S)-3-(4-{3-[4-(4-fluoro-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 95);

Acido (2S)-3-{4-[3-(4-bencil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 96);

Acido (2S)-2-metoxi-3-{4-[3-(3-fenilamino-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 97);

Acido (2S)-3-{4-[3-(4-butil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 98);

Acido (2S)-3-(4-{3-[4-(2-fluoro-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 99);

Acido (2S)-2-metoxi-3-{4-[3-(9-oxo-9H-fluoren-2-iloxi)-propoxi]-fenil}-propiónico (Compuesto 100);

Acido (2S)-2-metoxi-3-{4-[3-(2-metil-benzotiazol-5-iloxi)-propoxi]-fenil}-propiónico (Compuesto 101);

Acido (2S)-2-metoxi-3-{4-[3-(3-morfolin-4-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 102);

Acido (2S)-3-{4-[3-(bifenil-2-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 103);

Acido (2S)-3-{4-[3-(4-ciclopentil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 104);

Acido (2S)-3-{4-[3-(4-ciano-3-fluoro-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 105);

Acido (2S)-3-{4-[3-(2,4-difluoro-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 106);

Acido (2S)-2-metoxi-3-{4-[3-(4-trifluorometil-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 107);

Acido (2S)-2-metoxi-3-{4-[3-(3-trifluorometil-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 108);

Acido (2S)-2-metoxi-3-{4-[3-(5-oxo-5,6,7,8-tetrahidro-naftalen-2-iloxi)-propoxi]-fenil}-propiónico (Compuesto 109);

Acido (2S)-3-{4-[3-(3,5-difluoro-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 110);

Acido (2S)-3-{4-[3-(isoquinolin-5-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 111);

Acido (2S)-2-metoxi-3-{4-[3-(4-trifluorometoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 112);

Acido (2S)-3-{4-[3-(4-fluoro-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 113);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenilacetil-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 114);

Acido (2S)-2-metoxi-3-(4-{3-[4-(1-metil-1-fenil-etil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 115);

Acido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-7-iloxi)-propoxi]-fenil}-propiónico (Compuesto 116);

Ester bencílico de ácido 4-{3-[4-(2-Carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (Compuesto 117);

Acido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-croman-6-iloxi)-propoxi]-fenil}-propiónico (Compuesto 118);

Acido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-croman-6-iloxi)-propoxi]-fenil}-propiónico (Compuesto 119);

Acido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-croman-7-iloxi)-propoxi]-fenil}-propiónico (Compuesto 120);

Acido (2S)-2-metoxi-3-(4-{3-[4-(4-trifluorometil-fenoxi)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 121);

Acido (2S)-3-{4-[2-(4-benzoil-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 122);

Acido (2S)-3-{4-[2-(bifenil-4-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 123);

Acido (2S)-3-{4-[2-(bifenil-4-iloxi)-acetil]-fenil}-2-metoxi-propiónico (Compuesto 124);

Acido (2S)-2-metoxi-3-{4-[2-(4-fenoxi-fenoxi)-acetil]-fenil}-propiónico (Compuesto 125);

Acido (2S)-3-{4-[2-(4-benzoil-fenoxi)-acetil]-fenil}-2-metoxi-propiónico (Compuesto 126);

Acido (2S)-3-{4-[3-(bifenil-4-iloxi)-propil]-fenil}-2-metoxi-propiónico (Compuesto 127);

Acido (2S)-3-{4-[4-(bifenil-4-iloxi)-butil]-fenil}-2-metoxi-propiónico (Compuesto 128);

Acido (2S)-3-{4-[5-(bifenil-4-iloxi)-pentil]-fenil}-2-metoxi-propiónico (Compuesto 129);

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-metoxi-propiónico (Compuesto 130);

Acido 3-(4-{3-[4-(4-fluoro-benzoil)-fenoxi]-propoxi}-3-metoxi-fenil)-2-metoxi-propiónico (Compuesto 131);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-metoxi-fenil}-2-metoxi-propiónico (Compuesto 132);

Acido 2-metoxi-3-{3-metoxi-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 133);

Acido (2S)-3-(4-[3-(bifenil-4-iloxi)-propoxi]-3-cloro-fenil}-2-metoxi-propiónico (Compuesto 134);

Acido 3-{3-Cloro-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 135);

Acido '3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-cloro-fenil}-2-metoxi-propiónico (Compuesto 136);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3,5-dicloro-fenil}-2-metoxi-propiónico (Compuesto 137);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-fluoro-fenil}-2-metoxi-propiónico (Compuesto 138);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-trifluorometil-fenil}-2-metoxi-propiónico (Compuesto 139);

Acido (2S)-3-{6-[3-(bifenil-4-iloxi)-propoxi]-4'-metoxi-bifenil-3-il}-2-metoxi-propiónico (Compuesto 140);

Acido 3-{6-[3-(bifenil-4-iloxi)-propoxi]-4'-fluoro-bifenil-3-il}-2-metoxi-propiónico (Compuesto 141);

Acido 3-{6-[3-(bifenil-4-iloxi)-propoxi]-[1,1';4',1''] terfenil-3-il}-2-metoxi-propiónico (Compuesto 142);

Acido 3-{6-[3-(bifenil-4-iloxi)-propoxi]-2'-metoxi-bifenil-3-il}-2-metoxi-propiónico (Compuesto 143);

Acido 2-metoxi-3-{6-[3-(4-fenoxi-fenoxi)-propoxi]-[1,1';4',1'']terfenil-3-il}-propiónico (Compuesto 144);

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-styril-fenil}-2-metoxi-propiónico (Compuesto 145);

Acido 3-(4-{3-[4-(hidroxi-fenil-metil)-fenoxi]-propoxi}-3-fenetil-fenil)-2-metoxi-propiónico (Compuesto 146);

Acido 3-{4-[3-(4-bencil-fenoxi)-propoxi]-3-fenetil-fenil}-2-metoxi-propiónico (Compuesto 147);

Acido (2S)-3-{3-alil-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 148);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-3-propil-fenil}-propiónico (Compuesto 149);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-metil-fenil}-2-metoxi-acrílico (Compuesto 150);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-metil-fenil}-2-metoxi-propiónico (Compuesto 151);

Acido 3-{3-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 152);

Acido '2-metoxi-3-{3-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 153);

Acido 3-{3-[3-(4-benzoil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 154);

Acido 2-metoxi-3-{3-[5-(4-fenoxi-fenoxi)-pent-1-inil]-fenil}-propiónico (Compuesto 155);

Acido 2-metoxi-3-{3-[5-(4-fenoxi-fenoxi)-pentil]-fenil}-propiónico (Compuesto 156);

Acido 2-metoxi-3-{3-[5-(4-fenoxi-fenoxi)-pentanoil]-fenil}-propiónico (Compuesto 157);

Acido 3-{4-[3-(3-alil-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 158);

Acido (2S)-2-metoxi-3-{4-[3-(3-propil-bifenil-4-iloxi)-propoxi]-fenil}-propiónico (Compuesto 159);

Acido (2S)-3-{4-[3-(2-alil-4-fenoxi-fenoxi)-propoxi]- fenil}-2-metoxi-propiónico (Compuesto 160);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenoxi-2-propil-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 161);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-metil-fenil}-2-metoxi-propiónico (Compuesto 162);

Acido 2-metoxi-3-{3-metil-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 163);

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-metil-fenil}-2-metoxi-propiónico (Compuesto 164);

Acido (2S)-3-{4-[3-(dibenzofuran-2-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 165);

Acido (2S)-3-[4-{3-{4-[(4-fluoro-fenil)-hidroxiimino-metil]-fenoxi}-propoxi)-fenil]-2-metoxi-propiónico (Compuesto 166);

Acido (2S)-3-[4-(3-{4-[(4-fluoro-fenil)-hidroxi-metil]-fenoxi}-propoxi)-fenil]-2-metoxi-propiónico (Compuesto 167);

Acido (2S)-2-metoxi-3-(4-{3-[4-(4-piperidin-1-il-benzoil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 168);

Acido (2S)-2-metoxi-3-(4-{3-[4-(4-morfolin-4-il-benzoil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 169);

Acido (2S)-3-(4-{3-[4-(4-hidroxi-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 170);

Sal de sodio de ácido 2S-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]fenil}propanóico (Compuesto 171);

Acido (2S)-3-[4-(3-{4-[hidroxiimino-(4-hidroxi-fenil)-metil]-fenoxi}-propoxi)-fenil]-2-metoxi-propiónico (Compuesto 172);

Acido (2S)-3-{4-[3-(4-benzoil-3-hidroxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 173);

Acido (2S)-3-(4-{3-[4-(2,4-Dimetoxi-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 174);

Acido 3-{4-[3-(4-bencil-fenoxi)-propoxi]-3-metoxi-fenil}-2-metoxi-propiónico (Compuesto 175);

Acido (*S*)-3-(4-benciloxi-fenil)-2-isopropoxi-propiónico (Compuesto 176);

Sal de sodio de ácido 2S-2-isopropoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]fenil}propanóico (Compuesto 176A);

Acido 2-metoxi-3-{3-metoxi-4-[3-(4-fenilacetil-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 177);

Acido 3-{4-[3-(4-Butoxi-fenoxi)-propoxi]-3-metoxi-fenil}-2-metoxi-propiónico (Compuesto 178);

Acido 2-metoxi-3-{3-metoxi-4-[3-(4-oxo-2-fenil-4H-cromen-6-iloxi)-propoxi]-fenil}-propiónico (Compuesto 179);

Acido 2-metoxi-3-(3-metoxi-4-{3-[4-(4-trifluorometil-fenoxi)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 180);

Acido 3-{4-[3-(4-benciloxi-fenoxi)-propoxi]-3-metoxi-fenil}-2-metoxi-propiónico (Compuesto 181);

Acido 3-{4-[3-(4-dibenzofuran-3-il-fenoxi)-propoxi]-3-metoxi-fenil}-2-metoxi-propiónico (Compuesto 182);

Acido (2S)-3-{4-[4-(bifenil-4-iloxi)-butoxi]-fenil}-2-metoxi-propiónico (Compuesto 183);

Acido (2S)-3-{4-[4-(4-benzoil-fenoxi)-butoxi]-fenil}-2-metoxi-propiónico (Compuesto 184);

Acido (2S)-2-metoxi-3-{4-[4-(4-fenoxi-fenoxi)-butoxi]-fenil}-propiónico (Compuesto 185);

Acido (2S)-2-metoxi-3-{4-[2-(2,3,6-trifluoro-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 186);

Acido (2S)-3-[4-(3-benciloxi-benciloxi)-fenil]-2-metoxi-propiónico (Compuesto 187);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-metoxi-fenil}-2-metoxi-propiónico (Compuesto 188);

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-metoxi-fenil}-2-metoxi-propiónico (Compuesto 189);

Acido 2-metoxi-3-{2-metoxi-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 190);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-cloro-fenil}-2-metoxi-propiónico (Compuesto 191);

Acido 3-{2-cloro-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 192);

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-cloro-fenil}-2-metoxi-propiónico (Compuesto 193);

Acido (2S)-4-{3-[4-(2-Carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (Compuesto 194);

Acido (2S)-3-{4-[3-(4-Dibenzotiofen-4-il-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 195);

Acido (2S)-3-{4-[3-(4'-hidroxi-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 196);

Acido (2S)-4'-{3-[4-(2-Carboxi-2-metoxi-etil)-fenoxi]-propoxi}-bifenil-4-carboxílico (Compuesto 197);

Acido (2S)-3-{4-[2-(4-benzoil-fenoxi)-ciclohexiloxi]-fenil}-2-metoxi-propiónico (Compuesto 198);

Acido (2S)-3-(4-{2-[4-(4-fluoro-benzoil)-fenoxi]-ciclohexiloxi}-fenil)-2-metoxi-propiónico (Compuesto 199);

Acido (2S)-3-(4-{3-[3-(4-fluoro-fenil)-benzofuran-6-iloxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 200);

Acido (2S)-2-metoxi-3-{4-[3-(5,6,7,8-tetrahidro-naftalen-2-iloxi)-propoxi]-fenil}-propiónico (Compuesto 201);

Acido (2S)-3-{4-[3-(4-benciloxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 202);

Acido (2S)-3-{4-[3-(4-butoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 203);

Acido (2S)-3-{4-[3-(4-heptiloxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 204);

Acido (2S)-3-{4-[3-(6-benzoil-naftalen-2-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 205);

Acido (2S)-3-{4-[3-(benzo[1,3]dioxol-5-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 206);

Acido (2S)-3-{4-[3-(9H-fluoren-2-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 207);

Acido (2S)-2-metoxi-3-{4-[3-(4-octil-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 208);

Acido (2S)-2-metoxi-3-{4-[3-(naftalen-1-iloxi)-propoxi]-fenil}-propiónico (Compuesto 209);

Acido (2S)-3-{4-[3-(1H-indol-7-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 210);

Acido (2S)-3-{4-[3-(4'-fluoro-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 211);

Acido (2S)-3-{4-[3-(4'-cloro-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 212);

Acido (2S)-3-{4-[3-(3',5'-bis-trifluorometil-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 213);

Acido (2S)-3-{4-[3-(4-dibenzofuran-4-il-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 214);

Acido (2S)-2-metoxi-3-{4-[3-(4'-fenoxi-bifenil-4-iloxi)-propoxi]-fenil}-propiónico (Compuesto 215);

Acido (2S)-2-metoxi-3-{4-[3-(4-tiofen-2-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 216);

Acido (2S)-3-{4-[3-(3'-cloro-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 217);

Acido (2S)-3-{4-[3-(2'-cloro-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 218);

Acido (2S)-3-{4-[3-(2'-fluoro-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 219);

Acido (2S)-3-{4-[3-(4-benzo[1,3]dioxol-5-il-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 220);

Acido (2S)-3-{4-[3-(4'-t-butil-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 221);

Acido (2S)-2-metoxi-3-{4-[3-(3'-trifluorometoxi-bifenil-4-iloxi)-propoxi]-fenil}-propiónico (Compuesto 222);

Acido (2S)-2-metoxi-3-{4-[3-(4'-trifluorometoxi-bifenil-4-iloxi)-propoxi]-fenil}-propiónico (Compuesto 223);

Acido (2S)-3-(4-{3-[4-(2-cloro-benzoilamino)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 224);

Acido (2S)-2-metoxi-3-(4-{3-[4-(2-metoxi-benzoilamino)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 225);

Acido (2S)-3-(4-{3-[4-(2,2-dimetil-propionilamino)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 226);

Acido (2S)-3-(4-{3-[4-(3-fluoro-benzoilamino)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 227);

Acido (2S)-2-metoxi-3-(4-{3-[4-(3-metoxi-benzoilamino)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 228);

Acido (2S)-2-metoxi-3-(4-{3-[4-(3-metil-benzoilamino)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 229);

Acido (2S)-3-(4-{3-[4-(4-fluoro-benzoilamino)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 230);

Acido (2S)-3-(4-{3-[4-(4-cloro-benzoilamino)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 231);

Acido (2S)-2-metoxi-3-(4-{3-[4-(4-metoxi-benzoilamino)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 232);

Acido (2S)-2-metoxi-3-{4-[3-(4-fenilacetilamino-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 233);

Acido (2S)-3-(4-{3-[4-(2-cloro-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 234);

Acido (2S)-2-metoxi-3-(4-{3-[4-(naftaleno-1-carbonil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 235);

Acido (2S)-3-(4-{3-[4-(3-fluoro-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 236);

Acido (2S)-2-metoxi-3-(4-{3-[4-(3-metoxi-benzoil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 237);

Acido (2S)-2-metoxi-3-(4-{3-[4-(naftaleno-2-carbonil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 238);

Acido (2S)-2-metoxi-3-(4-{3-[4-(4-metil-benzoil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 239);

Acido (2S)-3-(4-{3-[4-(2,2-dimetil-propionil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 240);

Acido (2S)-3-{4-[3-(4-isobutiril-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 241);

Acido (2S)-2-metoxi-3-(4-{3-[4-(3-fenil-propionil)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 242);

Acido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-fluoro-fenil}-2-metoxi-propiónico (Compuesto 243);

Acido 2-fenoxi-3-[4-(4-fenoxi-fenoxi)propoxifenil]propanóico (Compuesto 244);

Acido (2S,2'S)-3-(4-{3-[4-(2'-carboxi-2'-metoxi-etil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 245);

Intermedio α-metoxicinamato, 2*S*-2-metoxi-3-(4-hidroxifenil)propanoato de etilo (Compuesto 246);

Acido 2*S*-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]fenil}propanóico (Compuesto 247);

Acido (2S)-(2'*RS*)-2-metoxi-{4-[2'-metil-3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 248);

Acido 2(S)-3-[4-(3-benciloxi-propoxi)-fenil]-2-metoxipropiónico (Compuesto 249);

Acido (2S)-3-[4-(5-benciloxi-pentiloxi)-fenil]-2-metoxipropiónico (Compuesto 250);

Acido (2S)-2-etoxi-{4-[3-(4-fenoxi-fenoxi)-propoxil]-fenil}-propiónico (Compuesto 251);

Acido (2S)-2-benciloxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 252);

Acido (2S)-3-{4-[3-(4-{4-[2-(t-butil-dimetil-silaniloxi)-etoxi]-benzoil}-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 253);

Acido (2S)- 3-[4-(3-{4-[4-(2-hidroxi-etoxi)-benzoil]-fenoxi}-propoxi)-fenil]-2-metoxi-propiónico (Compuesto 254);

Acido (2S)-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-2-propoxi-propiónico (Compuesto 255);

Acido (2S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-fenil}-2-etoxi-propiónico (Compuesto 256);

Acido (2S)- 3-{4-[3-(4-bencil-fenoxi)-propoxi]-fenil}-2-etoxi-propiónico (Compuesto 257);

Acido (2S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-cloro-fenil}-2-etoxi-propiónico (Compuesto 258);

Acido (2S)-4'-{3-[4-(2-carboxi-2-metoxi-etil)-2-metoxi-fenoxi]-propoxi}-bifenil-4-carboxílico (Compuesto 259);

Acido (2S)-3-{4-[3-(4'-t-butil-bifenil-4-iloxi)-propoxi}-2-metoxi-propiónico (Compuesto 260);

Acido (2S)-3-(4-{3-[4-(4-hidroxi-fenoxi)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 261);

Acido (2S)-2-metoxi-3-(4-{3-[4-(2,2,3,3-tetrafluoro-propoxi)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 262);

Acido (2S)-2-metoxi-3-(4-{3-[4-(3-metil-butoxi)-fenoxi]-propoxi}-fenil)-propiónico (Compuesto 263);

Acido (2S)-3-{4-[3-(4-Isobutoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 264);

Acido (2S)-3-{4-[3-(4-Isopropoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 265);

Acido (2S)-3-{4-[3-(4-Ciclohexilmetoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 266);

Acido (2S)-2-metoxi-3-{4-[3-(4-phenetiloxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 267);

Acido (2S)-3-(4-{3-[4-(3-Dimetilamino-propoxi)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 268);

Acido (2S)-3-{4-[3-(4-Carboximetoxi-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 269);

Acido (2S)-3-(4-{3-[4-(1H-Indol-5-il)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 270);

Acido (2S)-2-metoxi-3-{4-[3-(4-piridin-3-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 271);

Acido (2S)-2-metoxi-3-{4-[3-(4-piridin-4-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 272);

Acido (2S)-2-metoxi-3-{4-[3-(4-quinolin-8-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 273);

Acido (2S)-3-{4-[3-(4'-Ciano-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 274);

Acido (2S)-2-metoxi-3-(4-{3-[4'-(1*H*-tetrazol-5-il)bifenil-4-iloxi]-propoxi}-fenil)-propiónico (Compuesto 275);

Acido (2S)-3-{4-[3-(4-Imidazol-1-il-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 276);

Acido (2S)-3-(4-{3-[4-(1,3-Dioxo-1,3-dihidro-isoindol-2-il)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 277);

Acido (2S)-3-(4-{3-[4-(4-Acetil-piperazin-1-il)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico (Compuesto 278);

Acido (2S)-2-metoxi-3-{4-[3-(4-piperazin-1-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 279);

Acido (2S)-2-metoxi-3-{4-[3-(4-morfolin-4-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 280);

Acido (2S)-3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-cloro-fenil}-2-etoxi-propiónico (Compuesto 281);

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-cloro-fenil}-2-etoxi-propiónico (Compuesto 282);

Acido (2S)-3-{4-[2-(bifenil-4-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 283);

Acido (2S)-2-metoxi-3-{4-[3-(3-trifluorometil-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 284);

Acido (2S)-2-metoxi-3-[4-(3-fenoxi-propoxi)-fenil]-propiónico (Compuesto 285);

Acido (2S)-3-{4-[3-(bifenil-3-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 286);

Acido (2S)-2-metoxi-3-{4-[3-(2-metil-benzotiazol-5-iloxi)-propoxi]-fenil}-propiónico (Compuesto 287);

Acido (2S)-2-metoxi-3-{4-[3-(3-morfolin-4-il-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 288);

Acido (2S)-2-metoxi-3-{4-[3-(5,6,7,8-tetrahidro-naftalen-2-iloxi)-propoxi]-fenil}-propiónico (Compuesto 289);

Acido 2-metoxi-3-{4-[2-(4-fenoxi-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 290);

Acido 3-{3-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 291);

Acido 3-{3-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Isómero 2) (Compuesto 292);

Acido (2S)-3-{4-[3-(2-ciano-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 293);

Acido (2S)-2-metoxi-3-{4-[3-(2-metoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 294);

Acido (2S)-2-{3-[4-(2-carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (Compuesto 295);

Acido (2S)-3-{4-[3-(3-ciano-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 296);

Acido (2S)-3-{4-[3-(3-dimetilamino-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 297);

Acido (2S)-3-{3-[4-(2-carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (Compuesto 298);

Acido (2S)-3-{4-[3-(indan-5-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 299);

Acido (2S)-2-metoxi-3-{4-[3-(naftalen-2-iloxi)-propoxi]-fenil}-propiónico (Compuesto 300);

Acido (2S)-3-{4-[3-(1H-indol-5-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 301);

Acido (2S)-2-metoxi-3-{4-[3-(quinolin-6-iloxi)-propoxi]-fenil}-propiónico (Compuesto 302);

Acido (2S)-2-metoxi-3-{4-[3-(3-metoxi-fenoxi)-propoxi]-fenil}-propiónico (Compuesto 303);

Acido (2S)-3-{4-[3-(3-fluoro-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 304);

Acido (2S)-3-{4-[3-(2-isopropil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (Compuesto 305);

Acido (2S)-2-metoxi-3-[4-(2-fenoxi-etoxi)-fenil]-propiónico (Compuesto 306);

Acido (2S)-3-{4-[2-(2-ciano-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 307);

Acido (2S)-2-metoxi-3-{4-[2-(2-metoxi-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 308);

Acido (2S)-3-{4-[2-(bifenil-2-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 309);

Acido (2S)-2-{2-[4-(2-carboxi-2-metoxi-etil)-fenoxi]-etoxi}-benzóico (Compuesto 310);

Acido (2S)-3-{4-[2-(2-isopropil-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 311);

Acido (2S)-3-{4-[2-(3-ciano-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 312);

Acido (2S)-3-{4-[2-(3-dimetilamino-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 313);

Acido (2S)-3-{4-[2-(bifenil-3-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 314);

Acido (2S)-3-{2-[4-(2-carboxi-2-metoxi-etil)-fenoxi]-etoxi}-benzóico (Compuesto 315);

Acido (2S)-3-{4-[2-(indan-5-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 316);

Acido (2S)-2-metoxi-3-{4-[2-(naftalen-2-iloxi)-etoxi]-fenil}-propiónico (Compuesto 317);

Acido (2S)-2-metoxi-3-{4-[2-(quinolin-6-iloxi)-etoxi]-fenil}-propiónico (Compuesto 318);

Acido (2S)-2-metoxi-3-{4-[2-(3-morfolin-4-il-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 319);

Acido (2S)-2-metoxi-3-{4-[2-(2-metil-benzotiazol-5-iloxi)-etoxi]-fenil}-propiónico (Compuesto 320);

Acido (2S)-2-metoxi-3-{4-[2-(3-metoxi-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 321);

Acido (2S)-3-{4-[2-(3-fluoro-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 322);

Acido 2-metoxi-3-[3-(3-fenoxi-propoxi)-fenil]-propiónico (isómero 1) (Compuesto 323);

Acido 3-{3-[3-(2-ciano-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 324);

Acido 3-{3-[3-(3-ciano-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 325);

Acido 2-metoxi-3-[3-(3-fenoxi-propoxi)-fenil]-propiónico (isómero 2) (Compuesto 326);

Acido 3-{3-[3-(2-ciano-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 327);

Acido 3-{3-[3-(3-ciano-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 328);

Acido 2-metoxi-3-{3-[3-(2-metoxi-fenoxi)-propoxi]-fenil}-propiónico (isómero 1) (Compuesto 329);

Acido 2-metoxi-3-{3-[3-(2-metoxi-fenoxi)-propoxi]-fenil}-propiónico (isómero 2) (Compuesto 330);

Acido 3-{3-[3-(2-isopropil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 331);

Acido 3-{3-[3-(2-isopropil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 332);

Acido 3-{3-[3-(2-carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (isómero 1) (Compuesto 333);

Acido 3-{3-[3-(2-carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (isómero 2) (Compuesto 334);

Acido 2-metoxi-3-{3-[3-(3-metoxi-fenoxi)-propoxi]-fenil}-propiónico (isómero 1) (Compuesto 335);

Acido 2-metoxi-3-{3-[3-(3-metoxi-fenoxi)-propoxi]-fenil}-propiónico (isómero 2) (Compuesto 336);

Acido 2-metoxi-3-{3-[3-(naftalen-2-iloxi)-propoxi]-fenil}-propiónico (isómero 1) (Compuesto 337);

Acido 2-metoxi-3-{3-[3-(naftalen-2-iloxi)-propoxi]-fenil}-propiónico (isómero 2) (Compuesto 338);

Acido 2-metoxi-3-{3-[3-(2-metil-benzotiazol-5-iloxi)-propoxi]-fenil}-propiónico (isómero 1) (Compuesto 339);

Acido 2-metoxi-3-{3-[3-(2-metil-benzotiazol-5-iloxi)-propoxi]-fenil}-propiónico (isómero 2) (Compuesto 340);

Acido 3-{3-[3-(2-cloro-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 341);

Acido 3-{3-[3-(2-cloro-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 342);

Acido 3-{3-[3-(3,4-dimetil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 343);

Acido 3-{3-[3-(3,4-dimetil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 344);

Acido 2-{3-[3-(2-carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (isómero 1) (Compuesto 345);

Acido 2-{3-[3-(2-carboxi-2-metoxi-etil)-fenoxi]-propoxi}-benzóico (isómero 2) (Compuesto 346);

Acido 3-{3-[3-(bifenil-3-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 347);

Acido 3-{3-[3-(bifenil-3-iloxi)-propoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 348);

Acido 2-metoxi-3-{3-[3-(quinolin-6-iloxi)-propoxi]-fenil}-propiónico (isómero 1) (Compuesto 349);

Acido 2-metoxi-3-{3-[3-(quinolin-6-iloxi)-propoxi]-fenil}-propiónico (isómero 2) (Compuesto 350);

Acido 3-{3-[2-(2-isopropil-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 351);

Acido 2-metoxi-3-{3-[2-(3-metoxi-fenoxi)-etoxi]-fenil}-propiónico (isómero 1)(Compuesto 352);

Acido 3-{3-[2-(3-fluoro-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (isómero 1) (Compuesto 353);

Acido 2-metoxi-3-{3-[2-(5,6,7,8-tetrahidro-naftalen-2-iloxi)-etoxi]-fenil}-propiónico (isómero 1) (Compuesto 354);

Acido 2-metoxi-3-{3-[2-(3-metoxi-fenoxi)-etoxi]-fenil}-propiónico (isómero 2) (Compuesto 355);

Acido 3-{3-[2-(3-fluoro-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (isómero 2) (Compuesto 356);

Acido 2-metoxi-3-{3-[2-(5,6,7,8-tetrahidro-naftalen-2-iloxi)-etoxi]-fenil}-propiónico (isómero 2) (Compuesto 357);

Acido (2S)-2-metoxi-3-{4-[2-(4-trifluorometil-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 358);

Acido (2S)-2-metoxi-3-(4-{2-[4-(1-metil-1-fenil-etil)-fenoxi]-etoxi}-fenil)-propiónico (Compuesto 359);

Acido (2S)-3-{4-[2-(4-bencil-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 360);

Acido (2S)-2-metoxi-3-{4-[2-(4-oxo-2-fenil-4H-cromen-7-iloxi)-etoxi]-fenil}-propiónico (Compuesto 361);

Acido (2S)-3-{4-[2-(4-ciclopentil-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 362);

Acido (2S)-3-{4-[2-(9H-fluoren-2-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 363);

Acido (2S)-3-{4-[2-(4-butil-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 364);

Acido (2S)-3-{4-[2-(2'-fluoro-bifenil-4-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 365);

Acido (2S)-3-(4-{2-[4-(2,2-dimetil-propionil)-fenoxi]-etoxi}-fenil)-2-metoxi-propiónico (Compuesto 366);

Acido 3-(4-{2-[4-(2,2-dimetil-propionilamino)-fenoxi]-etoxi}-fenil)-2-metoxi-propiónico (Compuesto 367);

Acido (2S)-3-(4-{2-[4-(ciclopentanecarbonil-amino)-fenoxi]-etoxi}-fenil)-2-metoxi-propiónico (Compuesto 368);

Acido (2S)-3-[4-(2-{4-[(furan-2-carbonil)-amino]-fenoxi}-etoxi)-fenil]-2-metoxi-propiónico (Compuesto 369);

Acido (2S)-2-metoxi-3-[4-(2-{4-[(piridino-3-carbonil)-amino]-fenoxi}-etoxi)-fenil]-propiónico (Compuesto 370);

Acido (2S)-2-metoxi-3-{4-[2-(2-pirrolidin-1-il-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 371);

Acido (2S)-2-metoxi-3-{4-[2-(piridin-2-iloxi)-etoxi}-fenil}-propiónico (Compuesto 372);

Acido (2S)-2-metoxi-3-{4-[2-(2-morfolin-4-il-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 373);

Acido (2S)-3-{4-[2-(4'-t-butil-bifenil-4-iloxi)-etoxi]-fenil}-2-metoxi-propiónico (Compuesto 374);

Acido (2S)-2-etoxi-3-{4-[2-(4-fenoxi-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 375);

Acido (2R)-2-etoxi-3-{4-[2-(4-fenoxi-fenoxi)-etoxi]-fenil}-propiónico (Compuesto 376);

Acido (2S)-3-{4-[2-(bifenil-4-iloxi)-etoxi]-fenil}-2-propoxi-propiónico (Compuesto 377);

Acido 3-{3-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-etoxi-propiónico (isómero 1) (Compuesto 378);

Acido 3-{3-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-etoxi-propiónico (isómero 2) (Compuesto 379).

En la presente invención también se incluyen los compuestos representados mediante la Fórmula Estructural (I), donde Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante las Fórmulas Estructurales (I) o (VI), donde el Anillo de Fenilo **A** es el correspondiente grupo fenilo o fenilo sustituido de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_3-O-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_4-O-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_5-O-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379.

Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-CH_2-C\equiv CH-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_2-C\equiv CH-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_3-C\equiv CH-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_4-C\equiv CH-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_5-C\equiv CH-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

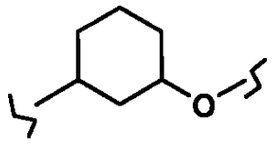
También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-CH_2CO-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_2CO-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379.

Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

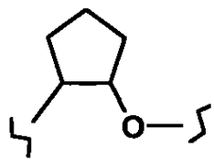
También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W es $-(CH_2)_3CO-$ y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W está representado mediante la siguiente fórmula estructural:



; y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde W está representado mediante la siguiente fórmula estructural:



; y Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W, W_1 o W_2 y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde Ar-O-W- es el correspondiente grupo de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en los Ejemplos 1-379, W es $-CH(CH_3)W_3CH(CH_3)O-$ y W_3 es un enlace covalente, metileno o etileno. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

También están incluidos los compuestos representados mediante la Fórmula Estructural (I), donde Ar es el correspondiente grupo aromático de uno cualquiera de los Compuestos 1-379 o de uno de los compuestos descritos en

los Ejemplos 1-379, W es $-W_4C(=O)W_5O-$ o $-W_4C(=CH_2)W_5O-$ y W_4 y W_5 son independientemente metileno o etileno. Preferiblemente, R_1 está en *para* respecto al átomo de carbono unido a W y está representado mediante la Fórmula Estructural (II), más preferiblemente la Fórmula Estructural (III) o (IV) e incluso más preferiblemente la Fórmula Estructural (V).

Los profármacos son compuestos de la presente invención, que tienen grupos escindibles químicamente o metabólicamente y se vuelven mediante solvólisis o en condiciones fisiológicas el compuesto de la invención que son farmacéuticamente activos *in vivo*. Entre los profármacos se incluyen derivados ácido bien conocidos para los practicantes de la técnica, tales como, por ejemplo, los ésteres preparados mediante reacción del compuesto ácido de origen con un alcohol adecuado, o las amidas preparadas mediante reacción del compuesto ácido de origen con una amina adecuada. Los ésteres alifáticos o aromáticos sencillos derivados de grupos ácido pendientes del el compuesto de esta invención son profármacos preferidos. En algunos casos es deseable preparar profármacos de tipo éster doble tales como ésteres (aciloxi)alquílicos o ésteres ((alcoxicarbonil)oxi)alquílicos. Los ésteres particularmente preferidos como profármacos son de metilo, etilo, propilo, isopropilo, n-butilo, isobutilo, t-butilo, morfolinoetilo, y N,N-dietilglicolamido.

Los profármacos de ésteres metílicos pueden ser preparados mediante reacción de la forma ácida de un compuesto de la presente invención en un medio tal como metanol con un catalizador de esterificación ácido o alcalino (v.g., NaOH, H_2SO_4). Los profármacos de ésteres metílicos se preparan de una manera similar utilizando etanol en lugar de metanol.

Los profármacos de ésteres morfoliniletílicos pueden ser preparados mediante reacción de la sal de sodio de un compuesto de la presente invención (en un medio tal como dimetilformamida) con hidrocloruro de 4-(2-cloroetil)morfolina (asequible de Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

El término "farmacéuticamente aceptables" significa que el portador, el diluyente, los excipientes y las sales deben ser compatibles con los otros ingredientes de la formulación, y no perjudiciales para el recipiente de los mismos. Las formulaciones farmacéuticas de la presente invención se preparan mediante procedimientos conocidos en la técnica utilizando ingredientes bien conocidos y fácilmente asequibles.

También se incluyen en la presente invención las sales farmacéuticamente aceptables, los hidratos, los estereoisómeros y los solvatos de los compuestos de la presente invención y las mezclas de tales compuestos, sales, hidratos, estereoisómeros y/o solvatos.

En virtud de su radical ácido, ciertos compuestos de la presente. invención forman sales con bases farmacéuticamente aceptables. Tales sales farmacéuticamente aceptables se pueden formar con una base que proporcione un catión farmacéuticamente aceptable, entre lás que se incluyen las sales de metales alcalinos (especialmente sodio y potasio), sales de metales alcalinotérreos (especialmente calcio y magnesio), sales de aluminio y sales de amonio, así como sales formadas a partir de bases orgánicas fisiológicamente aceptables tales como trimetilamina, trietilamina, morfolina, piridina, piperidina, picolina, diciclohexilamina, N,N'-dibenciletilenodiamina, 2-hidroxietilamina, bis-(2-hidroxietil)amina, tri-(2-hidroxietil)amina, procaína, dibencilpiperidina, N-bencil-β-fenetilamina, dehidroabietilamina, N,N'-

bisdehidroabietilamina, glucamina, N-metilglucamina, colidina, quinina, quinolina, y aminoácidos alcalinos tales como lisina y arginina. Estas sales pueden ser preparadas mediante métodos conocidos para los expertos en la técnica.

Los compuestos de la presente invención que están sustituidos con un grupo alcalino, pueden existir en forma de sales con ácidos farmacéuticamente aceptables. En la presente invención se incluyen tales sales. Entre los ejemplos de tales sales se incluyen hidrocloruros, hidrobromuros, sulfatos, metanosulfonatos, nitratos, maleatos, acetatos, citratos, fumaratos, tartratos [v.g. (+)-tartratos, (-)-tartratos o mezclas de los mismos incluyendo mezclas racémicas, succinatos, benzoatos y sales con aminoácidos tales como ácido glutámico.

Ciertos compuestos de la presente invención pueden contener uno o más centros quirales, y existen en diferentes formas ópticamente activas. Cuando los compuestos de la presente invención contienen un centro quiral, el compuesto existe en dos formas enantioméricas y en la presente invención se incluyen tanto los enantiómeros como las mezclas de enantiómeros, tales como las mezclas racémicas. Los enantiómeros pueden ser resueltos mediante métodos conocidos para los expertos en la técnica, por ejemplo mediante formación de sales diastereoisoméricas que pueden ser separadas, por ejemplo, mediante cristalización; formación de derivados o complejos diastereoisoméricos o que pueden ser separados, por ejemplo, mediante cristalización, cromatografía gas-líquido o de líquidos; reacción selectiva de un enantiómero con un reactivo especifico del enantiómero, por ejemplo esterificación enzimática; o cromatografía gas-líquido o cromatografía de líquidos en un entorno quiral, por ejemplo sobre un soporte quiral por ejemplo sílice con un ligando quiral unido o en

presencia de un disolvente quiral. Se deberá apreciar que cuando el enantiómero deseado es convertido en otra entidad química mediante uno de los procedimientos de separación descritos antes, se requiera una etapa anterior para liberar la forma enantiomérica deseada. Alternativamente, se pueden sintetizar enantiómeros específicos mediante síntesis asimétricas utilizando reactivos ópticamente activos, sustratos, catalizadores o disolventes, o convirtiendo un enantiómero en la otra transformación asimétrica.

Cuando un compuesto de la presente invención tiene uno o más sustituyentes quirales este puede existir en formas diastereoisoméricas. Los pares diastereoisoméricos pueden ser separados mediante métodos conocidos para los expertos en la técnica, por ejemplo cromatografía o cristalización y los enantiómeros individuales de cada par pueden ser separados como se ha descrito antes. En la presente invención se incluyen cada diastereoisómero de tales compuestos y las mezclas de los mismos.

Ciertos compuestos de la presente invención pueden existir in forma zwitteriónica y en la presente invención se incluyen cada forma zwitteriónica y las mezclas de las mismas.

Ciertos compuestos de la presente invención y sus sales pueden existir en más de una forma cristalina. Las formas polimorfas de los compuestos de la presente invención forman parte de esta invención y pueden ser preparadas mediante cristalización de un compuesto dado en diferentes afecciones. Por ejemplo, utilizando diferentes disolventes o diferentes mezclas disolventes para recristalización; cristalización a diferentes temperaturas; diversos modos de enfriamiento, oscilando de enfriamiento muy rápido a muy lento durante la cristalización. Las formas polimorfas también se pueden obtener calentando o fundiendo un compuesto de la

presente invención seguido de enfriamiento gradual o rápido. La presencia de formas polimorfas puede ser determinada mediante espectroscopía de RMN con una sonda sólida, espectroscopía IR, calorimetría de barrido diferencial, difracción de rayos X de polvo u otras técnicas semejantes.

Un "sujeto" es a mamífero, preferiblemente un humano, pero también puede ser un animal que necesite tratamiento veterinario, v.g., animales de compañía (v.g., perros, gatos, y similares), animales de granja (v.g., vacas, ovejas, cerdos, caballos, y similares) y animales de laboratorio (v.g., ratas, ratones, cobayas, y similares).

"Tratamiento" o "tratar", según se utiliza aquí, hace referencia tanto al tratamiento terapéutico como al tratamiento profiláctico. El "Tratamiento terapéutico" hace referencia a prevenir la progresión adicional o a mejorar los síntomas asociados a una enfermedad o afección. El "Tratamiento Profiláctico" hace referencia a la inhibición, prevención o retraso del comienzo de los síntomas de una enfermedad o afección en un sujeto que tenga el riesgo de padecer la enfermedad o afección. En el "Tratamiento profiláctico" también se incluye reducir la gravedad de los síntomas de una enfermedad o afección tratando a un sujeto que tenga el riesgo de desarrollar la enfermedad o afección antes de que aparezcan los síntomas.

Se pretende que la redacción "cantidad eficaz" o "cantidad farmacéuticamente eficaz" incluya una cantidad que sea suficiente para mediar en una enfermedad o afección y prevenga progresión adicional o mejore los síntomas asociados a la enfermedad o afección. Una "cantidad eficaz" o "cantidad farmacéuticamente eficaz" también se puede incluir una cantidad suficiente para prevenir o retrasar el comienzo de una enfermedad o afección en un paciente que tenga el riesgo de

desarrollar la enfermedad o afección, esto es, tratamiento profiláctico. Cuando se administra profilácticamente semejante cantidad a un paciente también puede ser eficaz para disminuir la gravedad de la afección mediada. Se pretende que semejante cantidad incluya una cantidad que sea suficiente para modular un receptor PPAR, tal como un receptor PPARγ o PPARα, que media en una enfermedad o afección. Entre las afecciones mediadas por los receptores PPARα o PPARγ se incluyen la diabetes sacarina, las enfermedades cardiovasculares, el Síndrome X, la obesidad y las enfermedades gastrointestinales. Otras enfermedades semejantes se describen más abajo.

Los compuestos de la presente invención y las sales farmacéuticamente aceptables, solvatos, estereoisómeros e hidratos de los mismos tienen propiedades farmacológicas valiosas y pueden ser utilizados en preparaciones farmacéuticas que contienen el compuesto o las sales, ésteres o profármacos farmacéuticamente aceptables de los mismos, combinados con un portador o diluyente farmacéuticamente aceptable. Son útiles como sustancias terapéuticas para tratar (terapéuticamente o profilácticamente) la hiperglicemia, la dislipidemia, la diabetes de Tipo II, la diabetes de Tipo I, la hipertrigliceridemia, el síndrome X, la resistencia a la insulina, la insuficiencia cardíaca, la dislipidemia diabética, la hiperlipidemia, la hipercolesteremia, la hipertensión, la obesidad, la anorexia-bulimia, el síndrome del ovario poliquístico, la anorexia nerviosa, las enfermedades cardiovasculares (especialmente la aterosclerosis) u otras enfermedades en las que la resistencia a la insulina es un componente u otras alteraciones mediadas por un receptor PPAR. Entre los portadores farmacéuticamente aceptables adecuados se incluyen cargas sólidas inertes o diluyentes y soluciones

acuosas u orgánicas estériles. El compuesto activo estará presente en tales composiciones farmacéuticas en cantidades suficientes para proporcionar la cantidad de dosificación deseada en el intervalo descrito aquí. Las técnicas para la formulación y administración de los compuestos de la presente invención se pueden encontrar en *Remington: the Science y Practice de Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995).

Para la administración oral, el compuesto o las sales del mismo se pueden combinar con un portador o diluyente sólido o líquido adecuado para formar cápsulas, tabletas, píldoras, polvos, jarabes, soluciones, suspensiones y similares.

Las tabletas, píldoras, cápsulas, y similares también pueden contener un aglutinante tal como goma de tragacanto, acacia, almidón de maíz o gelatina; excipientes tales como fosfato dicálcico; un agente disgregante tal como almidón de maíz, almidón de patata, ácido algínico, un lubricante tal como estearato de magnesio; y un agente edulcorante tal como sacarosa, lactosa o sacarina. Cuando la forma de dosificación unitaria es una cápsula, ésta puede contener, además de las sustancias del tipo anterior, un portador líquido tal como un aceite graso.

Pueden estar presentes otras varias sustancias como revestimientos o para modificar la forma física de la unidad de dosificación. Por ejemplo, las tabletas pueden estar revestidas con goma laca, azúcar o ambos. Un jarabe o elixir puede contener, además del ingrediente activo, sacarosa como agente edulcorante, metil- y propilparabenos como conservante, un colorante y un agente aromatizante tal como aroma de cereza o naranja. Tales composiciones y preparaciones deben contener al menos el 0,1 por ciento de compuesto activo. Por supuesto, se puede variar el porcentaje de compuesto

activo en estas composiciones y puede estar convenientemente entre aproximadamente el 2 por ciento y aproximadamente 60 por ciento del peso de la unidad. La cantidad de compuesto activo en tales composiciones terapéuticamente útiles es tal que se obtendrá una dosificación eficaz.

Los compuestos activos también pueden ser administrados intranasalmente, por ejemplo, en forma de gotas líquidas o pulverización. Para la inhalación oral o nasal, los compuestos para el uso según la presente invención se liberan convenientemente en forma de un inhalador de polvo seco, o de una presentación de pulverización en aerosol a partir de envases presurizados o de un nebulizador, con el uso de un propelente adecuado, v.g., diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas adecuado. En el caso del aerosol presurizado la unidad de dosificación puede ser determinada proporcionando una válvula para liberar una cantidad medida. Las cápsulas y cartuchos de gelatina para el uso en un inhalador o insuflador pueden ser formuladas conteniendo una mezcla de polvo del compuesto y una base en polvo adecuada por ejemplo de lactosa o almidón.

Para la administración parenteral el compuesto de la presente invención, o las sales o las sales del mismo se pueden combinar con medios acuosos u orgánicos estériles para formar soluciones o suspensiones inyectables. Por ejemplo, se pueden utilizar soluciones en aceite de sésamo o cacahuete, propilenglicol acuoso y similares, así como soluciones acuosas de las sales farmacéuticamente aceptables solubles en agua de los compuestos. Las dispersiones también se pueden preparar en glicerol, polietilenglicoles líquidos y mezclas de los mismos en aceites. En condiciones normales de almacenamiento y uso, estas preparaciones contienen un

conservante para evitar el crecimiento de microorganismos.

Entre las formas farmacéuticas adecuadas para el uso inyectable se incluyen las soluciones o dispersiones acuosas estériles y los polvos estériles para la preparación extemporánea de soluciones o dispersiones inyectables estériles. En todos los casos, la forma debe ser estéril y debe ser fluida hasta el punto de que exista la posibilidad de aplicar mediante jeringa cada una de ellas. Debe ser estable en las condiciones de fabricación y almacenamiento y debe ser preservada de cualquier contaminación. El portador puede ser un medio disolvente o de dispersión conteniendo, por ejemplo, agua, etanol, poliol (v.g. glicerol, propilenglicol y polietilenglicol líquido), mezclas adecuadas de los mismos, y aceites vegetales. Las soluciones inyectables preparadas de esta manera pueden ser administradas después intravenosamente, intraperitonealmente, subcutáneamente, o intramuscularmente, siendo preferida la administración intramuscular en humanos.

Los compuestos también pueden ser formulados en composiciones rectales tales como supositorios o enemas de retención, v.g., conteniendo bases convencionales para supositorios tales como manteca de cacao u otros glicéridos.

Además de las formulaciones descritas previamente, el compuesto también puede ser formulado en forma de una preparación de depósito. Tales formulaciones de acción duradera pueden ser administradas mediante implantación, por ejemplo, subcutáneamente o intramuscularmente o mediante inyección intramuscular. Así, por ejemplo, como una emulsión en un aceite aceptable, o resinas de intercambio iónico, o como derivados escasamente solubles, por ejemplo, como sales escasamente solubles.

La dosificación eficaz del ingrediente activo empleado puede variar dependiendo del compuesto concreto empleado, el modo de administración, la afección que vaya a ser tratada y la gravedad de la afección que vaya a ser tratada.

Cuando se utiliza aquí, en el Síndrome X se incluyen el síndrome de resistencia a la insulina pre-diabético y las complicaciones resultantes del mismo, la resistencia a la insulina, la diabetes no dependiente de insulina, la dislipidemia, la obesidad por hiperglicemia, la coagulopatía, la hipertensión y otras complicaciones asociadas con la diabetes. Entre los métodos y tratamientos mencionados aquí se incluyen los anteriores y abarcan el tratamiento terapéutico y/o la profilaxis de una cualquiera o de cualquier combinación de las siguientes: hiperglicemia, dislipidemia, diabetes de Tipo II, diabetes de Tipo I, hipertrigliceridemia, síndrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesteremia, hipertensión, obesidad, anorexia-bulimia, síndrome del ovario poliquístico, anorexia nerviosa, enfermedades cardiovasculares (especialmente aterosclerosis) u otras enfermedades en las que la resistencia a la insulina es un componente u otras alteraciones mediadas por un receptor PPAR.

Las composiciones se formulan y administran de la misma manera general según se detalla aquí. Los compuestos de la presente invención pueden ser utilizados eficazmente solos o combinados con uno o más agentes activos adicionales dependiendo de la terapia objetivo deseada. La terapia de combinación incluye la administración de una formulación de dosificación farmacéutica sencilla que contiene un compuesto de la presente invención y uno o más agentes activos adicionales, así como la administración de un compuesto

de la presente invención y cada agente activo en su propia formulación de dosificación farmacéutica separada. Por ejemplo, se puede administrar al paciente un compuesto de un secretagogo de insulina tal como biguanidas, tiazolidinodionas, sulfonilureas, insulina, o inhibidores de la α-glucosidasa juntos en una composición de dosificación oral sencilla tal como una tableta o cápsula, o se puede administrar cada agente en formulaciones de dosificación oral separada. Cuando se utilizan formulaciones de dosificación separadas, se pueden administrar un compuesto de la presente invención y uno o más agentes activos adicionales esencialmente al mismo tiempo, esto es, concurrentemente, o en períodos asombrosamente separados, es decir, sucesivamente. Se entiende que en la terapia de combinación se incluyen todos estos regímenes.

Un ejemplo de combinación terapéutica o tratamiento profiláctico de la aterosclerosis puede ser aquel en el que se administra un compuesto de la presente invención o una sal del mismo combinado con uno o más de los siguientes agentes activos: agentes antihiperlipidémicos; agentes para aumentar HDL en plasma; agentes antihipercolesterolémicos, fibratos, vitaminas, aspirina, y similares. Como se ha observado antes, el compuesto de la presente invención puede ser administrado combinado con más de un agente activo adicional.

Otro ejemplo de terapia de combinación se puede observar al tratar (terapéuticamente o profilácticamente) la diabetes y las alteraciones relacionadas donde el compuesto de la presente invención y sales del mismo pueden ser utilizados eficazmente combinados, por ejemplo, con sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la α-glucosidasa, otros secretagogos de insulina, insulina así como los agentes activos comentados antes para tratar la aterosclerosis.

Entre otros ejemplos de los agentes terapéuticos que pueden ser utilizados combinados con el compuesto de la presente invención se incluyen sintetizadores de insulina, agonistas de PPARγ, glitazonas, troglitazona, pioglitazona, englitazona, MCC-555, BRL 49653, biguanidas, metformin, fenformin, insulina, miméticos de insulina, sufonilureas, tolbutamida, glipizida, inhibidores de la alfa-glucosidasa, acarbosa, agente reductor de colesterol, inhibidores de la HMG-CoA reductasa, lovastatina, simvastatina, pravastatina, fluvastatina, atrovastatina, rivastatina, otras estatinas, secuestrantes, colestiramina, colestipol, derivados dialquilamino-alquílicos de un dextrano entrecruzado, alcohol nicotinílico, ácido nicotínico, una sal de ácido nicotínico, agonistas de PPARα, derivados de ácido fenofíbrico, gemfibrozil, clofibrato, fenofibrato, benzafibrato, inhibidores de la absorción de colesterol, beta-sitosterol, inhibidores de la acil CoA:colesterol aciltransferasa, melinamida, probucol, agonistas de PPARδ, compuestos antiobesidad, fenfluramina, dexfenfluramina, fentiramina, sulbitramina, orlistat, inhibidores del neuropeptido Y5, agonistas del receptor β_3 adrenérgico, e inhibidores de los transportadores de los ácidos biliares ileales.

Se puede utilizar una cantidad eficaz de un compuesto de la presente invención para la preparación de un medicamento útil para el tratamiento (terapéutico y profiláctico) de la hiperglicemia, la dislipidemia, la diabetes de Tipo II, la diabetes de Tipo I, la hipertrigliceridemia, el síndrome X, la resistencia a la insulina, la insuficiencia cardíaca, la dislipidemia diabética, la hiperlipidemia, la hipercolesteremia, la hipertensión, la obesidad, la anorexia-bulimia, el síndrome del ovario poliquístico, la anorexia nerviosa, las enfermedades cardiovasculares (especialmente la

aterosclerosis), la reducción de los niveles de triglicéridos, el aumentos del nivel en plasma de lipoproteínas de alta densidad u otras enfermedades en las que la resistencia a la insulina es un componente u otras alteraciones mediadas por un receptor PPAR. Está incluido el tratamiento, la prevención o reducción del riesgo de desarrollar aterosclerosis, y para prevenir o reducir el riesgo de tener un primer o subsiguiente evento de enfermedad aterosclerótica enfermedad en mamíferos, particularmente en humanos. En general, una cantidad eficaz de un compuesto de la presente invención (1) reduce los niveles de glucosa en suero de un paciente, o más específicamente HbA1c, típicamente en aproximadamente un 0,7%; (2) reduce los niveles de triglicérido en suero de un paciente, típicamente en aproximadamente un 20%; y/o (3) aumenta los niveles de HDL en suero en un paciente, preferiblemente en aproximadamente un 30%.

Adicionalmente, se pueden utilizar juntas una cantidad eficaz de un compuesto de la presente invención y una cantidad eficaz de uno o más de los agentes activos enumerados antes para la preparación de un medicamento útil para los tratamientos anteriormente descritos.

Preferiblemente los compuestos de la invención o las formulaciones farmacéuticas que contienen estos compuestos están en una forma de dosificación unitaria para la administración a un mamífero. La forma de dosificación unitaria puede ser cualquier forma de dosificación unitaria conocida en la técnica incluyendo, por ejemplo, una cápsula, una bolsa IV, una tableta o un vial. La cantidad de ingrediente activo (a saber, un compuesto de la presente invención o las sales del mismo) en una dosis unitaria de composición es una cantidad terapéuticamente eficaz y se puede variar según el tratamiento concreto implicado. Se puede apreciar que es

necesario realizar variaciones rutinarias de la dosificación dependiendo de la edad y la afección del paciente. La dosificación también dependerá de la ruta de administración que puede ser mediante una variedad de rutas incluyendo oral, aerosol, transdérmica, subcutánea, intravenosa, intramuscular, intraperitoneal e intranasal.

Las formulaciones farmacéuticas de la invención se preparan combinando (v.g., mezclando) una cantidad eficaz de un compuesto de la invención junto con un portador o diluyente farmacéuticamente aceptable. Las presentes formulaciones farmacéuticas se preparan mediante procedimientos conocidos utilizando ingredientes bien conocidos y fácilmente asequibles.

Al elaborar las composiciones de la presente invención, el ingrediente activo se mezclará usualmente con un portador, o se diluirá en un portador, o se englobará en un portador que puede estar en forma de cápsula, saquito, papel u otro contenedor. Cuando el portador sirve como diluyente, debe ser un material sólido, sólido liofilizado o pasta, semi-sólido o líquido que actúe como vehículo, o puede estar en forma de tabletas, píldoras, polvos, grageas, elixires, suspensiones, emulsiones, soluciones, jarabes, aerosoles (en forma de sólido o en un medio líquido), o pomada, que contenga, por ejemplo, hasta el 10% en peso del compuesto activo. Los compuestos de la presente invención se formulan preferiblemente antes de la administración.

Para las formulaciones farmacéuticas se puede utilizar cualquier portador adecuado conocido en la técnica. En tales formulaciones, el portador puede ser sólido, líquido o una mezcla de un sólido y un líquido. Por ejemplo, para la inyección intravenosa el compuesto de la invención se puede disolver a una concentración de aproximadamente 0,05 a aproximadamente 5,0 mg/ml en

una solución acuosa con el 4% de dextrosa/0,5% de citrato de Na.

Entre las formulaciones en forma sólida se incluyen polvos, tabletas y cápsulas. Un portador sólido puede ser una sustancia o más que pueda actuar también como agente aromátizante, lubricante, solubilizante, agente suspensor, aglutinante, agente disgregante de tabletas y material encapsulante.

Las tabletas para la administración oral pueden contener excipientes adecuados tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio, junto con agentes disgregantes, tales como maíz, almidón, o ácido algínico, y/o agentes aglutinantes, por ejemplo, gelatina o acacia, y agentes lubricantes tales como estearato de magnesio, ácido esteárico, o talco.

En los polvos el portador es un sólido finamente dividido que se mezcla con el ingrediente activo finamente dividido. En las tabletas el ingrediente activo se mezcla con un portador que tiene las propiedades de aglutinación necesarias en las proporciones adecuadas y se compacta en la forma y el tamaño deseado.

Ventajosamente, las composiciones que contienen el compuesto de la presente invención o las sales del mismo pueden ser proporcionadas en formas unitarias de dosificación, preferiblemente cada unidad de dosificación conteniendo de aproximadamente 1 a aproximadamente 500 mg puede ser administrada si bien se deberá entender fácilmente, por supuesto, que la cantidad del compuesto o de los compuestos de la presente invención que se va a administrar realmente será determinada por un médico, a la luz de todas las circunstancias relevantes.

Los polvos y las tabletas contienen preferiblemente de aproximadamente el 1 a aproximadamente el 99 por ciento en peso del ingrediente activo que es el compuesto novedoso de la invención. Los portadores sólidos adecuados son el carbonato de sodio, el estearato de magnesio, el talco, el azúcar, la lactosa, la pectina, la dextrina, el almidón, la gelatina, el tragacanto, la metilcelulosa, la carboximetilcelulosa de sodio, las ceras de bajo punto de fusión, y la manteca de cacao.

Las siguientes formulaciones farmacéuticas 1 a 8 son únicamente ilustrativas y no se pretende que limiten el alcance de la invención de ningún modo. "Ingrediente Activo" hace referencia a un compuesto según la presente invención o las sales del mismo.

Formulación 1

Se preparan cápsulas de gelatina duras utilizando los siguientes ingredientes:

	Cantidad (mg/cápsula)
Ingrediente Activo	250
Almidón, seco	200
Estearato de magnesio	10
Total	460 mg

Formulación 2

Se prepara una tableta utilizando los ingredientes de más abajo:

	Cantidad (mg/tableta)
Ingrediente Activo	250
Celulosa, microcristalina	400
Dióxido de silicio, ahumado	10
Acido esteárico	5
Total	665 mg

Los componentes se combinan y comprimen para formar tabletas pesando cada una 665 mg.

Formulación 3

Se prepara una solución en aerosol conteniendo los siguientes componentes:

	Peso
Ingrediente Activo	0,25
Etanol	25,75
Propelente 22 (Clorodifluorometano)	74,00
Total	100,00

El Ingrediente Activo se mezcla con etanol y la mezcla se añade a una porción del propelente 22, se enfría a 30°C y se transfiere a un dispositivo de carga. La cantidad requerida se introduce después en un recipiente de acero inoxidable y se diluye con el resto del propelente. Después se ajustan las unidades de válvula al recipiente.

Formulación 4

Se elaboran como sigue Tabletas, conteniendo cada una 60 mg de Ingrediente Activo:

Ingrediente Activo	60 mg
Almidón	45 mg
Celulosa microcristalina	35 mg
Polivinilpirrolidona (en forma de una solución al 10% en agua)	4 mg
Sal de sodio de Carboximetilalmidón	4,5 mg
Estearato de magnesio	0,5 mg
Talco	1 mg
Total	150 mg

El Ingrediente Activo, el almidón y la celulosa se hacen pasar a través de un tamiz U.S. con malla del Núm. 45 y se mezclan cuidadosamente. La solución acuosa que contiene la polivinilpirrolidona se mezcla con el polvo resultante, y la mezcla se hace pasar después a través de un tamiz U.S. con malla del Núm. 14. Los gránulos producidos de este modo se secan a 50°C y se hacen pasar a través de un tamiz U.S. con malla del Núm. 18. La sal de sodio de carboximetilalmidón, el estearato de magnesio y el talco que se habían hecho pasar previamente a través de un tamiz U.S. con malla del Núm. 60, se añaden después a los gránulos que, después de mezclar, se comprimen en una máquina para comprimir tabletas para producir tabletas pesando cada una 150 mg.

Formulación 5

Cápsulas, conteniendo cada una 80 mg de Ingrediente Activo, se elaboran como sigue:

Ingrediente Activo	80 mg
Almidón	59 mg
Celulosa microcristalina	59 mg
Estearato de magnesio	2 mg
Total	200 mg

El Ingrediente Activo, la celulosa, el almidón, y el estearato de magnesio se combinan, se hacen pasar a través de un tamiz U.S. con malla del Núm. 45, y se cargan en cápsulas de gelatina dura en cantidades de 200 mg.

Formulación 6

Supositorios, conteniendo cada uno 225 mg de Ingrediente Activo, se elaboran como sigue:

Ingrediente Activo	225 mg
Glicéridos de ácidos grasos saturados	2,000 mg
Total	2,225 mg

El Ingrediente Activo se hacen pasar a través de un tamiz U.S. con malla del Núm. 60 y se suspende en los glicéridos de ácidos grasos saturados reblandecidos previamente utilizando el mínimo calor necesario. La mezcla se vierte después en un molde para supositorios con una capacidad nominal de 2 g y se deja enfriar.

Formulación 7

Suspensiones, conteniendo cada una 50 mg de Ingrediente Activo por dosis de 5 ml, se elaboran como sigue:

Ingrediente Activo	50 mg
Sal de sodio de carboximetilcelulosa	50 mg
Jarabe	1,25 ml
Solución de ácido benzóico	0,10 ml
Aroma	q.v.
Color	q.v.
Agua purificada hasta un total de	5 ml

El Ingrediente Activo se hace pasar a través de un tamiz U.S. con malla del Núm. 45 y se mezcla con la sal de sodio de carboximetilcelulosa y el jarabe para formar una pasta suave. La solución de ácido benzóico, el aroma y el color se diluyen con una porción del agua y se añaden, con agitación. Después se añade suficiente agua para producir el volumen requerido.

Formulación 8

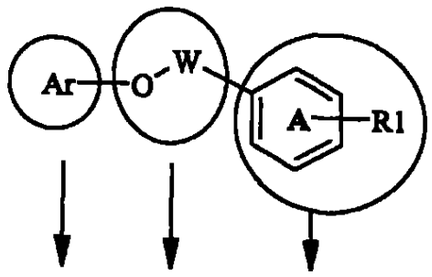
Se puede preparar una formulación intravenosa como sigue:

Ingrediente Activo	100 mg
Solución salina isotónica	1,000 ml

La solución de las sustancias anteriores se administra generalmente de manera intravenosa a un sujeto a un ritmo de 1 ml por minuto.

Los compuestos de la presente invención, en general, pueden ser preparados según los Esquemas de Reacción descritos más abajo. Cuando se describen diferentes aspectos de los presentes compuestos, los términos "Cola", "Conector" y "Cabeza" se utilizan según se ilustra su concepto más abajo en el Esquema de Reacción General.

Esquema de Reacción General



Cola-Conector-Cabeza

A) Cola-OH + **Y_1-Conector'-Cabeza** ⟶ Cola-Conector-Cabeza

B) Y_1-Conector'-Y_2 + Y_3-Cabeza ⟶ **Y_1-Conector'-Cabeza**

C) **Cola-Conector'-Y_2** + Y_3-Cabeza ⟶ Cola-Conector-Cabeza

D) Cola-OH + Y_1-Conector'-Y_2 ⟶ **Cola-Conector'-Y_2**

Y_1 = OH o LG (grupo eliminable)

Y_2 = Y_1 o H

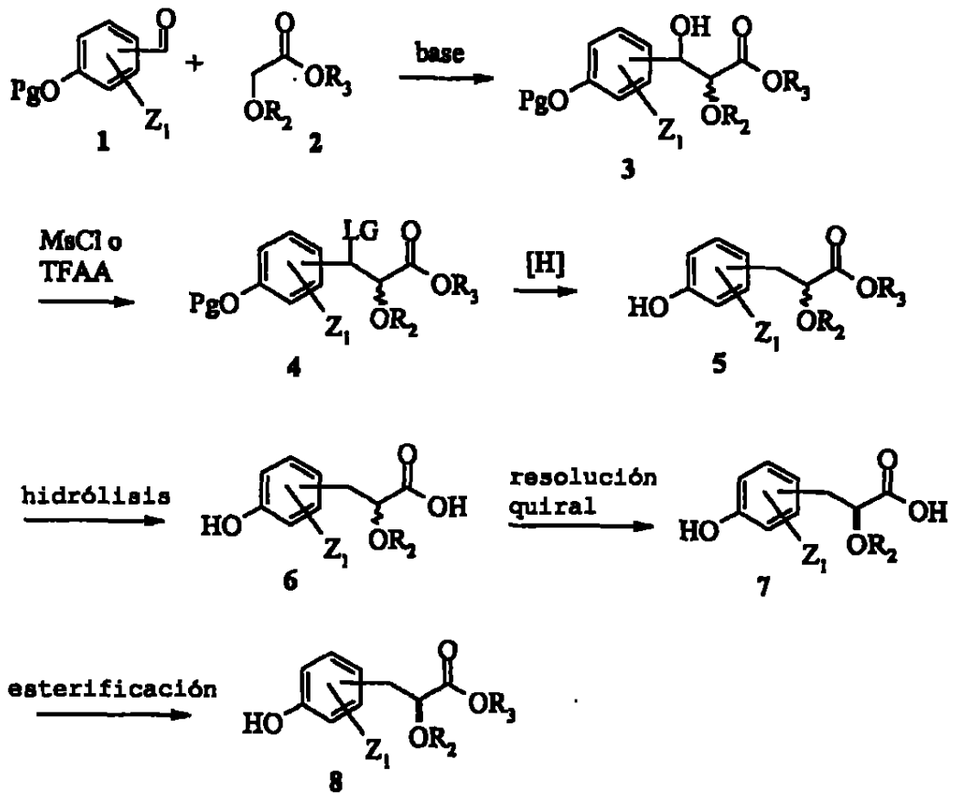
Y_3 = OH, OTf, o I

Conector' = Conector modificado para acomodar la sustitución con Y

Como se muestra en el Esquema de Reacción General, los compuestos de la presente invención pueden ser divididos en tres regiones denominadas Cola, Conector y Cabeza. Mediante un análisis retrosintético, las desconexiones de los enlaces claves se producen entre cada una de estas tres regiones. Según la ruta A, una porción de cola nucleófila se acopla a un compuesto electrófilo conector-porción de cabeza, que a su vez es derivado acoplando la región del conector a la porción de cabeza mediante la ruta B. Alternativamente, según la ruta C, la porción de cabeza puede ser acoplada al compuesto porción de cola-conector, derivado acoplando la porción de cola nucleófila al conector electrófilo

mediante la ruta D. Los siguientes esquemas de reacción ilustran las rutas sintéticas más detalladas para preparar los compuestos de la presente invención.

Esquema de Reacción A: Síntesis de la Porción de Cabeza



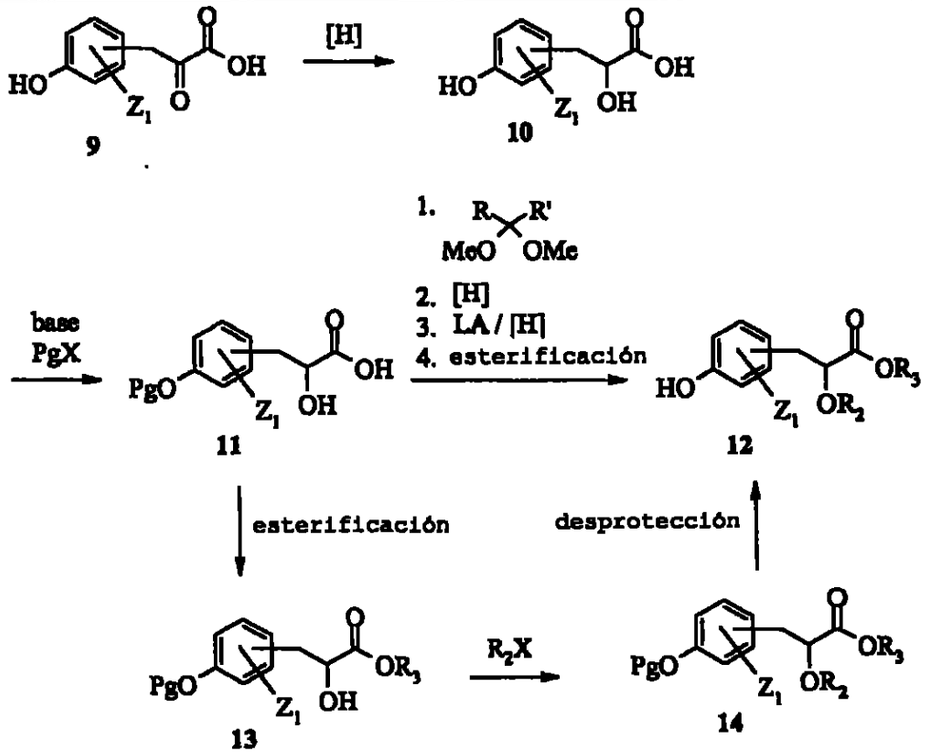
Z_1 = H, alifático, aralquilo, heteroalquileno, alcoxi, halo, haloalquilo

Pg = grupo protector, tal como CH_3 o $PhCH_2$

En el Esquema de Reacción A se muestra la preparación de una porción de cabeza general de los presentes compuestos. La condensación de un aldehído aromático (1) con un éster de ácido alfa-alcoxiacético (2) en presencia de una base adecuada, tal como bis(trimetilsilil)amiduro de litio produce el hidroxiéster (3). El grupo hidroxilo libre es convertido

en un grupo eliminable mediante tratamiento o bien con cloruro de metanosulfonilo o bien con anhídrido trifluoroacético. Cuando el alcohol aromático se protege como un éter bencílico (Pg es $PhCH_2$), la hidrogenolisis exhaustiva utilizando hidrógeno sobre Pd/C produce el compuesto (5). La hidrólisis del éster de (5) utilizando una solución acuosa del hidróxido proporciona el compuesto ácido (6), que puede ser resuelto en los enantiómeros correspondientes utilizando una amina quiral apropiada, tal como (-)-cinconidina. El ácido (7) puede ser esterificado utilizando el alcohol apropiado en condiciones ácidas, tal como etanol y ácido sulfúrico, o un haluro de alquilo en condiciones alcalinas, tal como carbonato de cesio en DMF para dar el compuesto (8).

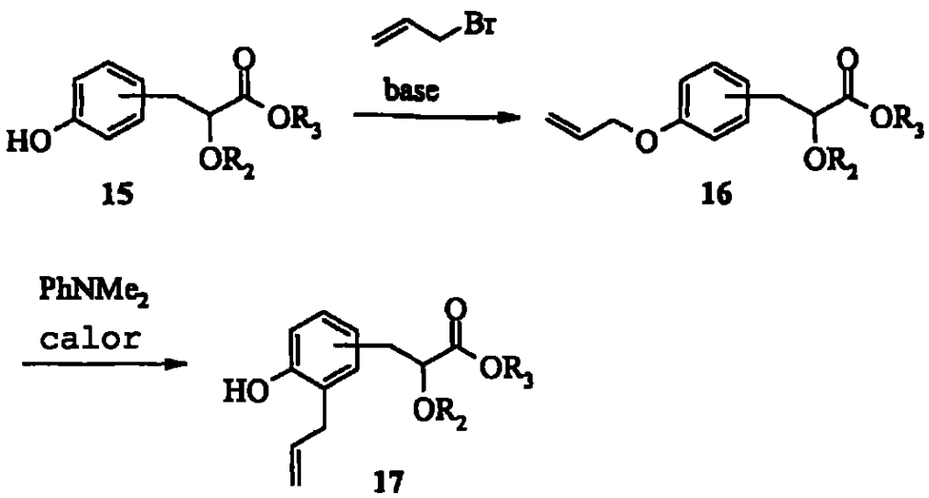
Esquema de Reacción B: Síntesis de la Porción de Cabeza



R, R' = H o alquilo

Una ruta alternativa para la porción de cabeza se muestra en el Esquema de Reacción B. La función cetona del cetoácido (**9**) es sometida a un agente reductor, tal como *B*-clorodiisopinocanfenilborano, para dar el hidroxiácido (**10**). El grupo hidroxilo fenólico se protege después con el grupo protector para dar el compuesto (**11**). El compuesto (**11**) que se ha hecho reaccionar con un dimetilcetal seguido de la escisión del éter del fenol da un intermedio dioxolanona, que proporciona un 2-alcoxiácido tras el tratamiento con un ácido de Lewis adecuado, tal como $TiCl_4$ y un reactivo reductor, tal como un trialquilsilano. La esterificación produce el 2-alcoxiéster (**12**). Alternativamente, el ácido (**11**) puede ser esterificado para producir el éster (**13**), que puede ser tratado con un electrófilo tal como un haluro de alquilo, y un aditivo tal como NaH u óxido de plata (I) para proporcionar el compuesto éter (**14**).

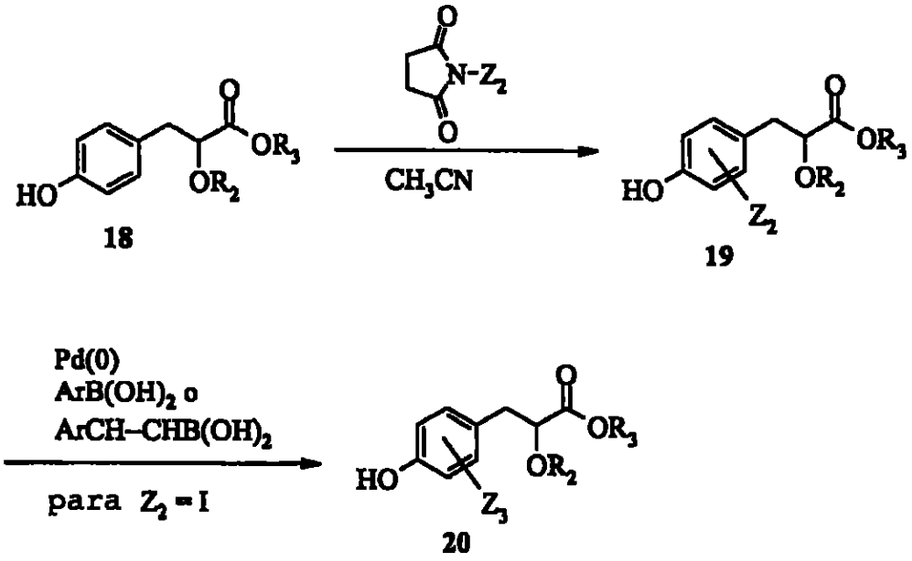
Esquema de Reacción C: Síntesis de la Porción de Cabeza



Como se muestra en el Esquema de Reacción C, se puede utilizar una transposición de Claisen para alquilar la porción de cabeza. El alcohol arílico (**15**) se trata con un bromuro de alilo en presencia de una base

adecuada, tal como NaH para dar el éter alílico (16). El calentamiento del compuesto éter (16) en dimetilanilina proporciona el compuesto de la porción de cabeza alilado (17).

Esquema de Reacción D: Síntesis de la Porción de Cabeza

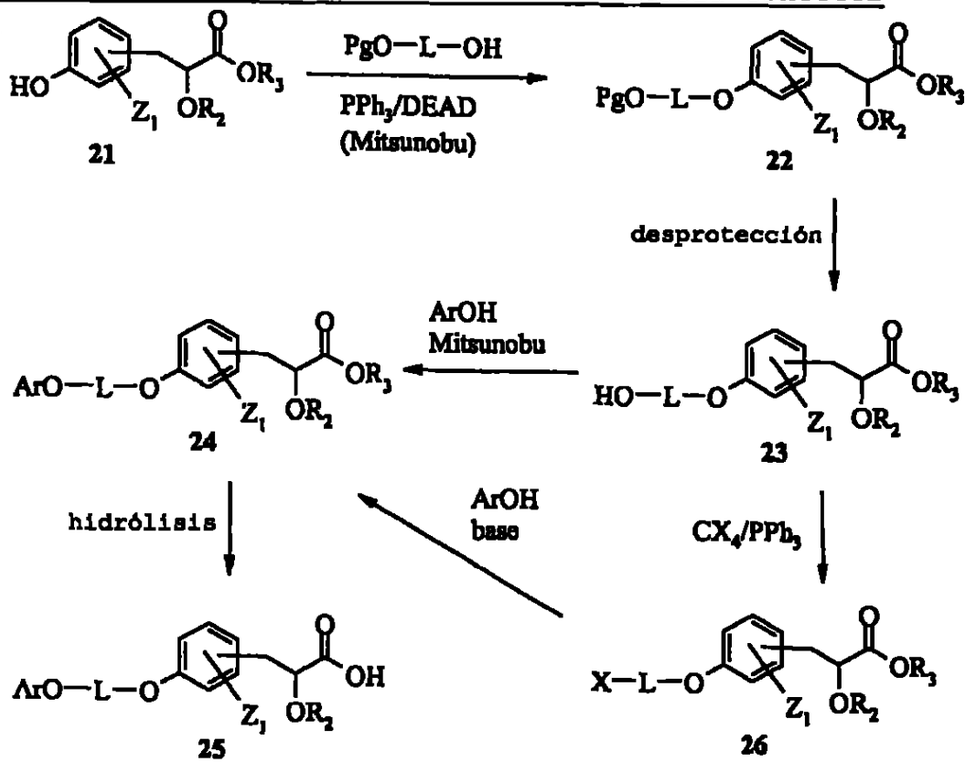


Z_2 = Cl, Br, I

Z_3 = Ar, -CH=CHAr

Como se muestra en el Esquema de Reacción D, se puede introducir una sustitución con halógeno en la porción de cabeza tratando el alcohol arílico (18) con una *N*-halosuccinimida en un disolvente orgánico para producir el compuesto (19). El compuesto (19) experimenta después una reacción de acoplamiento en presencia de un catalizador de paladio para producir los correspondientes compuestos de arilo y estirenilo (20).

Esquema de Reacción E: Síntesis de Cabeza-Conector

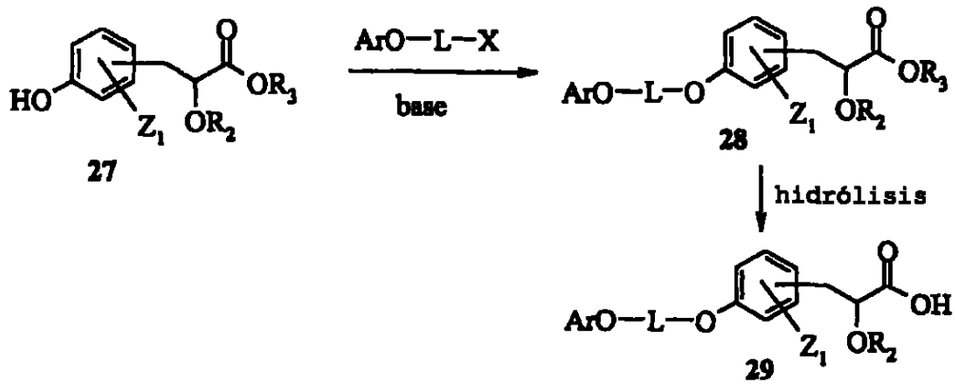


L = Conector: alifático, aralquilo, heteroalquileno
X = Cl, Br, I

En el Esquema de Reacción E se ilustra una síntesis de los presentes compuestos mediante la ruta conector-porción de cabeza general (Esquema General, rutas A y B). El compuesto de la porción de cabeza (21) es acoplado a un diol adecuadamente monoprotegido utilizando una trialquilfosfina o triarilfosfina y un derivado azodicarboxilato (condiciones de Mitsunobu) para producir el éter arílico (22). La desprotección de la función alcohol en el conector proporciona el compuesto (23), que después experimenta una reacción de acoplamiento de Mitsunobu con un alcohol arílico (ArOH) de la porción de la cola para dar el compuesto (24). La hidrólisis del éster adicional proporciona el compuesto ácido (25).

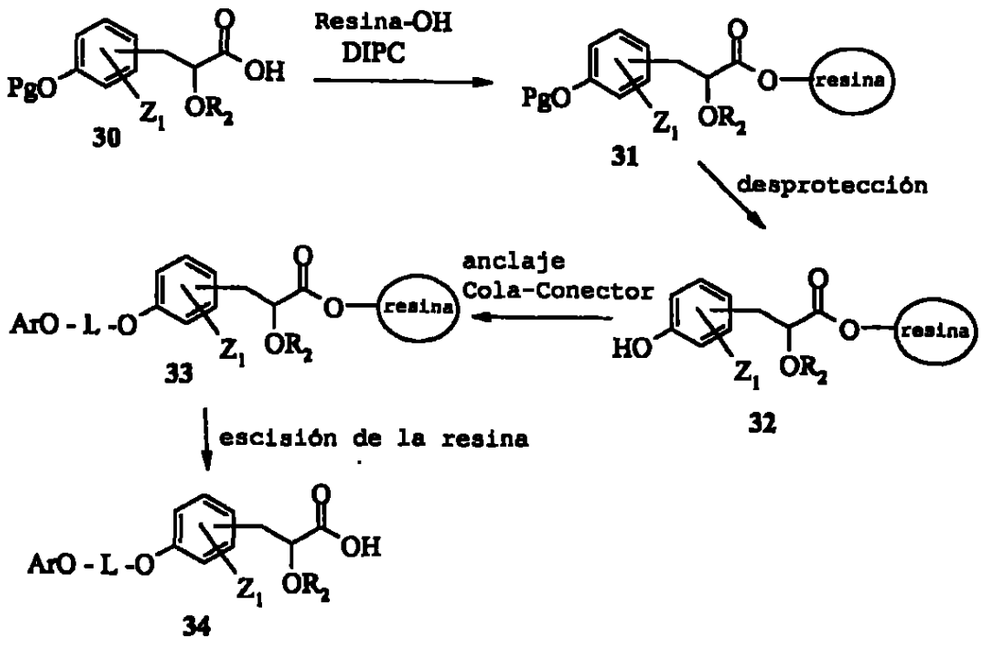
Alternativamente, el compuesto alcohol (**23**) puede ser convertido en el correspondiente haluro (**26**) utilizando un tetrahaluro de carbono y trifenilfosfina. El tratamiento del compuesto (**26**) con un alcohol arílico (ArOH) de la porción de cola en presencia de una base adecuada, tal como carbonato de cesio proporciona el compuesto (**24**), que después experimenta hidrólisis para dar el compuesto ácido (**25**).

Esquema de Reacción F: Síntesis de Cabeza-Conector



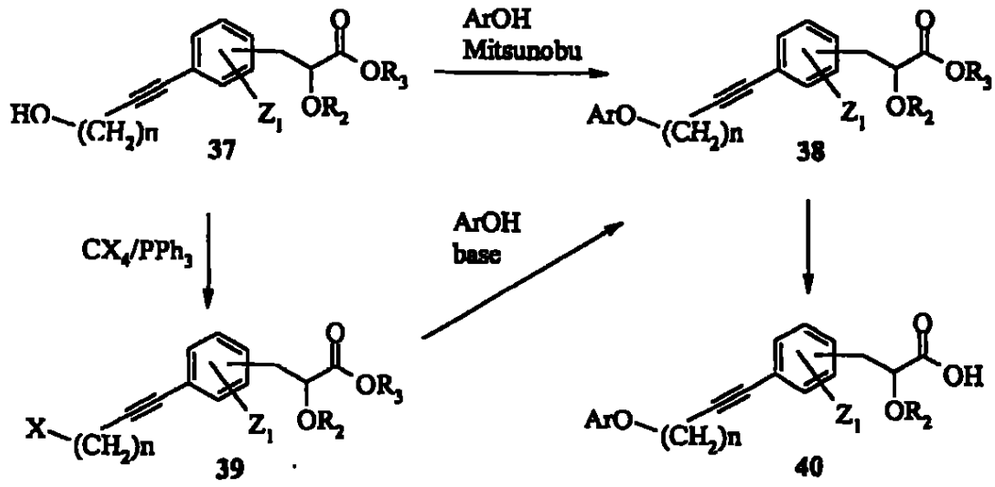
Como se muestra en el Esquema de Reacción F, el compuesto de la presente invención puede ser preparado mediante la ruta general porción de cola-conector a porción de cabeza (Esquema General, ruta C). El compuesto porción de cabeza del alcohol (**27**) se trata con un haluro porción de cola-conector (ArO-L-X) en presencia de una base adecuada, tal como carbonato de potasio o cesio para proporcionar el compuesto (**28**), que después experimenta hidrólisis del éster para producir el compuesto ácido (**29**).

Esquema de Reacción G: Síntesis en Fase Sólida



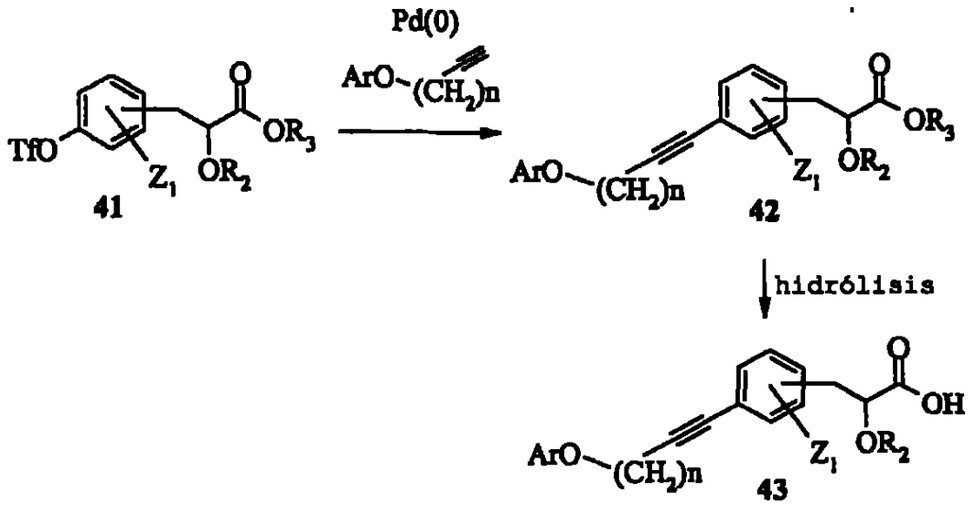
Como se muestra en el Esquema de Reacción G, la porción de cabeza puede ser anclada a una resina permitiendo una síntesis en fase sólida de los compuestos objetivo. El ácido carboxílico (**30**) es anclado a una resina adecuada, tal como la resina Wang, utilizando un reactivo de acoplamiento apropiado, tal como diisopropilcarbodiimida (DIPC). La escisión del grupo protector del alcohol arílico, tal como un éter t-butildimetilsilílico (t-$BuMe_2Si$) con el reactivo apropiado, tal como fluoruro de tetra-*n*-butilammonio da el alcohol arílico (**32**). Las regiones de la cola y del conector son introducidas como se describe en los Esquemas de Reacción E y F para producir el compuesto (**33**). El ácido carboxílico (**34**) puede ser liberado de la resina en las condiciones adecuadas, tal como con ácido trifluoroacético.

Esquema de Reacción H: Síntesis de Cabeza-Conector



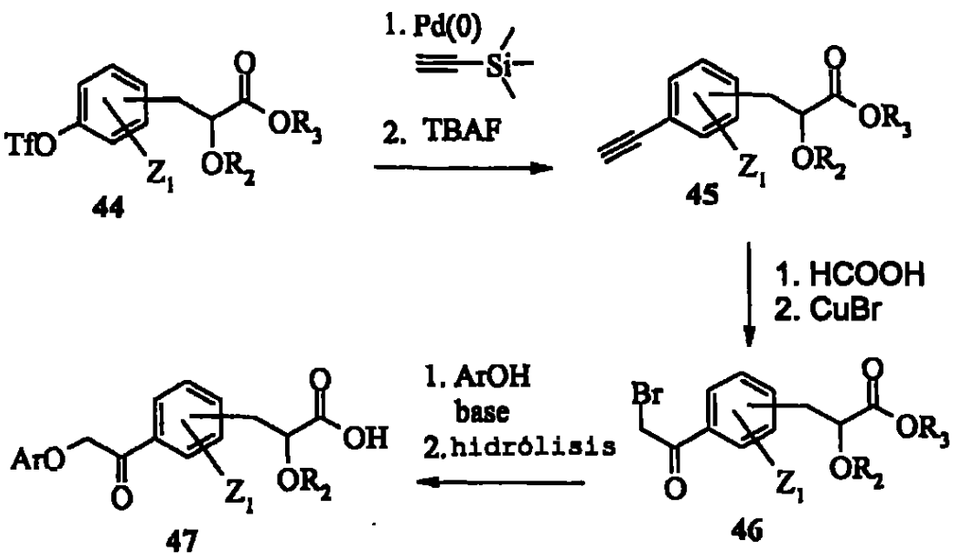
En el Esquema de Reacción H se ilustra una ruta sintética para preparar el compuesto de la presente invención que tiene conectores alquinílicos. El compuesto porción de cabeza (**35**) puede ser convertido en el correspondiente triflato de arilo (**36**) (o yoduro de arilo) utilizando fenil triflamida y una base apropiada, tal como NaH. La reacción de acoplamiento catalizada con paladio del compuesto (**36**) con un alcohol alquinílico da el intermedio conector-porción de cabeza (**37**). El acoplamiento del compuesto (**37**) con diferentes alcoholes de la porción de cola se puede lograr como se describe en el Esquema de Reacción E para proporcionar el compuesto (**38**), que después experimenta una hidrólisis para producir el compuesto ácido (**40**).

Esquema de Reacción I: Síntesis de Cabeza-Conector



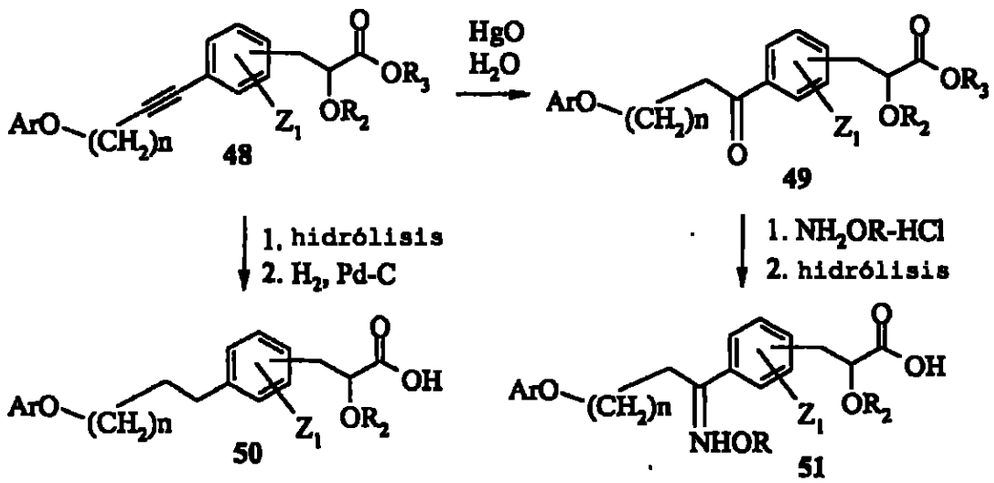
Como alternativa al Esquema de Reacción H, el compuesto porción de cabeza del triflato (**41**) se puede combinar con una porción de cola-conector para dar el compuesto acoplado (**42**) en una etapa como se muestra en el Esquema de Reacción I. El compuesto (**42**) experimenta después una hidrólisis para dar el compuesto ácido (**43**).

Esquema de Reacción J: Síntesis de Cabeza-Conector



Como se muestra en el Esquema de Reacción J, el compuesto porción de cabeza del triflato (**44**) puede ser acoplado a trimetilsililacetileno utilizando catálisis con paladio para dar la porción de cabeza acetilénica (**45**) tras la escisión mediada por fluoruro del grupo sililo. El alquino (**45**) es hidrolizado en condiciones ácidas acuosas a la metilcetona, que después es bromada con un agente adecuado, tal como bromuro de cobre (I) para dar la bromocetona (**46**). El tratamiento del compuesto (**46**) con un alcohol arílico de la porción de cola en presencia de una base adecuada, tal como carbonato de potasio y la hidrólisis con una base acuosa proporciona el compuesto ácido (**47**).

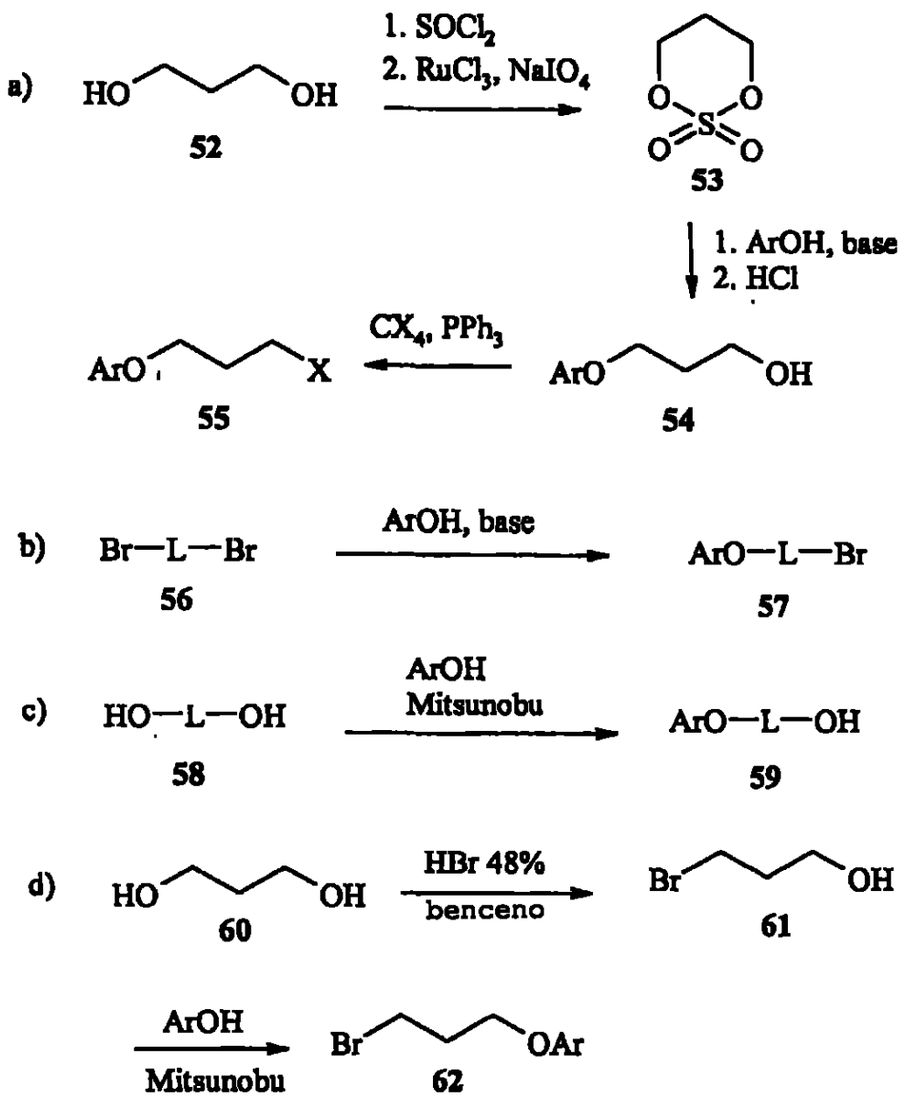
Esquema de Reacción K: Modificación Alquino-Conector



Como se muestra en el Esquema de Reacción K, se puede modificar una funcionalidad alquino en la región conectora de los presentes compuestos. El alquino se puede oxidar a cetona para dar el compuesto (**49**) utilizando un agente oxidante adecuado, tal como óxido mercúrico. La cetona puede ser modificada adicionalmente a las correspondientes oximas (**51**) mediante tratamiento con una alcoxiamina seguido de hidrólisis. Alternativamente, la funcionalidad alquinilo puede ser

reducida hasta el alquileno como en el compuesto (50) utilizando un agente reductor apropiado, tal como hidrógeno sobre paladio sobre carbono.

Esquema de Reacción L: Síntesis del Conector

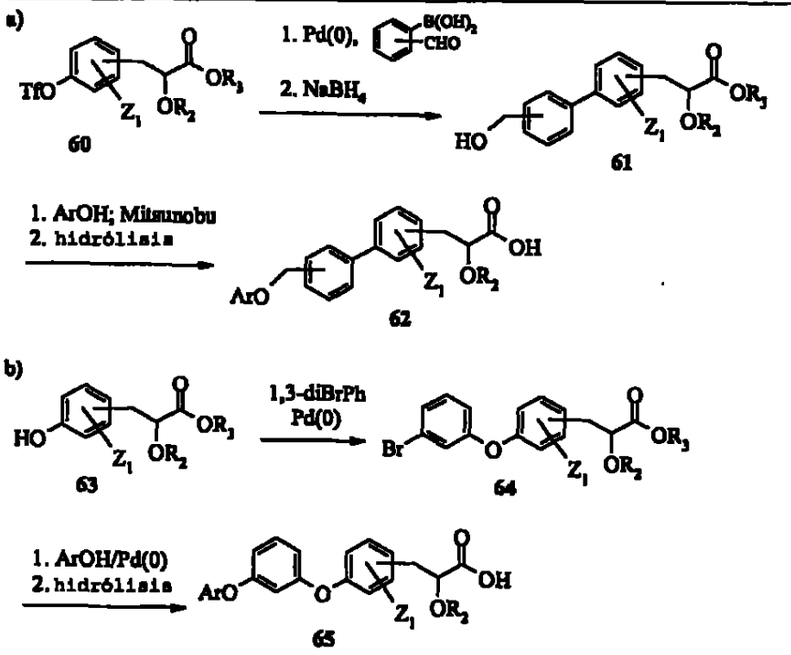


En el Esquema de Reacción L se ilustran diferentes rutas sintéticas para la región conectora. En la ruta (a), el 1,3-propanodiol (**52**) es convertido en el éster sulfonato cíclico (**53**) tras el tratamiento con cloruro de tionilo seguido de los reactivos de oxidación apropiados, tales como tricloruro de rutenio y peryodato de sodio. La apertura del anillo del intermedio (**53**) se efectúa tras el tratamiento con un alcohol de la porción de cola y una base adecuada tal como t-butóxido de potasio, seguido de un procedimiento de tratamiento ácido para dar el compuesto alcohol conector (**54**). El alcohol es convertido después en el haluro utilizando un reactivo apropiado, tal como un tetrahaluro de carbono y una triarilfosfina para proporcionar el compuesto (**55**). En la ruta (b), el compuesto dibromo-concector (**56**) se hace reaccionar con aproximadamente un equivalente en moles del alcohol arílico de la porción de cola en presencia de una base adecuada, tal como carbonato de potasio para dar el compuesto bromo-éter (**57**).

En la ruta (c), el compuesto del diol-conector (**58**) es acoplado a aproximadamente un equivalente en moles del alcohol de la porción de cola en las condiciones de reacción de Mitsunobu para dar el compuesto hidroxi-éter (**59**).

En la ruta (d), el 1,3-propanodiol (**60**) es convertido en el haluro (**61**), que después se hace reaccionar con el alcohol arílico de la porción de cabeza en las condiciones de reacción de Mitsunobu para dar el compuesto bromo-éter (**62**).

Esquema de Reacción M: Síntesis del Conector Modificado

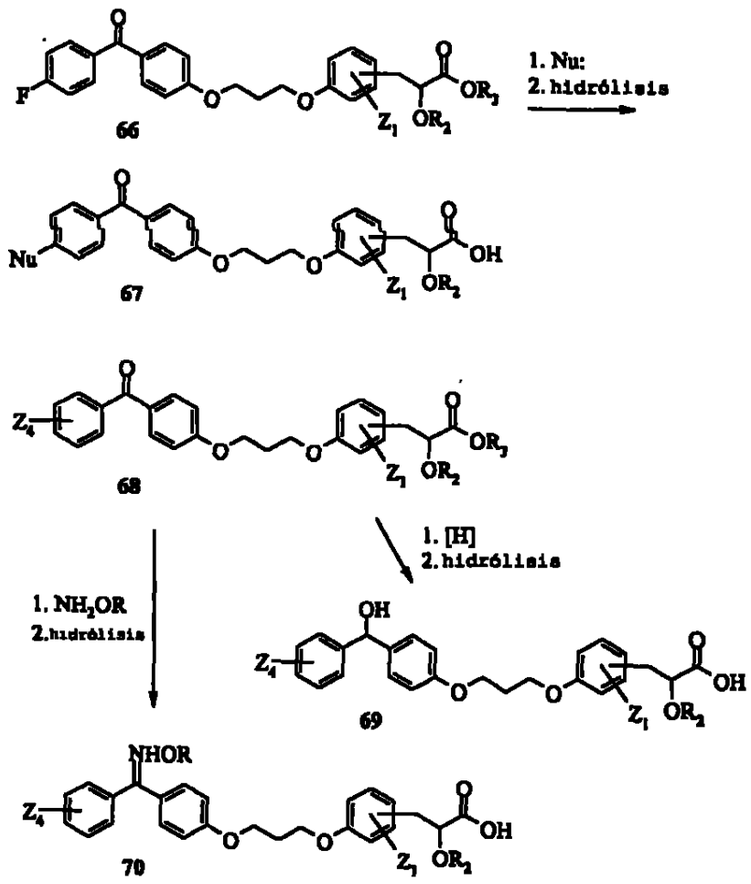


En el Esquema de Reacción M se ilustran las rutas sintéticas para los compuestos con conectores que contienen arilo. En la ruta (a), el compuesto triflato de la porción de cabeza (**60**) es acoplado a un ácido arilborónico en presencia de un catalizador de paladio. La reducción del intermedio aldehído utilizando un reactivo adecuado tal como borohidruro de sodio, proporciona el compuesto alcohol arílico (**61**). El compuesto (**61**) puede ser acoplado al alcohol arílico (ArOH) de la porción de cola en las condiciones de Mitsunobu seguido de hidrólisis del éster para dar el compuesto ácido (**62**).

En la ruta (b), el alcohol de la porción de cabeza (**63**) es acoplado a aproximadamente un equivalente en moles de dibromuro de arilo en presencia de un catalizador de paladio para dar el bromuro de arilo (**64**). El compuesto (**64**) es acoplado después de un modo similar al alcohol arílico (ArOH) de la porción de cola seguido

de hidrólisis del éster para proporcionar el compuesto ácido (**65**).

Esquema de Reacción N: Modificación de la porción de cola



66 **67** **68** **69** **70**

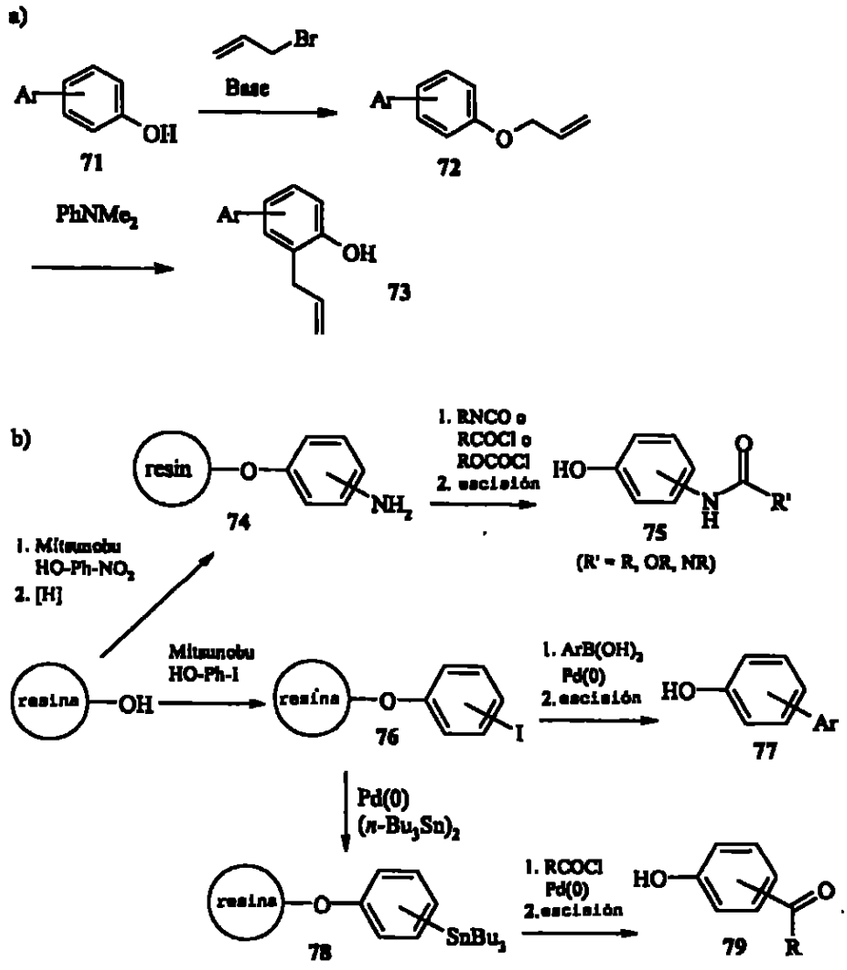
Nu: = nucleófilo
Z_4 = sustituyente Ar adecuado

En el Esquema de Reacción N se muestra una ruta sintética para modificar la región de la porción de cola de los presentes compuestos. El compuesto de *para*-fluorobenzofenona (**66**) se trata con un nucleófilo adecuado tal como aminas secundarias y alcóxidos, y después se somete a hidrólisis del éster para dar el compuesto ácido (**67**).

La funcionalidad carbonilo de la benzofenona (**68**)

puede ser reducida utilizando un reactivo apropiado, tal como hidrógeno sobre paladio sobre carbono para producir el correspondiente alcohol (**69**) tras la hidrólisis del éster. El radical cetona del compuesto (**68**) también puede ser modificado a las correspondientes oximas (**70**) mediante tratamiento con una alcoxiamina seguido de hidrólisis.

Esquema de Reacción O: Síntesis de la Porción de cola Modificada



En el Esquema de Reacción O se muestran las rutas sintéticas para preparar la región de la porción de cola de los compuestos. Se utiliza una transposición de Claisen para alquilar el anillo de arilo de la porción de

cola como se muestra en la ruta (a). El alcohol arílico (71) se trata con un bromuro de alilo en presencia de una base adecuada, tal como NaH para dar el éter alílico (72). El calentamiento de este éter en dimetilanilina da la porción de cabeza alilada (73).

Los métodos en fase sólida para sintetizar la porción de cola se describen en la ruta (b). El alcohol arílico es acoplado a una resina adecuada, tal como la resina de Wang en condiciones de Mitsunobu. El acoplamiento de la resina con una alcohol nitroarílico da un intermedio que es reducido en condiciones apropiadas, tal como cloruro de estaño (II) in DMF para dar la anilina (74). La funcionalidad nitrógeno se hace reaccionar adicionalmente con los reactivos adecuados, tales como los isocianatos, los cloruros de ácido o cloroformiatos para dar las correspondientes ureas, carbamatos y amidas, respectivamente. La escisión de la resina en condiciones ácidas, tales como ácido trifluoroacético en diclorometano proporciona la porción de cola sustituida con amino del compuesto alcohol arílico (75).

Alternativamente, el acoplamiento de la resina a un alcohol yodo arílico da el yoduro intermedio (76). El yoduro de arilo (76) puede ser acoplado después directamente a ácidos arilborónicos bajo catálisis con paladio para dar los alcoholes arílicos de la porción de cola biarílica (77) tras la escisión de la resina en condiciones ácidas. El yoduro intermedio (76) también puede ser convertido en el trialquilestannano (78) en presencia de un catalizador de paladio. El posterior acoplamiento catalizado por paladio a los reactivos adecuados, tal como cloruro de ácido y tras la escisión de la resina en condiciones ácidas proporciona el compuesto arílico de la porción de cola sustituido con carbonilo (79).

EJEMPLOS

Análisis instrumental

Se registraron los espectros de ^1H RMN en espectrómetros Varian 400 MHz o Bruker 200, 300 ó 500 MHz a temperatura ambiente. Los datos son dados como sigue: desviación química en ppm a partir de un patrón interno de tetrametilsilano en la escala δ, multiplicidad (a = amplio, s = singlete, d = doblete, t = triplete, c = cuartete, q = quintete y m = multiplete), integración y constante de acoplamiento. Se registraron las ^{13}C RMN en un espectrómetro Bruker 200, 300 ó 500 MHz a temperatura ambiente. Las desviaciones químicas son dadas en ppm de tetrametilsilano en la escala δ, empleando la resonancia del solvente como patrón interno ($CDCl_3$ a 77,0 ppm y DMSO-d_6 a 39,5 ppm). Los espectros de masas de alta resolución fueron obtenidos en espectrómetros VG ZAB 3F o VG 70 SE. Se llevó a cabo la cromatografía en capa fina analítica en placas de gel de sílice 60-F de 0,25 mm de EM Reagent. Se realizó la visualización con luz ultravioleta.

Procedimientos de síntesis estándar

Se usaron determinados procedimientos de síntesis estándar en la preparación de muchos de los compuestos ejemplificados de la presente invención. Estos procedimientos estándar eran:

Procedimiento estándar para el procedimiento de acoplamiento-hidrólisis de Mitsounobu (A): Se trató una solución de trifenilfosfina (1,42 mmol) en 10 ml de THF seco a 0°C con azodicarboxilato de dietilo (1,42 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido (2S)-3-[4-(3-hidroxiprop-1-inil)fenil]-2-mnetoxipropiónico (1,19 mmol)y 4-fenilfenol (1,42 mmol) en 5 ml de THF seco a la solución y se agitó la mezcla a temperatura ambiente durante la noche,. Se concentró la mezcla a sequedad a vacío y se purificó por cromatografía

en gel de sílice (gel de sílice, hexanos/acetato de etilo 10:1 a 3:1). Se combinaron las fracciones con Rf de 0,5 y 0,42 (hexanos/acetato de etilo 2:1) correspondientes a la pareja de compuesto y fenol de partida, respectivamente, y se concentraron a sequedad. Se disolvió la mezcla en 4 ml de NaOH 1 N y 12 ml de metanol y se agitó a temperatura ambiente hasta que la "TLC" (cromatografía en capa fina) indicó la desaparición del material de partida. Se eliminó el metanol a vacío y se diluyó la solución acuosa con 30 ml de salmuera y se lavó con éter dietílico (3 x 15 ml). Se acidificó la fase acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 ml). Se secó la capa orgánica ($MgSO_4$) y se concentró a vacío.

Procedimiento estándar para el procedimiento de acoplamiento de Mitsounobu (B): Se trató una solución de trifenilfosfina (1,42 mmol) en 10 ml de tolueno o THF a 0°C con DEAD o DIAD (1,42 mmol) y se agitó durante 20 min. Se añadió una solución del éster etílico del ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico (1,19 mmol) y el correspondiente alcohol (1,42 mmol) en 5 ml de tolueno o THF a la solución y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a sequedad a vacío y se purificó por cromatografía en columna de gel de sílice.

Procedimiento de hidrólisis estándar (C): Se disolvió éster etílico del ácido (2S)-3-{4-[4-(bifenil-4-iloxi)but-1-inil]fenil}-2-metoxipropiónico (0,5 g, 1,17 mmol) en 20 ml de NaOH 1N (o LiOH) y 60 ml de metanol y se agitó a temperatura ambiente hasta que la TLC indicó la desaparición del material de partida (aprox. 3 h). Se eliminó el metanol a vacío y se diluyó la solución acuosa con 20 ml de salmuera y se lavó con éter dietílico (3 x 60 ml). Se acidificó la fase orgánica con HCl 1N (hasta pH 1-2) y se extrajo con acetato de etilo (3 x 60 ml). Se secó la fase orgánica ($MgSO_4$) y se concentró a vacío.

Procedimiento estándar para la monoprotección de dioles (D): Se enfrió una solución del diol correspondiente (1 eq) en THF seco a 0°C. Se añadió hidruro de sodio (1 eq) y se agitó la mezcla de reacción durante 30 min a esa temperatura. Se añadió cloruro de *terc*-butildimetilsililo (0,95 eq) y se agitó la mezcla a temperatura ambiente durante la noche. Se añadió entonces una solución de Na_2CO_3 al 10% y se extrajo la mezcla con acetato de etilo. Se lavaron las capas orgánicas combinadas con salmuera, se secaron ($MgSO_4$) y se concentraron a vacío. Se purificó el residuo por cromatografía en gel de sílice.

Procedimiento estándar para la escisión de los alcoholes protegidos (E): Se trató una solución de mezcla del correspondiente alcohol protegido en THF con fluoruro de tetrabutilamonio (1M en THF) (2 eq). Se agitó la solución a temperatura ambiente hasta completarse la reacción por TLC, se apagó luego con agua y se extrajo con acetato de etilo, para obtener un producto bruto, que fue purificado por cromatografía en gel de sílice.

Procedimiento estándar (F): Se llevó a cabo al reacción en una jeringa de polipropileno equipada con una frita de polipropileno. Se suspendió una suspensión del fenol unido a resina (1 eq) en THF (0,02 M). Se añadió una solución de 1,3-propanodiol (5 eq) en THF, seguido de una mezcla de trifenilfosfina (5 eq) y azodicarboxilato de diisopropilo (5 eq) en THF. Se agitó la mezcla a temperatura ambiente durante la noche. Se eliminó el solvente de la reacción y se lavó la resina secuencialmente con THF (2x), CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), metanol y CH_2Cl_2 (3x). Se secó el polímero resultante a vacío durante la noche para producir el alcohol inmovilizado buscado.

Procedimiento estándar (G): Se llevó a cabo la reacción en una jeringa de polipropileno equipada con una frita de polipropileno. Se suspendió una suspensión del alcohol unido a la resina (1 eq) en una mezcla de THF/CH_2Cl_2 1:1

(0,015 M). Se añadió una solución de fenol (10 eq) disuelto en una mezcla de THF/CH_2Cl_2 1:1, seguido de una mezcla de trifenilfosfina (5 eq) y azodicarboxilato de diisopropilo (5 eq) en THF/CH_2Cl_2 1:1. Se agitó la mezcla a temperatura ambiente durante la noche y se eliminó el solvente de la reacción. Se lavó la resina secuencialmente con THF/CH_2Cl_2 1:1 (2x), THF (2x), CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), metanol y CH_2Cl_2 (2x). Se secó la resina a vacío durante 5 h y se trató con TFA al 50% en CH_2Cl_2. Se filtró y concentró la solución y se purificó el residuo por HPLC-cromatografía MS para producir el producto deseado.

Procedimiento estándar (H): Se añadió una solución de hidróxido de litio 1N en agua (0,245 ml) a una solución del éster (0,073 mmol) en tetrahidrofurano (1 ml) a temperatura ambiente. Se agitó la mezcla de reacción a temperatura ambiente durante 1,5 h, se diluyó con agua (10 ml) y se extrajo con acetato de etilo (3 X 10 ml). Se acidificó la capa acuosa con HCl 1N a pH 1 con éter dietílico (5 X 15 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío para producir el ácido correspondiente.

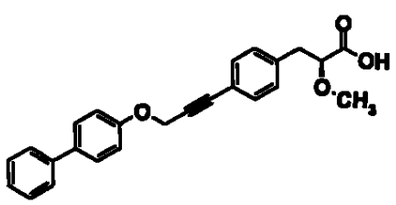
Procedimiento estándar (I): Se sometió a reflujo una mezcla del correspondiente fenol (1 eq) y del derivado bromoalquilo (1 eq) con K_2CO_3 (3 eq) en acetonitrilo durante la noche. Se enfrió la mezcla de reacción y se concentró a sequedad para obtener un producto bruto, que fue purificado por cromatografía en gel de sílice para obtener el producto.

Procedimiento estándar (J): Se trató una mezcla del correspondiente fenol (1,5 eq) y del derivado bromoalquilo (1 eq) en DMF con Cs_2CO_3 (3 eq). Se agitó la reacción a temperatura ambiente durante la noche y se filtró después. Se eliminó la DMF a vacío y se añadió metanol al residuo, tratando la mezcla con NaOH 1M (10 eq) y se agi-

tó durante 3 h. Se evaporó el solvente y se disolvieron las sales en agua. Se acidificó la fase acuosa a pH 2 y se extrajo con diclorometano, se filtró a través de una jeringa hidrofóbica y se purificó la capa orgánica por HPLC-MS.

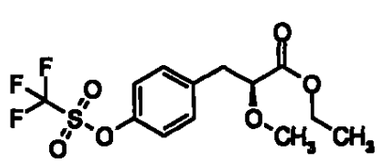
Ejemplo 1

Ácido (2*S*)-3-{4-[3-(bifenil-4-iloxi)-prop-1-inil]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2*S*)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico

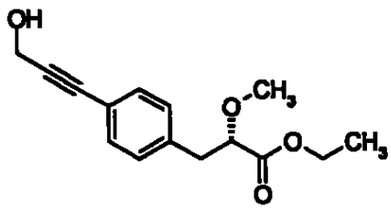


A una solución de éster etílico de ácido (*S*)-2-metoxi-3-hidroxifenilpropiónico (0,388 g, 1,73 mmol) in 40 ml de THF seco enfriado a -20°C se añadió hidruro de sodio (0,073 g, 1,82 mmol, dispersión en aceite al 60%). Se agitó la mezcla a -20°C durante 30 min. Se añadió triflimuro de fenilo (0,68 g, 1,90 mmol) en una porción y se agitó la solución a temperatura ambiente durante la noche y se concentró a sequedad a vacío. Se repartió el residuo entre agua (20 ml) y éter dietílico (20 ml). Se separaron las capas y se extrajo la solución acuosa con éter dietílico (2 x 20 ml). Se lavaron las capas orgánicas combinadas con Na_2CO_3 10% (6 x 20 ml) y salmuera (20 ml), se secó ($MgSO_4$) y se concentró a un aceite amarillo (574 mg,

97 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,34-7,16 (m, 4H), 4,18 (c, 2H, *J*=7,0), 3,93 (dd, 1H, *J*=7,3, 5,6), 3,36 (s, 3H), 3,05 (s, 1H), 3,02 (d, 1H, *J*=2,4 Hz), 1,22 (t, 3H, *J*=7,25).

Etapa B

Éster etílico del ácido (2*S*)-3-[4-(3-hidroxiprop-1-inil)-fenil]-2-metoxipropiónico



Se calentó una solución de éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxi-fenil)propiónico (0,861 g, 2,53 mmol), alcohol propargílico (0,88 ml, 15,18 mmol), trietilamina (1,41 ml, 10,12 mmol) y diclorobis(trifenilfosfina)paladio (II) en 10 ml de DMF seca a 90°C durante 2 horas. Se enfrió la mezcla de reacción a temperatura ambiente, se diluyó con 50 ml de agua y se extrajo con éter dietílico (3 x 30 ml). Se lavaron las capas orgánicas combinadas con HCl 0,5 N (2 x 20 ml) y salmuera (20 ml), se secó ($MgSO_4$) y se concentró. Se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 2:1, R_f 0,17) para obtener un aceite amarillo-marrón (0,211 g, 32%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,35 (d, 2H, *J*=8,1), 7,18 (d, 2H, *J*=8,1), 4,48 (s, 2H), 4,17 (c, 2H, *J*=7,3), 3,93 (dd, 1H, *J*=7,3, 5,7), 3,34 (s, 3H), 3,02 (s, 1H), 2,99 (d, 1H, *J*=2,2), 1,8 (s, 1H), 1,22 (t, 3H, *J*=7,3).

Etapa C

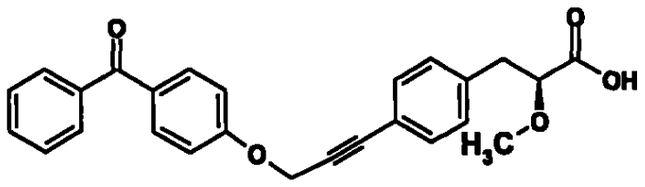
Ácido (2S)-3-{4-[3-(bifenil-4-iloxi)prop-1-inil]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-hidroxiprop-1-

inil)fenil]-2-metoxipropiónico usando el procedimiento de acoplamiento-hidrólisis estándar de Mitsunobu (Procedimiento estándar A) para producir un sólido blanco. P.f. 111-112°C. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,58-7,52 (m, 4H), 7,45-7,30 (m, 5H), 7,19 (d, 1H, *J*=8,3), 7,10 (dd, 3H, *J*=6,7, 1,9), 4,94 (s, 2H), 3,98 (dd, 1H, *J*=7,5, 4,3); 3,37 (s, 3H), 3,13 (dd, 1 H, J=14,5, 4,6), 2,99 (dd, 1H, *J*=14,2, 7,8). MS (ES) para $C_{25}H_{22}O_4$ $[M+NH_4]^+$: 404, $[M+Na]^+$:409.

Ejemplo 2

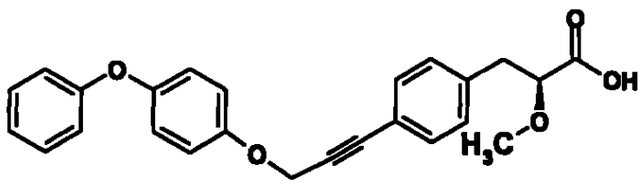
Ácido (2*S*)-3-{4-[3-(4-benzoilfenoxi)-prop-1-inil]fenil}-2-metoxipropiónico:



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-hidroxiprop-1-inil)fenil]-2-metoxipropiónico (del Ejemplo 1, Etapa B) mediante el procedimiento de acoplamiento-hidrólisis estándar de Mitsunobu (Procedimiento estándar A) para producir un sólido blanco oleoso. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,84-7,71 (m, 4H), 7,55-7,33 (m, 5H), 7,17 (d, 2H, *J*=8,0), 7,07 (d, 2 H, *J*=8,8), 4,96 (s, 2H), 3,96 (dd, 1H, *J*=7,7, 4,4), 3,35 (s, 3H), 3,11 (dd, 1H, *J*=14,3, 4,4), 2,97 (dd, 1H, *J*=14,3, 7,3).

Ejemplo 3

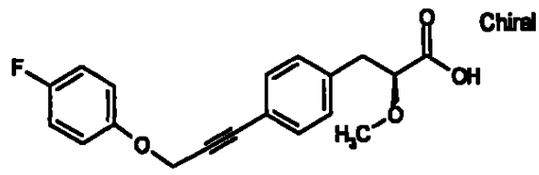
Ácido (2S)-2-metoxi-3-{4-[3-(4-fenoxifenoxi)prop-1-inil]-fenil}propiónico:



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-hidroxiprop-1-inil)fenil]-2-metoxipropiónico (del Ejemplo 1, Etapa B) mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento estándar A), para producir un sólido blanco oleoso (41 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,38-7,15 (m, 5H), 7,02-6,76 (m, 8H), 4,86 (s, 2H), 3,98 (dd, 1H, *J*=7,3, 4,4), 3,36 (s, 3H), 3,12 (dd, 1H, *J*=14,3, 4,4), 2,98 (dd, 1H, *J*=14,3, 7,3). MS (ES) para $C_{25}H_{22}O_5$ $[M+NH_4]^+$: 420,2, $[M+Na]^+$: 425,2.

Ejemplo 4

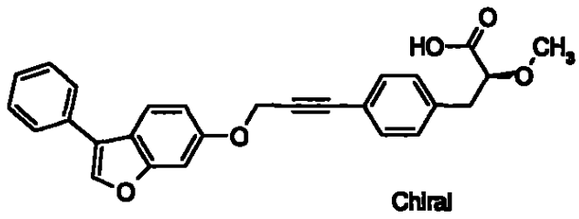
<u>Ácido (2S)-3-{4-[3-(4-fluorofenoxi)prop-1-inil]fenil}-2-metoxipropiónico</u>



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-hidroxiprop-1-inil)fenil]-2-metoxipropiónico (del Ejemplo 1, Etapa B) mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento estándar A), para producir un sólido blanco del compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,34 (d, J = 8,1 Hz, 2 H); 7,16 (d, J = 8,0 Hz, 2 H); 6,98-6,86 (m, 4 H); 4,84 (s, 2 H); 3,97 (dd, J = 7,7, 4,4 Hz, 1 H); 3,36 (s, 3 H); 3,12 (dd, J = 14,3, 4,4 Hz, 1 H); 2,98 (dd, J = 14,3, 7,3 Hz, 1 H). MS (ES) para $C_{19}H_{17}FO_4$ $[M+NH_4]^+$: 346, $[M+Na]^+$: 351.

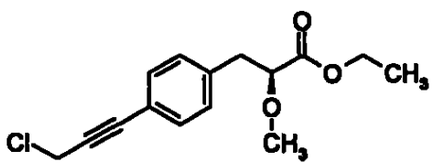
Ejemplo 5

Ácido (2S)-2-metoxi-3-{4-[3-(3-fenilbenzofuran-6-iloxi)-prop-1-inil]fenil}propiónico



Etapa A

Éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)-fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-hidroxiprop-1-inil)fenil]-2-metoxipropiónico (0,060 g, 0,23 mmol) (del Ejemplo 1, etapa B) en DMF seca (5 ml) y se trató con trietilamina (0,69 mmol) y cloruro de mesilo (0,46 mmol). Se agitó la mezcla de reacción durante la noche y se extrajo el producto bruto con H_2O/éter. Se secó y concentró la capa orgánica para obtener un producto, el cual fue purificado en sílice usando hexano/acetato de etilo (5/1), para obtener el compuesto del título en forma de aceite (0,020g, rendimiento del 30%). MS (ES) para $C_{15}H_{17}ClO_3$ $[M+H]^+$: 281,2

Etapa B

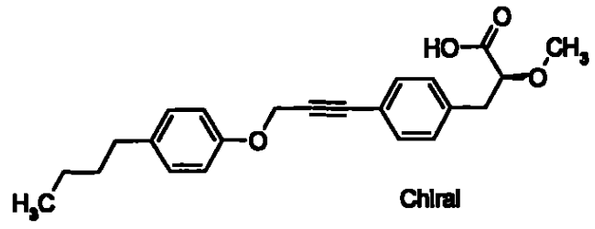
Ácido (2S)-2-metoxi-3-{4-[3-(3-fenilbenzofuran-6-iloxi)-prop-1-inil]fenil}propiónico

Se trató una solución de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxi-pro-

piónico de la etapa A (0,071 mmol, 1 eq) en 0,7 ml de DMF en un tubo de 16 x 100 mm tratado con 3-fenil-6-hidroxibenzofurano (0,078 mmol, 1,1 eq), carbonato de cesio (0,213 mmol, 3 eq) y NaI (0,071 mmol, 1 eq) y se agitó a temperatura ambiente durante la noche. Se filtraron los reactivos y se lavaron con DMF varias veces. Se evaporó el solvente a vacío y se reconstituyó el residuo en una mezcla de etanol (2 ml) y NaOH (1M) (1 ml) y se agitó a temperatura ambiente hasta que la reacción se hubo completado por HPLC-MS. Se añadió luego HCl (1M) (hasta pH=3) y se eliminó el solvente a vacío. Se reconstituyó el residuo en CH_2Cl_2/H_2O y se filtró a través de una jeringa hidrofóbica. Se separó la capa orgánica, se concentró y se purificó por HPLC-MS para obtener el compuesto del título. MS(ES) para $C_{27}H_{22}O_5$ $[M+H]^+$: 427,2.

Ejemplo 6

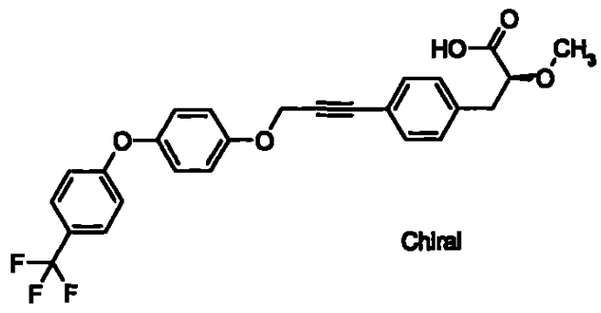
<u>Ácido (2S)-3-{4-[3-(4-butil-fenoxi)-prop-1-inil]-fenil}-2-metoxi-propiónico</u>



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloro-prop-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 4-*n*-butilfenol de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{23}H_{26}O_4$ $[M-H]^-$: 365,2

Ejemplo 7

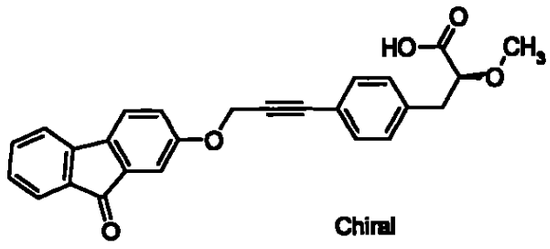
Ácido (2S)-2-metoxi-3-(4-(3-[4-(4-trifluorometilfenoxi)-fenoxi]prop-1-inil)fenil)propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 4-(4-trifluorometilfenoxi)fenol de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{26}H_{21}F_3O_5$ $[M-H]^-$: 469,2

Ejemplo 8

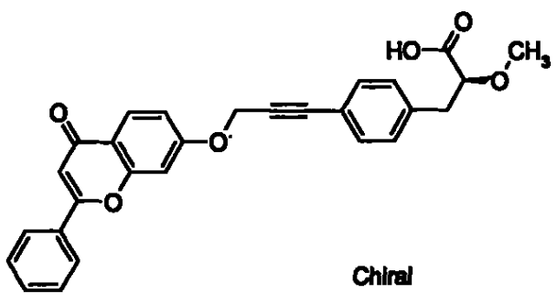
Ácido (2S)-2-metoxi-3-(4-[3-(9-oxo-9H-fluoren-2-iloxi)-prop-1-inil]fenil)propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 2-hidroxi-9-fluorenona de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{26}H_{20}O_5$ $[M-H]^-$: 411,2.

Ejemplo 9

Ácido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-7-iloxi)prop-1-inil]fenil}propiónico

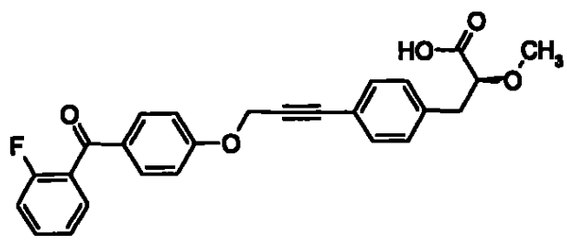


Chiral

Se preparó el compuesto del título a partir del éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 7-hidroxiflavona de un modo de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{28}H_{22}O_6[M+H]^+$: 455,2.

Ejemplo 10

Ácido (2S)-3-(4-{3-[4-(2-fluorobenzoil)fenoxi]prop-1-inil}fenil)-2-metoxipropiónico

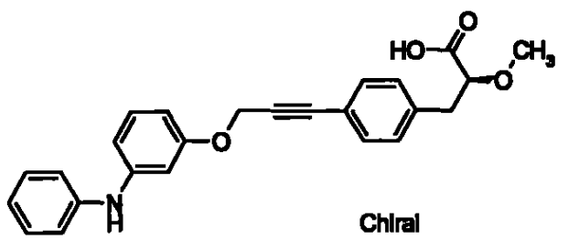


Chiral

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 2-fluoro-4-hidroxibenzofenona de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{26}H_{21}FO[M+H]^+$: 433,2.

Ejemplo 11

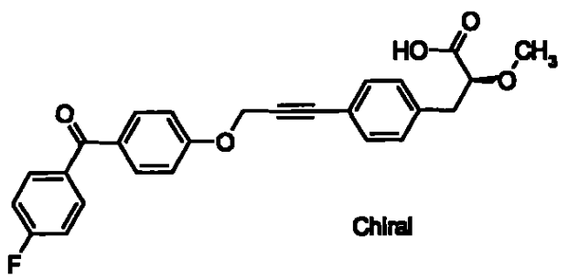
Ácido (2S)-2-metoxi-3-{4-[3-(3-fenilaminofenoxi)prop-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]2-metoxipropiónico del Ejemplo 5, etapa A, y 3-hidroxidifenilamina de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{25}H_{23}NO$ $[M+H]^+$: 402,2.

Ejemplo 12

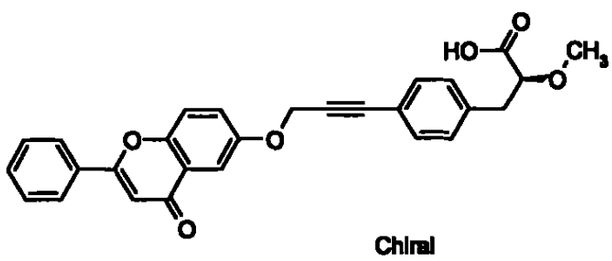
Ácido (2S)-3-(4-{3-[4-(4-fluorobenzoil)fenoxi]prop-1-inil}fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 4-fluoro-4'-hidroxibenzofenona de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{26}H_{21}FO[M+H]^+$: 433,2.

Ejemplo 13

Ácido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-6-iloxi)prop-1-inil]fenil}propiónico

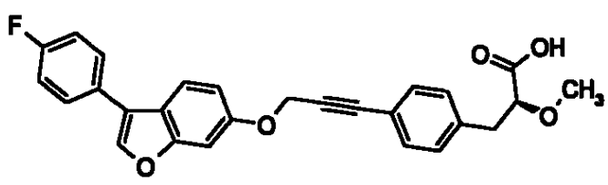


Chiral

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 6-hidroxiflavona de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{28}H_{22}O_6$[M+H]$^+$: 455,2.

Ejemplo 14

Ácido (2S)-3-(4-{3-[3-(4-fluorofenil)benzofuran-6-iloxi]-prop-1-inil}fenil)-2-metoxipropiónico

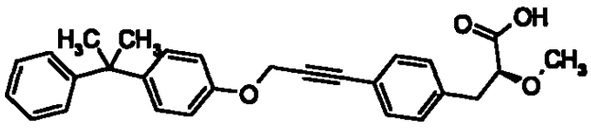


Chiral

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 6-hidroxi-3-(4-fluorofenil)benzofurano de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{27}H_{21}FO_5$ [M-H]$^-$: 443,2.

Ejemplo 15

Ácido (2S)-2-metoxi-3-(4-{3-[4-(1-metil-1-feniletil)-fenoxi]prop-1-inil}fenil)propiónico

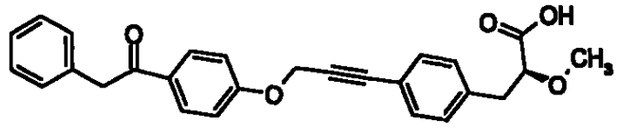


Chiral

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y 4-cumilfenol de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $[M+NH_4]^+$:446,2.

Ejemplo 16

Ácido (2S)-2-metoxi-3-{4-[3-(4-fenilacetilfenoxi)prop-1-inil]fenil}propiónico

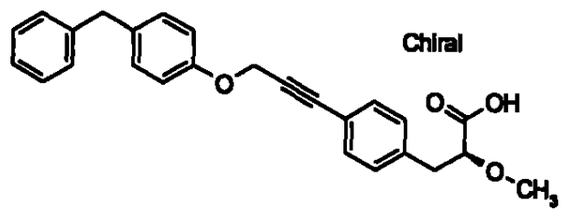


Chiral

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloroprop-1-inil)fenil]-2-metoxipropiónico del Ejemplo 5, etapa A, y bencil-4-hidroxifenilcetona de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{27}H_{24}O_5$ $[M-H]^-$: 427,2.

Ejemplo 17

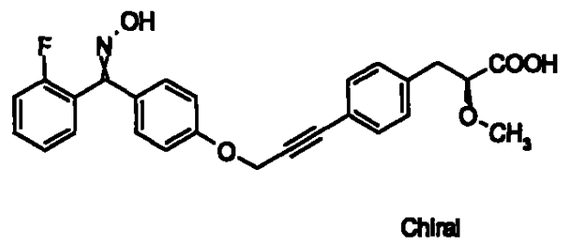
Ácido (2S)-3-{4-[3-(4-bencilfenoxi)prop-1-inil]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-cloro-prop-1-inil)-fenil]-2-metoxi-propiónico del Ejemplo 5, etapa A, y 4-hidroxidifenilmetano de un modo análogo al descrito para el Ejemplo 5, etapa B. MS(ES) para $C_{26}H_{24}O_4$ $[M-H]^-$: 399.

Ejemplo 18

Ácido (2S)-3-[4-(3-{4-[(2-fluorofenil)hidroxiimino-metil]fenoxi}prop-1-inil)fenil]-2-metoxipropiónico



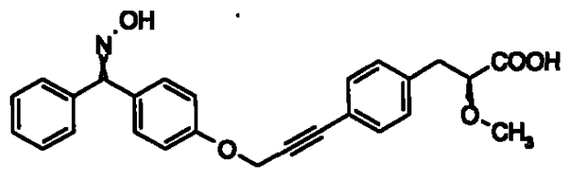
Chiral

Se mezcló ácido (2S)-3-(4-{3-[4-(2-fluoro-benzoil)fenoxi]prop-1-inil}fenil)-2-metoxipropiónico del Ejemplo 10, (0,01 mmol, 1 eq) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla de reacción durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5% al residuo a pH = 3. Se extrajo con acetato de etilo y se concentró, para obtener el producto del título como una mezcla de dos oximas. MS(ES) para $C_{26}H_{22}FNO_5$ $[M+H]^+$: 448,2, $[M-H]^-$:

446,2.

Ejemplo 19

Ácido (2S)-3-(4-{3-[4-(hidroxiiminofenilmetil)fenoxi]-prop-1-inil}fenil)-2-metoxipropiónico

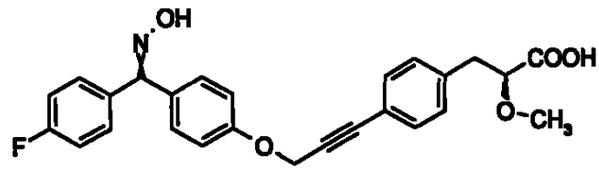


Chiral

Se mezcló ácido (2S)-3-{4-[3-(4-benzoil-fenoxi)prop-1-inil]fenil}-2-metoxipropiónico (0,01 mmol, 1 eq) (Ejemplo 2) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla de reacción durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5 % al residuo a pH = 3. Se extrajo con acetato de etilo y se concentró para obtener el producto del título como una mezcla de dos oximas. MS(ES) para $C_{26}H_{23}NO_5$ $[M+H]^+$: 430,2, $[M-H]^-$: 428,2.

Ejemplo 20

Ácido (2S)-3-[4-(3-{4-[(4-fluorofenil)hidroxiiminometil]-fenoxi}prop-1-inil)fenil]-2-metoxipropiónico



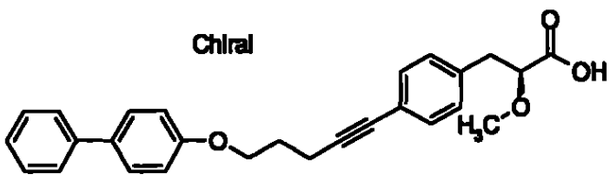
Chiral

Se mezcló ácido (2S)-3-(4-{3-[4-(4-fluoro-benzoil)fenoxi]prop-1-inil}fenil)-2-metoxipropiónico del Ejemplo 12 (0,01 mmol, 1 eq) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla de reacción durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5% al residuo a pH =

3. Se extrajo con acetato de etilo y se concentró para obtener el producto del título como una mezcla de dos oximas. MS(ES) para $C_{26}H_{22}FNO_5$ $[M+H]^+$: 448,2, $[M-H]^-$: 446,2.

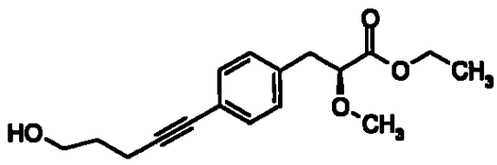
Ejemplo 21

Ácido (2S)-3-{4-[5-(bifenil-4-iloxi)pent-1-inil]fenil}-2-metoxipropiónico:



Etapa A

Éster etílico del ácido (2S)-3-[4-(5-hidroxipent-1-inil)-fenil]-2-metoxipropiónico



Se preparó este compuesto a partir de 4-pentin-1-ol siguiendo el procedimiento descrito en el Ejemplo 1, Etapa B. Aceite amarillo-marrón. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,33 (d, 2H, *J*=8,1), 7,16 (d, 2H, *J*=8,1), 4,17 (c, 2H, *J*=7,3), 3,92 (dd, 1H, *J*=7,3, 5,7), 3,80 (t, 2H, *J*=6,5), 3,34 (s, 3H), 3,01 (s, 1H), 2,98 (d, 1H, *J*=2,4), 2,68 (t, 2H, *J*=6,2), 1,86 (a, 1H), 1,23 (t, 3H, *J*=7,3).

Etapa B

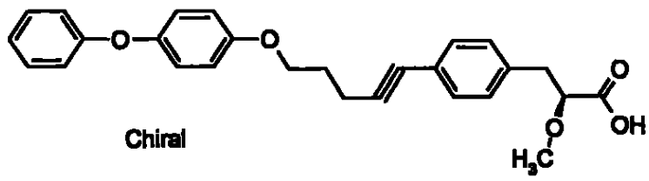
Ácido (2S)-3-{4-[5-(bifenil-4-iloxi)pent-1-inil]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(5-hidroxipent-1-

inil)fenil]-2-metoxipropiónico y 4-fenilfenol mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento estándar A) para producir un sólido oleoso blanco. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,56-7,28 (m, 9H), 7,15 (d, 2H, J=8,4), 6,98 (d, 2H, J=8,8), 4,15 (t, 2H, J=6,2), 3,97 (dd, 1H, J=7,7, 4,4), 3,36 (s, 3H), 3,11 (dd, 1H, J=14,3, 4,4), 2,97 (dd, 1H, J=14,3, 7,7), 2,62 (t, 2H, J=7,0), 2,08 (q, 2H, J=6,6).

Ejemplo 22

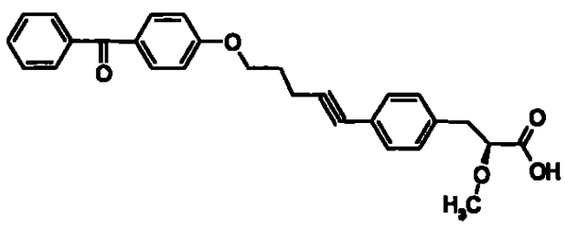
Ácido (2S)-2-metoxi-3-{4-[5-(4-fenoxifenoxi)pent-1-inil]-fenil}propiónico:



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico (Ejemplo 21, Etapa A) y 4-fenoxifenol mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento Estándar A) para producir un sólido blanco oleoso. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,26-7,19 (m, 4H), 7,07 (d, 2H, J=8,3), 6,98-6,78 (m, 7H), 4,01 (t, 2H, J=5,9), 3,91 (dd, 1H, J=7,3, 4,3), 3,30 (s, 3H), 3,05 (dd, 1H, J=14,2, 4,3), 2,90 (dd, 1H, J=14,2, 7,5), 2,54 (t, 2H, J=6,7), 1,98 (q, 2H, J=6,4). MS (ES para $C_{27}H_{26}O_5$ $[M+NH_4]^+$: 448, $[M+Na]^+$: 453.

Ejemplo 23

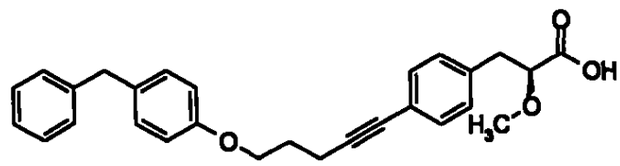
Ácido (2S)-3-{4-[5-(4-benzoilfenoxi)-pent-1-inil]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico (Ejemplo 21, Etapa A) y 4-hidroxibenzofenona mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento Estándar A) para producir un sólido oleoso blanco. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,82-7,70 (m, 3H), 7,54-7,43 (m, 4H), 7,31-7,23 (m, 2H), 7,14 (d, 2H, J=8,1), 6,95 (d, 2H, J=8,8), 4,19 (d, 2H, J=5,9), 3,96 (dd, 1H, J=7,7, 4,4), 3,34 (s, 3H), 3,09 (dd, 1H, J=14,3, 4,4), 2,95 (dd, 1H, J=14,3, 7,7), 2,61 (t, 2H, J=7,0), 2,08 (c, 2H, J=6,6).

Ejemplo 24

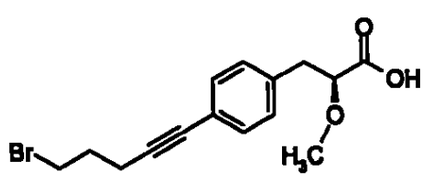
Ácido (2S)-3-{4-[5-(4-bencilfenoxi)pent-1-inil]fenil}-2-metoxipropiónico



Chiral

Etapa A

Éster etílico del ácido 3-[4-(5-bromopent-1-inil)fenil]-2-metoxipropiónico



Chiral

A una solución de éster etílico del ácido (2S)-3-[4-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico a partir del Ejemplo 21, Etapa A (0,17 mmol, 1 eq) en diclorometano (5 ml) y CBr_4 (0,34 mmol, 2 eq) a 0°C, se añadió Ph_3P (0,34 mmol, 2 eq) por porciones y se agitó la mezcla de reacción durante 1 hora, se eliminó el solvente a vacío y se purificó el residuo por cromatografía instantánea usando hexano/acetato de etilo como eluyente (6:1), para obtener el producto del título con un rendimiento del 85%.

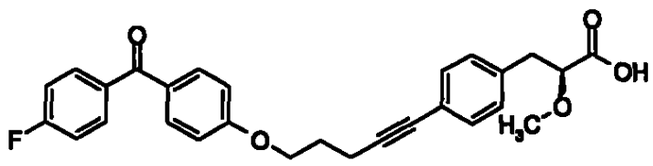
Etapa B

Ácido (2S)-3-{4-[5-(4-bencilfenoxi)pent-1-inil]fenil}-2-metoxipropiónico

Se trató una solución de éster etílico del ácido 3-[4-(5-bromopent-1-inil)fenil]-2-metoxipropiónico de la Etapa A (0,1 mmol, 1 eq) en 0,7 ml de DMF en un tubo de 16 x 100 mm con 4-hidroxidifenilmetano (0,11 mmol, 1,1 eq) y carbonato de cesio (0,3 mmol, 3 eq) y se agitó a temperatura ambiente durante la noche. Se filtraron los reactivos y se lavaron con DMF varias veces. Se evaporó el solvente a vacío y se reconstituyó el residuo en una mezcla de etanol (2 ml) y NaOH (1M) (1 ml) y se agitó a temperatura ambiente hasta que la reacción se hubo completado por HPLC-MS. Se añadió entonces HCl (1M) (hasta pH=3) y se eliminó el solvente a vacío. Se reconstituyó el residuo en CH_2Cl_2/H_2O y se filtró a través de una jeringa hidrofóbica. Se separó la capa orgánica, se concentró y se purificó por HPLC-MS, para obtener el compuesto del título. MS(ES) para $C_{28}H_{28}O_4[M+NH_4]^+$: 446,2.

Ejemplo 25

Ácido (2S)-3-(4-{5-[4-(4-fluorobenzoil)fenoxi]pent-1-inil}fenil)-2-metoxipropiónico

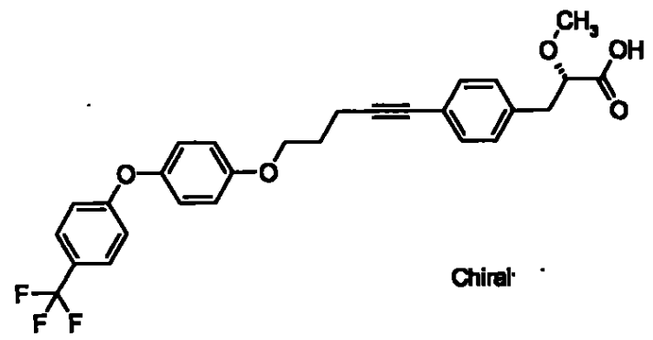


Chiral

Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 4-fluoro-4-hidroxibenzofenona de una forma análoga a la descrita para el Ejemplo 24, Etapa B. MS(ES) para $C_{28}H_{25}F_3O_5[M+H]^+$: 461,2.

Ejemplo 26

Ácido (2S)-2-metoxi-3-{4-{5-[4-(4-trifluorometilfenoxi)-fenoxi]pent-1-inil}fenil}propiónico

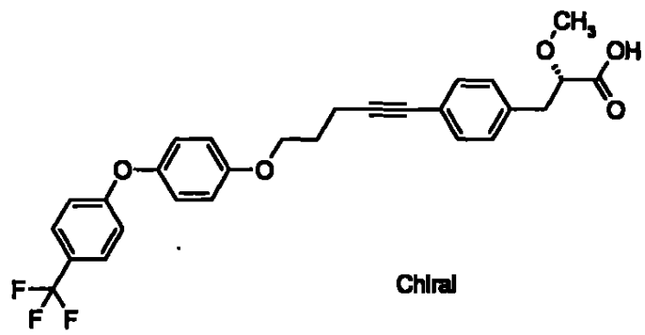


Chiral

Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 4-(4-trifluorometilfenoxi)fenol de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{28}H_{25}F_3O_5[M+NH_4]^+$: 516,2.

Ejemplo 27

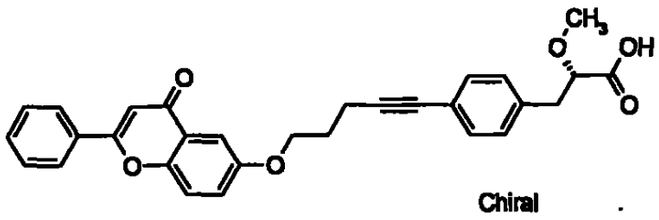
Ácido (2S)-2-metoxi-3-{4-[5-(4-oxo-2-fenil-4H-cromen-7-iloxi)pent-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 7-hidroxiflavona de una forma análoga a la descrita para el Ejemplo 24, Etapa B. MS(ES) para $C_{30}H_{26}O_6$[M+H]$^+$:483,2.

Ejemplo 28

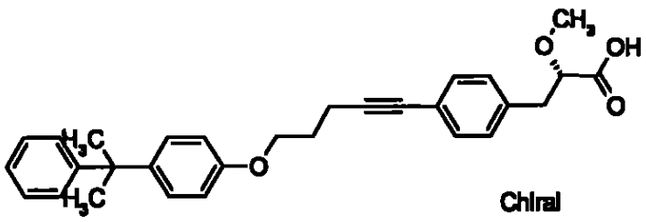
Ácido (2S)-2-metoxi-3-{4-[5-(4-oxo-2-fenil-4H-cromen-6-iloxi)pent-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 6-hidroxiflavona de una forma análoga a la descrita para el Ejemplo 24, Etapa B. MS(ES) para $C_{30}H_{26}O_6$[M+H]$^+$:483,2

Ejemplo 29

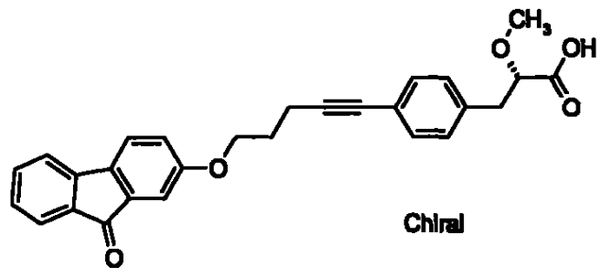
Ácido (2S)-2-metoxi-3-(4-{5-[4-(1-metil-1-feniletil)-fenoxi]pent-1-inil}fenil)propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 4-cumilfenol de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{30}H_{32}O_4$ $[M+NH_4]^+$:474,3

Ejemplo 30

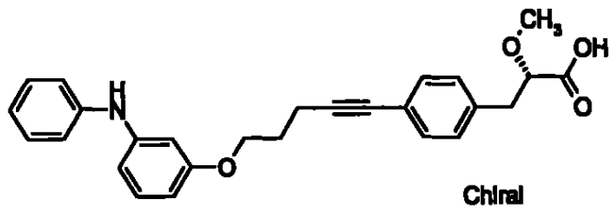
Ácido (2S)-2-metoxi-3-{4-[5-(9-oxo-9H-fluoren-2-iloxi)-pent-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido. 3-[4-(5-bromo-pent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 2-hidroxi-9-fluorenona de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{28}H_{24}O_5[M+H]^+$:441,2.

Ejemplo 31

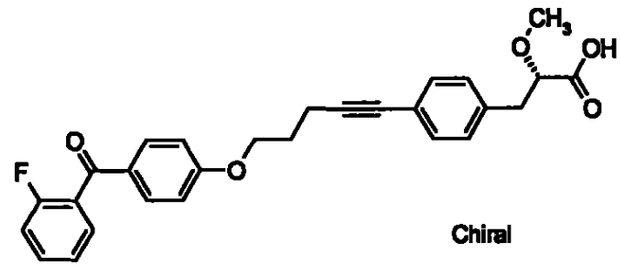
Ácido (2S)-2-metoxi-3-{4-[5-(3-fenilaminofenoxi)pent-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 3-hidroxidifenilamina de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{27}H_{27}NO_4[M+H]^+$:430,2.

Ejemplo 32

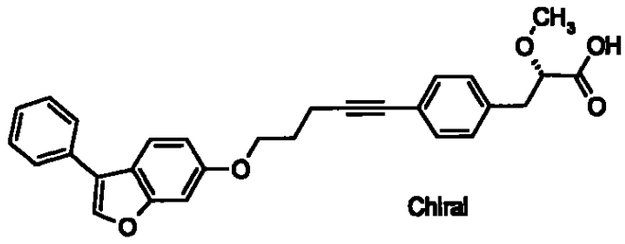
Ácido (2S)-3-{4-[5-[4-(2-fluorobenzoil)fenoxi]pent-1-inil}fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 2-fluoro-4'-hidroxibenzofenona de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{28}H_{25}FO_5[M+H]^+$:461,2.

Ejemplo 33

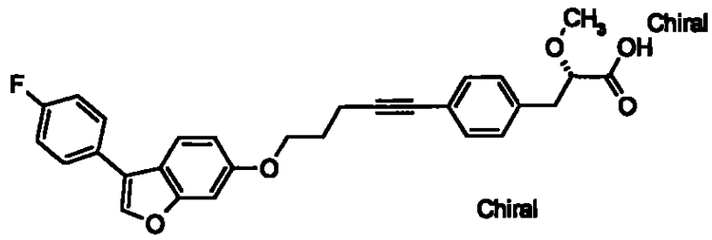
Ácido (2S)-2-metoxi-3-{4-[5-(3-fenilbenzofuran-6-iloxi)-pent-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 6-hidroxi-4-fenilbenzofenona de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{29}H_{26}O_5[M+H]^+$:455,2.

Ejemplo 34

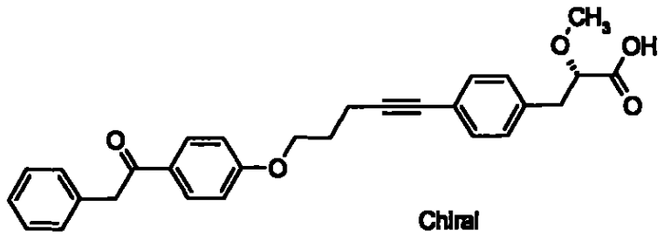
Ácido (2S)-3-(4-{5-[3-(4-fluorofenil)benzofuran-6-iloxi]-pent-1-inil}fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 3-(4'-fluorofenil)-6-hidroxibenzofenona de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{29}H_{25}FO_5[M+H]^+$:473,2.

Ejemplo 35

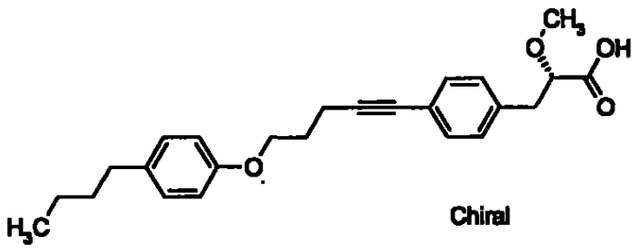
Ácido (2S)-2-metoxi-3-{4-[5-(4-fenilacetilfenoxi)pent-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y bencil-4-hidroxifenilcetona de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{29}H_{28}O_5[M-H]^-$: 455,2.

Ejemplo 36

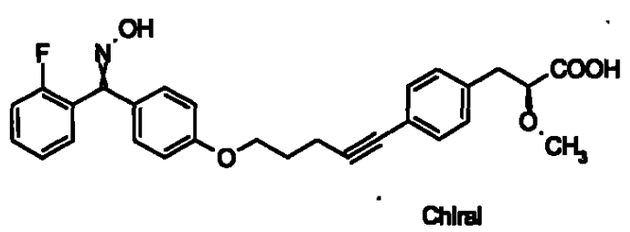
Ácido (2S)-3-{4-[5-(4-butilfenoxi)pent-1-inil]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(5-bromopent-1-inil)-fenil]-2-metoxipropiónico del Ejemplo 24, Etapa A, y 4-N-butilfenol de un modo análogo al descrito para el Ejemplo 24, Etapa B. MS(ES) para $C_{25}H_{30}O_4$ $[M-H]^-$:393,2.

Ejemplo 37

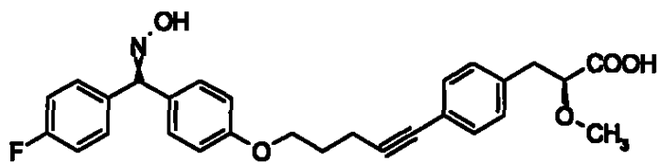
Ácido (2S)-3-[4-(5-{4-[(2-fluorofenil)hidroxiimino-metil]fenoxi}pent-1-inil)fenil]-2-metoxipropiónico



Se mezcló ácido (2S)-3-(4-{5-[4-(2-fluoro-benzoil)fenoxi]pent-1-inil}fenil)-2-metoxipropiónico del Ejemplo 32 (1 eq) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla de reacción durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5% al residuo a pH=3. Se extrajo con acetato de etilo y se concentró, para obtener el producto del título como una mezcla de dos oximas. MS(ES) para $C_{28}H_{26}FNO_5$ $[M+H]^+$: 476,2, $[M-H]^-$: 474,2.

Ejemplo 38

Ácido (2S)-3-[4-(5-{4-[(4-fluorofenil)hidroxiimino-metil]fenoxi}pent-1-inil)fenil]-2-metoxipropiónico

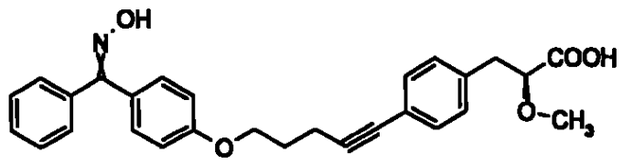


Chiral

Se mezcló ácido (2S)-3-(4-{5-[4-(4-fluoroben-zoil)fenoxi]pent-1-inil}fenil)-2-metoxipropiónico del Ejemplo 25 (1 eq) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5% al residuo a pH=3. Se extrajo con acetato de etilo y se concentró, para obtener el producto del título como una mezcla de dos oximas. MS(ES) para $C_{28}H_{26}FNO_5$ $[M+H]^+$: 476,2, $[M-H]^-$: 474,2.

Ejemplo 39

Ácido (2S)-3-(4-{5-[4-(hidroxiiminofenilmetil)fenoxi]-pent-1-inil}fenil)-2-metoxipropiónico



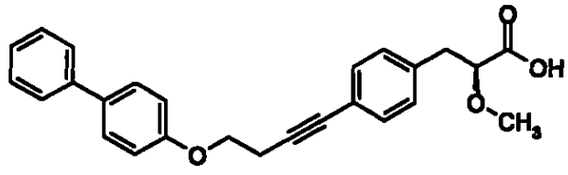
Chiral

Se mezcló ácido (2S)-3-{4-[5-(4-benzoil-fenoxi)pent-1-inil]fenil}-2-metoxipropiónico del Ejemplo 23 (1 eq) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla de reacción durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5% al residuo a pH=3. Se extrajo con acetato de etilo y se concentró, para obtener el producto

del título como una mezcla de dos oximas. MS(ES) para $C_{28}H_{27}NO_5$ $[M+H]^+$: 458,2.

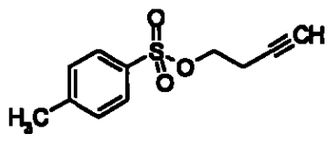
Ejemplo 40

Ácido (2S)-3-{4-[4-(bifenil-4-iloxi)but-1-inil]fenil}-2-metoxipropiónico:



Etapa A

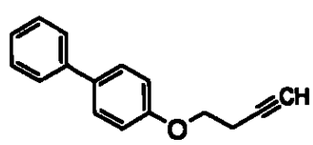
Éster but-3-inílico de ácido toluen-4-sulfónico



Se agitó una solución de 3-butin-1-ol (1 ml, 13,31 mmol), cloruro de p-toluensulfonilo (2,519 g, 13,21 mmol), trietilamina (2,03 ml, 14,53 mmol) y 4-dimetilaminopiridina (0,081 g, 0,66 mmol) en 20 ml de diclorometano a temperatura ambiente durante la noche. Se diluyó la solución con diclorometano (20 ml), se lavó con HCl 0,5N (40 ml) y salmuera (40 ml), se secó ($MgSO_4$) y se concentró para producir un aceite (2,82 g, 95 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,80 (d, 2H, *J*=8,3), 7,35 (d, 2H, *J*=8,1), 4,10 (t, 2H, *J*=7,0), 2,55 (dt, 2H, *J*=2,7, 7,0), 2,45 (s, 3H), 1,97 (t, 1H, *J*=2,7).

Etapa B

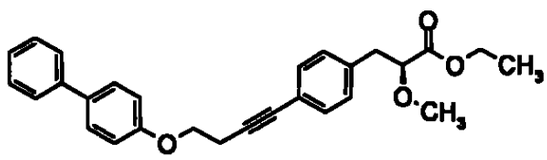
4-But-3-iniloxibifenilo



Se agitó una solución de 4-fenilfenol (0,774 g, 4,55 mmol) y *terc*-butóxido de potasio (0,51 g, 4,55 mmol) en tolueno (20 ml) durante 1 h a temperatura ambiente. Se añadieron yoduro de sodio (0,068 g, 0,45 mmol) y ácido éster but-3-inílico de ácido toluen-4-sulfónico (1,02 g, 4,55 mmol) y se calentó la mezcla a reflujo durante 24 horas. Se enfrió la mezcla a temperatura ambiente, se diluyó con éter dietílico (20 ml) y se lavó con agua (2 x 20 ml). Se secó la capa orgánica ($MgSO_4$) y se concentró a vacío. Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 3:1, R_f 0,57), para obtener un aceite (140 mg, 14%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,50 (m, 4H), 7,46-7,38 (m, 2H), 7,32 (d, 1H, *J*=7,3), 7,02-6,95 (m, 2H), 4,15 (t, 2H, *J*=7,0), 2,71 (dt, 2H, *J*=2,7, 7,3), 2,06 (t, 1H, *J*=2,7).

Etapa C

Éster etílico del ácido (2S)-3-{4-[4-(bifenil-4-iloxi)-but-1-inil]fenil}-2-metoxipropiónico



A una solución de éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico (1,157 g, 3,4 mmol) (Ejemplo 1, Etapa A) en 30 ml de piperidina desgasificada, se añadieron 4-but-3-iniloxibifenilo (0,9 g, 4,85 mmol), tetrakis(trifenilfosfina)paladio (0) (0,196 g, 0,17 mmol), trifenilfosfina (0,09 g, 0,34 mmol) y yoduro de cobre (I) (0,065 g, 0,34 mmol). Se agitó la solución durante 3 h a 80°C y se enfrió a temperatura ambiente. Se evaporó el solvente a vacío y se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/éter dietílico 9:1, R_f 0,27) para

obtener un aceite marrón (0,7 g, 48%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,58-7,30 (m, 9H), 7,17 (d, 2H, J=8,0), 7,02 (d, 2H, J=8,9), 4,22 (t, 2H, J=7,3), 4,18 (c, 2H, J=7,0), 3,93 (dd, 1H, J=7,3, 5,6), 3,35 (s, 3H), 3,02 (s, 1H), 2,99 (d, 1H, J=2,4), 2,92 (t, 2H, J=7,3), 1,24 (t, 3H, J=7,3).

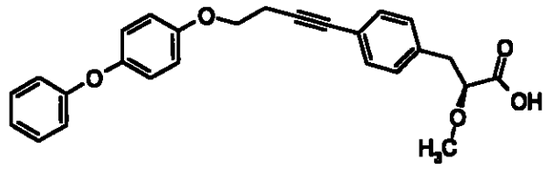
Etapa D

Ácido (2S)-3-{4-[4-(bifenil-4-iloxi)but-1-inil]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-{4-[4-(bifenil-4-iloxi)but-1-inil]fenil}-2-metoxipropiónico mediante el procedimiento estándar de hidrólisis C. Se purificó el residuo por cromatografía (gel de sílice, hexanos/acetato de etilo/ácido acético 50:50:1, R_f 0,25), para producir un sólido blanco (86 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,51 (m, 4H), 7,45-7,30 (m, 5H), 7,19 (d, 2H, J=8,0), 7,01 (d, 2H, J=8,8), 4,20 (t, 2H, J=6,9), 3,98 (dd, 1H, J=7,7, 4,4), 3,37 (s, 3 H), 3,11 (dd, 1H, J=14,3, 4,4), 3,00 (dd, 1H, J=14,3, 7,7), 2,91 (t, 2H, J=7,0).

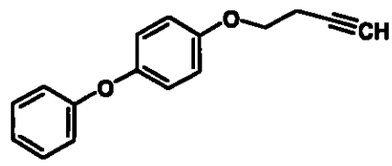
Ejemplo 41

Ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)but-1-inil]-fenil}propiónico



Etapa A

1-But-3-iniloxi-4-feniloxibenceno



Se preparó este compuesto a partir de 4-fenoxifenol y éster but-3-inílico del ácido toluen-4-sulfónico (Ejemplo 40, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa B. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 77,35-7,26 (m, 2H), 7,05-6,87 (m, 5H), 4,09 (t, 2H, *J*=7,0), 2,69 (dt, 2H, *J*=2,4, 7,0), 2,05 (t, 1H, *J*=2,1).

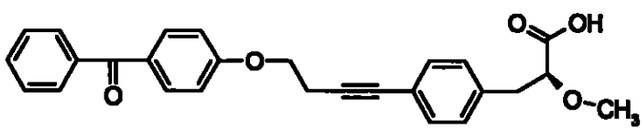
Etapa B

Ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)but-1-inil]-fenil}propiónico

Se preparó el compuesto del título a partir de 1-but-3-iniloxi-4-feniloxibenceno y éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxi-fenil)propiónico (Ejemplo 1, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa C. El derivado éster etílico estaba contaminado con el triflato de partida. Se hidrolizó la mezcla usando el Procedimiento estándar C. Se purificó el residuo por cromatografía (gel de sílice, hexanos/acetato de etilo-ácido acético 50:50:1, R_f 0,25), para producir un sólido blanco (7%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,35-7,28 (m, 4H), 7,16 (d, 2H, *J*=8,0), 7,02-6,87 (m, 7H), 4,13 (t, 2H, *J*=7,0), 3,97 (dd, 1H, *J*=7,7, 4,4), 3,36 (s, 3H), 3,11 (dd, 1H, *J*=14,3, 4,4), 2,97 (dd, 1H, *J*=14,3, 7,7), 2,87 (t, 2H, *J*=7,0).MS (ES) para $C_{26}H_{24}O_5$ $[M+NH_4]^+$: 434,2, $[M+Na]^+$: 439,2.

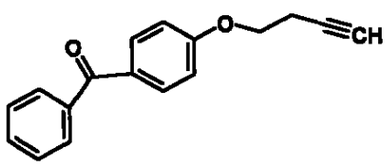
Ejemplo 42

Ácido (2S)-3-{4-[4-(4-benzoilfenoxi)-but-1-inil]fenil}-2-metoxipropiónico


O
O
OH
O
O-CH3

Etapa A

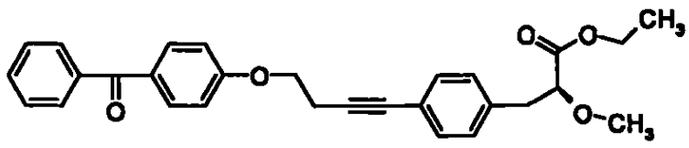
(4-But-3-iniloxifenil)fenilmetanona



Se preparó este compuesto a partir de 4-hidroxibenzofenona y éster but-3-inílico de ácido toluen-4-sulfónico (Ejemplo 40, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa B (8 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,84-7,73 (m, 4 H), 7,57-7,43 (m, 3H), 6,97 (d, 2H, *J*=8,6), 4,18 (t, 2H, *J*=7,0), 2,73 (dt, 2H, *J*=2,7, 7,0), 2,06 (t, 1H, *J*=2,7).

Etapa B

Éster etílico del ácido (2S)-3-{4-[4-(4-benzoilfenoxi)-but-1-inil]fenil}-2-metoxipropiónico



Se preparó este compuesto a partir de (4-but-3-iniloxifenil)fenilmetanona y éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico (Ejemplo 1, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 38, Etapa C (66 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,85-7,73 (m, 4H), 7,57-7,43 (m, 3H), 7,34 (d, 2H, *J*=8,1), 7,16 (d, 2H, *J*=8,3), 7,00 (d, 2H, *J*=8,6), 4,25 (t, 2H, *J*=7,0), 4,18 (c, 2H, *J*=7,0), 3,92 (dd, 1H, *J*=7,3, 5,6), 3,34 (s, 3H), 3,01 (s, 1H), 2,98 (d, 1H, *J*=3,5), 2,93 (t, 2H, *J*=7,0), 1,23 (t, 3H, *J*=7,3).

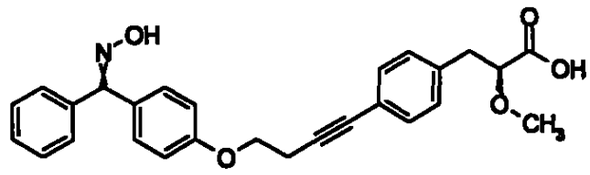
Etapa C

Ácido (2S)-3-{4-[4-(4-benzoilfenoxi)but-1-inil]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-{4-[4-(4-benzoil-fenoxi)but-1-inil]fenil}-2-metoxipropiónico mediante el procedimiento estándar de hidrólisis C para producir un sólido blanco. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,83-7,71 (m, 4H), 7,55-7,44 (m, 3H), 7,32 (d, 2H, *J*=8,0), 7,16 (d, 2H, *J*=8,4), 6,97 (d, 2H, *J*=9,1), 4,22 (t, 2H, *J*=7,0), 3,96 (dd, 1H, *J*=7,7, 4,4), 3,35 (s, 3H), 3,10 (dd, 1H, *J*=13,9, 4,4), 2,98 (dd, 1H, *J*=13,9, 7,7), 2,91 (t, 2H, *J*=7,0).

Ejemplo 43

Ácido (2S)-3-(4-{4-[4-(hidroxiiminofenilmetil)fenoxi]-but-1-inil}fenil)-2-metoxipropiónico

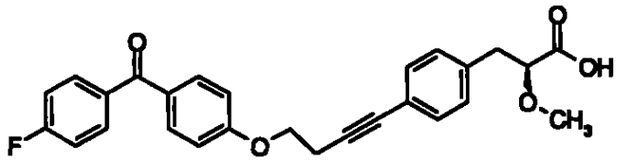


Chiral

Se mezcló ácido (2S)-3-{4-[4-(4-benzoil-fenoxi)but-1-inil]fenil}-2-metoxipropiónico del Ejemplo 42 (1 eq) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla de reacción durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5% al residuo a pH=3. Se extrajo con acetato de etilo y se concentró para obtener el producto del título como una mezcla de dos oximas. MS (ES) para $C_{27}H_{25}NO_5$ [M+H]+: 444,2

Ejemplo 44

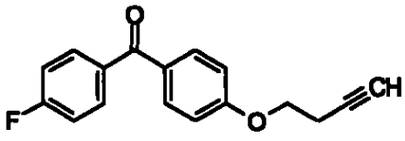
Ácido (2S)-3-(4-{4-[4-(4-fluorobenzoil)fenoxi]but-1-inil}fenil)-2-metoxipropiónico



Chiral

Etapa A

(4-But-3-iniloxifenil)-(4-fluorofenil)metanona



Se preparó este compuesto a partir de 4-fluorohidroxibenzofenona y éster but-3-inílico del ácido toluen-4-sulfónico (Ejemplo 40, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa B.

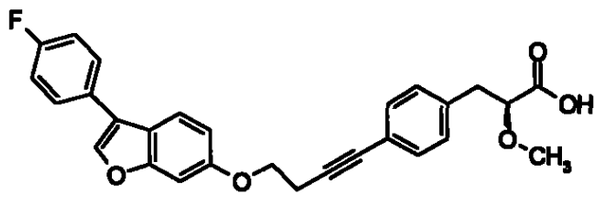
Etapa B

Ácido (2S)-3-(4-{4-[4-(4-fluorobenzoil)fenoxi]-but-1-inil}fenil)-2-metoxipropiónico

Se preparó el compuesto del título a partir de (4-but-3-iniloxifenil)-(4-fluorofenil)metanona y éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico (Ejemplo 1, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa C. El derivado éster etílico estaba contaminado con el triflato de partida. Se hidrolizó la mezcla usando el procedimiento de hidrólisis estándar C. Se purificó el residuo por cromatografía. MS(ES) para $C_{27}H_{23}FO$ $[M+H]^+$: 447,2.

Ejemplo 45

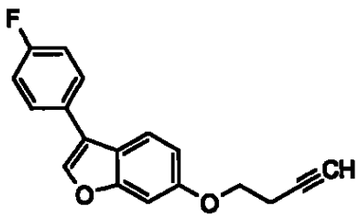
Ácido (2S)-3-{4-{4-[3-(4-fluorofenil)benzofuran-6-iloxi]-but-1-inil}fenil)-2-metoxipropiónico



Chiral

Etapa A

6-But-3-iniloxi-3-(4-fluorofenil)benzofurano



Se preparó este compuesto a partir de 6-hidroxi-3-(4-fluorofenil)benzofurano y éster but-3-inílico del ácido toluen-4-sulfónico (Ejemplo 40, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa B.

Etapa B

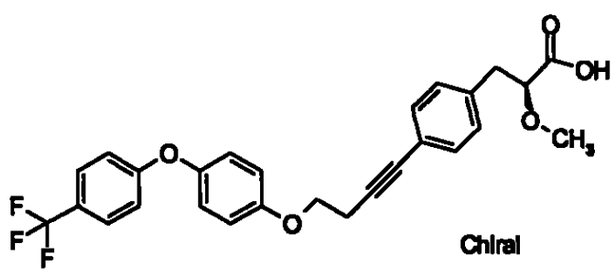
Ácido (2S)-3-(4-{4-[3-(4-fluorofenil)benzofuran-6-iloxi]-but-1-inil}fenil)-2-metoxipropiónico

Se preparó el compuesto del título a partir de 6-but-3-iniloxi-3-(4-fluorofenil)benzofurano y éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico (Ejemplo 1, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa C. El derivado éster etílico estaba contaminado con el triflato de partida. Se hidrolizó la mezcla usando el Procedimiento estándar C. Se purificó el residuo por cromatografía.

MS(ES) para $C_{28}H_{23}FO_5$ [M-H]$^-$: 457,2

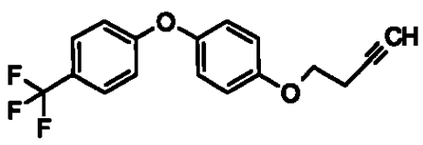
Ejemplo 46

Ácido (2S)-2-metoxi-3-(4-{4-[4-(4-trifluorometilfenoxi)-fenoxi]but-1-inil}fenil)propiónico



Etapa A

4-(3-Butiniloxi)-4'-trifluorometilfeniloxifenil



Se preparó este compuesto a partir de trifluorometilfenoxifenol y éster but-3-inílico del ácido toluen-4-sulfónico (Ejemplo 40, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa B.

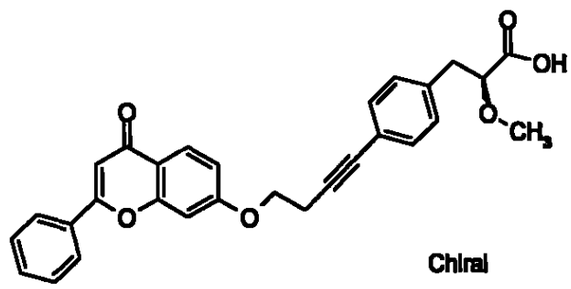
Etapa B

Ácido (2S)-2-metoxi-3-(4-{4-[4-(4-trifluorometilfenoxi)-fenoxi]but-1-inil}fenil)propiónico

Se preparó el compuesto del título a partir de 4-(3-butiniloxi)-4'-trifluorometilfeniloxifenilo y éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico (Ejemplo 1, Etapa A) siguiendo el procedimiento descrito en el Ejemplo 40, Etapa C. El derivado éster etílico estaba contaminado con el triflato de partida. Se hidrolizó la mezcla usando el Procedimiento estándar C. Se purificó el residuo por cromatografía. MS(ES) para $C_{27}H_{23}F_3O_5$ [M-H]-: 483,2

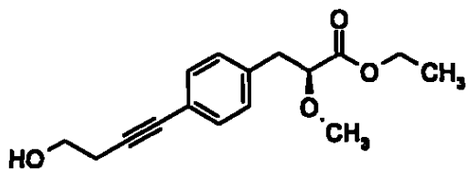
Ejemplo 47

Ácido (2S)-2-metoxi-3-{4-[4-(4-oxo-2-fenil-4H-cromen-7-iloxi)but-1-inil]fenil}propiónico



Etapa A

Éster etílico del ácido 3-[4-(4-hidroxibut-1-inil)fenil]-2-metoxipropiónico



Se preparó este compuesto a partir de 4-butin-1-ol siguiendo el procedimiento descrito en el Ejemplo 1, Etapa B.

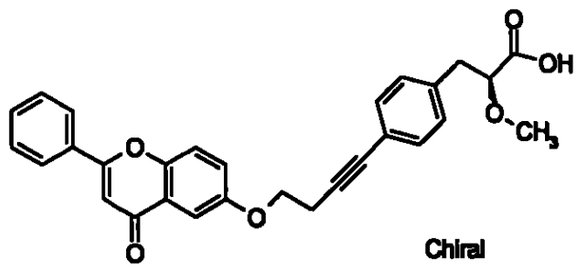
Etapa B

Ácido (2S)-2-metoxi-3-{4-[4-(4-oxo-2-fenil-4H-cromen-7-iloxi)but-1-inil]fenil}propiónico

Se preparó el compuesto del título a partir de 7-hidroxiflavona mediante el Procedimiento estándar de acoplamiento-hidrólisis A, pero utilizando, para la reacción de Mitsounobu, tolueno como solvente y DIAD en lugar de DEAD. MS(ES) para $C_{29}H_{24}O_6$ $[M+H]^+$: 429,2.

Ejemplo 48

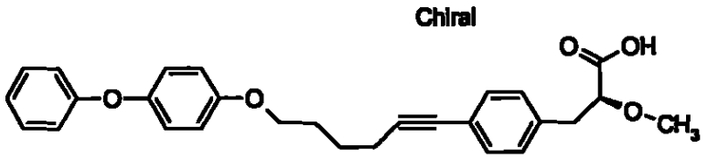
Ácido (2S)-2-metoxi-3-{4-[4-(4-oxo-2-fenil-4H-cromen-6-iloxi)but-1-inil]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(4-hidroxibut-1-inil)fenil]-2-metoxipropiónico del Ejemplo 47, Etapa A, y 6-hidroxiflavona siguiendo el procedimiento estándar de acoplamiento-hidrólisis A utilizando tolueno como solvente y DIAD en lugar de DEAD. MS(ES) para $C_{29}H_{24}O_6$ $[M+H]^+$: 469,2.

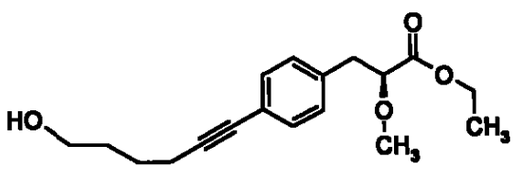
Ejemplo 49

Ácido (2S)-2-metoxi-3-{4-[6-(4-fenoxifenoxi)hex-1-inil]-fenil}propiónico



Etapa A

Éster etílico del ácido (2S)-3-[4-(6-hidroxihex-1-inil)-fenil]-2-metoxipropiónico



A una solución de éster etílico del ácido

(2S)-(3-(4-yodofenil)-2-metoxipropiónico (1,6 g, 4,81 mmol) en 100 ml de piperidina desgasificada se añadieron 5-hexin-1-ol (0,709 g, 7,24 mmol), tetrakis(trifenilfosfina)paladio (0) (0,278 g, 0,24 mmol), trifenilfosfina (0,125 g, 0,48 mmol) y yoduro de cobre (I) (0,091 g, 0,48 mmol). Se agitó la solución durante 3 horas a 80°C y se enfrió a temperatura ambiente. Se evaporó el solvente a vacío y se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 3:1), para obtener el compuesto del título como un aceite amarillo (1,18g, 74% de rendimiento). MS(ES) para $C_{18}H_{24}O_4[M+NH_4]^+$: 322,2.

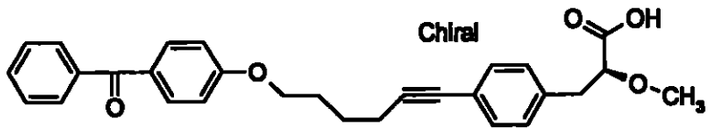
Etapa B

Ácido (2S)-2-metoxi-3-{4-[6-(4-fenoxifenoxi)hex-1-inil]-fenil}propiónico

Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(6-hidroxihex-1-inil)fenil]2-metoxipropiónico y 4-fenoxifenol mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento estándar A), para producir el compuesto del título. MS(ES) para $C_{28}H_{28}O_5[M+H]^+$: 445,2.

Ejemplo 50

Ácido (2S)-3-{4-[6-(4-benzoilfenoxi)hex-1-inil]fenil}-2-metoxipropiónico

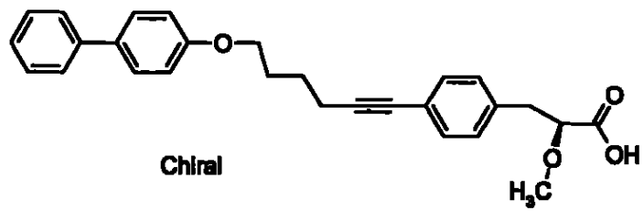


Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(6-hidroxihex-1-inil)fenil]-2-metoxipropiónico (Ejemplo 49, Etapa A) y 4-hidroxibenzofenona mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento estándar A), para producir el compuesto del título. MS(ES)

para $C_{29}H_{28}O_5[M+H]^+$: 457,2

Ejemplo 51

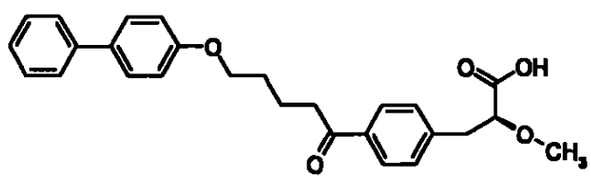
Ácido (2S)-3-{4-[6-(bifenil-4-iloxi)hex-1-inil]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido 3-[4-(6-hidroxihex-1-inil)-fenil]-2-metoxipropiónico (Ejemplo 49, Etapa A) y 4-fenilfenol mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento estándar A), para producir el compuesto del título. MS(ES) para $C_{28}H_{28}O_4[M+NH_4]^+$: 446,2.

Ejemplo 52

Ácido (2S)-3-{4-[5-(bifenil-4-iloxi)pentanoil]fenil}-2-metoxipropiónico

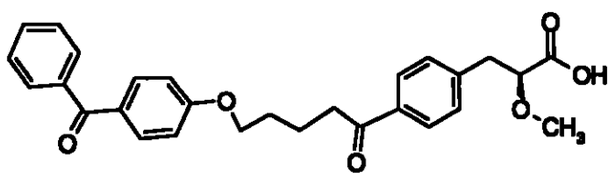


Se trató una solución de trifenilfosfina (0,24 g, 0,915 mmol) en 5 ml de THF seco a 0°C con azodicarboxilato de dietilo (0,159 g, 0,915 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido (2S)-3-[4-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico (Ejemplo 21, Etapa A) (0,18 g, 0,61 mmol) y 4-fenilfenol (0,156 g, 0,915 mmol) en 2 ml de THF seco y se agitó la mezcla a temperatura ambiente. Se concentró la mezcla a vacío y se purificó por cromatografía

en gel de sílice (gel de sílice, hexanos/acetato de etilo 10:1 to 3:1). Se combinaron y concentraron las fracciones con R_f de 0,48 y 0,45 (hexanos/acetato de etilo 2:1) correspondientes al compuesto acoplado y al fenol de partida, respectivamente. Se disolvió la mezcla en 5 ml de metanol y se trató con una mezcla de 75 mg de óxido de mercurio (II) y ácido sulfúrico al 4% en agua. Se agitó la solución a 55°C durante 3 h, se enfrió a temperatura ambiente, se diluyó con $NaHCO_3$ acuoso saturado (20 ml) y se extrajo con diclorometano (4 x 20 ml). Se lavaron las capas orgánicas combinadas con salmuera (20 ml), se secaron ($MgSO_4$) y se concentraron. Se disolvió el residuo en 6 ml de metanol y 2 ml de NaOH 1N y se agitó durante 2 horas. Se evaporó el metanol a vacío y se diluyó la solución acuosa con salmuera (6 ml) y se lavó con éter dietílico (3 x 15 ml). Se acidificó la capa acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 ml). Se secaron los extractos combinados ($MgSO_4$) y se concentraron a un sólido blanco (19 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,89 (d, 2H, J=8,4), 7,55-7,23 (m, 9H), 6,93 (d, 2H, J=8,8), 4,06-3,99 (m, 3H), 3,38 (s, 3H), 3,18 (dd, 1H, J=4,3, 4,4), 3,03 (t+m, 3 H, J=6,9), 1,96-1,86 (m, 4H).

Ejemplo 53

Ácido (2S)-3-{4-[5-(4-benzoilfenoxi)pentanoil]fenil}-2-metoxipropiónico



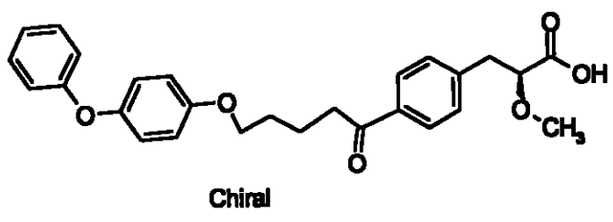
Chiral

Se trató una solución de trifenilfosfina (0,915 mmol) en 5 ml THF seco a 0°C con azodicarboxilato de dietilo (0,915 mmol) y se agitó durante 20 min. Se

añadió una solución de éster etílico del ácido (2S)-3-[4-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico (Ejemplo 21, Etapa A) (0,61 mmol) y 4-benzoilfenol (0,915 mmol) en 2 ml de THF seco y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a vacío y se purificó por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 10:1 to 3:1). Se combinaron y concentraron las fracciones con R_f de 0,48 y 0,45 (hexanos/acetato de etilo 2:1) correspondientes al compuesto acoplado y al fenol de partida, respectivamente Se disolvió la mezcla en 5 ml de metanol y se trató con una mezcla de 75 mg de óxido de mercurio (II) y ácido sulfúrico al 4% en agua. Se agitó la solución a 55°C durante 3 horas, se enfrió a temperatura ambiente, se diluyó con $NaHCO_3$ acuoso saturado (20 ml) y se extrajo con diclorometano (4 x 20 ml). Se lavaron las capas orgánicas combinadas con salmuera (20 ml), se secaron ($MgSO_4$) y se concentraron. Se disolvió el residuo en 6 ml de metanol y 2 ml de NaOH 1N y se agitó durante 2 horas. Se evaporó el metanol a vacío y se diluyó la solución acuosa con salmuera (6 ml) y se lavó con éter dietílico (3 x 15 ml). Se acidificó la capa acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 ml) y se concentró luego para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,91-7,72 (m, 5H), 7,56-7,32 (m, 6H), 6,92 (d, 2H, J=8,9), 4,12-4,03 (m, 3H), 3,42 (s, 3H), 3,19-3,05 (m, 4H), 1,95-1,92 (m, 4H).

Ejemplo 54

Ácido (2S)-2-metoxi-3-{4-[5-(4-fenoxifenoxi)pentanoil]-fenil}propiónico

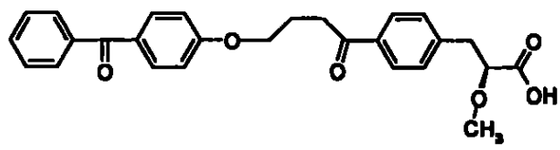


Chiral

Se trató una solución de trifenilfosfina (0,915 mmol) en 5 ml de THF seco a 0°C con azodicarboxilato de dietilo (0,915 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido (2S)-3-[4-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico (Ejemplo 21, Etapa A) (0,61 mmol) y 4-fenoxifenol (0,915 mmol) en 2 ml de THF seco y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a vacío y se purificó por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 10:1 a 3:1). Se combinaron y concentraron las fracciones con R_f de 0,48 y 0,45 (hexanos/acetato de etilo 2:1) correspondientes al compuesto acoplado y al fenol de partida, respectivamente. Se disolvió la mezcla en 5 ml de metanol y se trató con una mezcla de 75 mg de óxido de mercurio (II) y ácido sulfúrico al 4% en agua. Se agitó la solución a 55°C durante 3 horas, se enfrió a temperatura ambiente, se diluyó con $NaHCO_3$ acuoso saturado (20 ml) y se extrajo con diclorometano (4 x 20 ml). Se lavaron las capas orgánicas combinadas con salmuera (20 ml), se secaron ($MgSO_4$) y se concentraron. Se disolvió el residuo en 6 ml de metanol y 2 ml de NaOH 1N y se agitó durante 2 horas. Se evaporó el metanol a vacío y se diluyó la solución acuosa con salmuera (6 ml) y se lavó con éter dietílico (3 x 15 ml). Se acidificó la capa acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 ml) y se concentró después para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,91 (d, 2H, J=8,3), 7,36-7,27 (m, 4H), 7,07-6,83 (m, 7H), 4,08-3,96 (m, 3H), 3,41 (s, 3H), 3,22 (dd, 1H, J=14,0, 4,3), 3,14-3,01 (m, 4H), 1,26 (s, 1H).

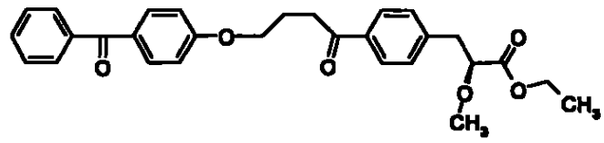
Ejemplo 55

Ácido 3-{4-[4-(4-benzoilfenoxi)butiril]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-{4-[4-(4-benzoilfenoxi)-butiril]fenil}-2-metoxipropiónico



Se disolvió éster etílico del ácido (2S)-3-{4-[4-(4-benzoilfenoxi)but-1-inil]fenil}-2-metoxipropiónico (Ejemplo 42, Etapa B) (0,08 g, 0,17 mmol) en 4 ml de metanol. Se añadieron a esta solución 3 ml de una solución de 0,075 g de óxido de mercurio (II) en 12 ml de ácido sulfúrico al 4%. Se agitó la mezcla a 55°C durante 3 horas, se enfrió a temperatura ambiente y se diluyó con 20 ml de una solución saturada de $NaHCO_3$. Se extrajo la mezcla con diclorometano (4 x 20 ml) y se secaron las capas orgánicas combinadas ($MgSO_4$) y se concentraron. Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 3:1), para obtener un aceite amarillo (72 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,92 (d, 2H, J=8,6), 7,83-7,72 (m, 4H), 7,60-7,42 (m, 3H), 7,34 (d, 2H, J=8,6), 6,95 (d, 2 H, J=8,9), 4,19 (c, 2H, J=7,3), 4,15 (t, 2H, J=6,2), 3,97 (dd, 1H, J=7,3, 5,4), 3,35 (s, 3H), 3,19 (t, 2H, J=7,0), 3,08 (d, 1H, J=5,1), 3,07 (d, 1H, J=7,5), 2,27 (q, 2H, J=6,2), 1,24 (t, 3H, J=7,3).

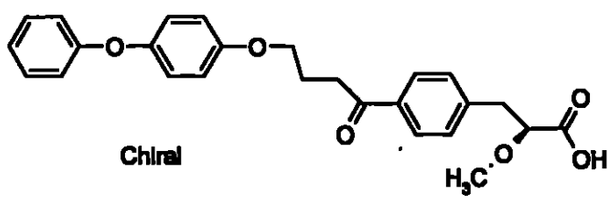
Etapa B

Ácido 3-{4-[4-(4-benzoilfenoxi)butiril]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-{4-[4-(4-benzoilfenoxi)butiril]fenil}-2-metoxipropiónico mediante el procedimiento estándar de hidrólisis C. Sólido blanco (71%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,90 (d, 2H, *J*=8,0), 7,80-7,70 (m, 4H), 7,58-7,39 (m, 3H), 7,32 (d, 2H, *J*=8,4), 6,92 (d, 3H, *J*=9,1), 4,13 (t, 2H, *J*=6,2), 4,02 (dd, 1H, *J*=7,3, 4,4), 3,38 (s, 3H), 3,20-3,00 (m, 4H), 2,25 (q, 2H, *J*=6,2).

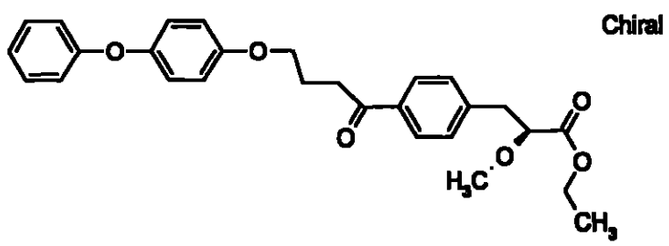
Ejemplo 56

Ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)butiril]fenil}propiónico



Etapa A

Éster etílico del ácido (2*S*)-3-{4-[4-(4-fenoxifenoxi)butiril]fenil}-2-metoxipropiónico



Se disolvió éster etílico del ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)but-1-inil]fenil}propiónico (0,17 mmol) del Ejemplo 41 en 4 ml de metanol. Se añadieron a esta solución 3 ml de una solución de 0,075 g de

óxido de mercurio(II) en 12 ml de ácido sulfúrico al 4%. Se agitó la mezcla a 55°C durante 3 horas, se enfrió a temperatura ambiente y se diluyó con 20 ml de una solución saturada de $NaHCO_3$. Se extrajo la mezcla con diclorometano (4 x 20 ml) y se secaron y concentraron las capas orgánicas combinadas ($MgSO_4$). Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 3:1), para obtener un aceite amarillo.

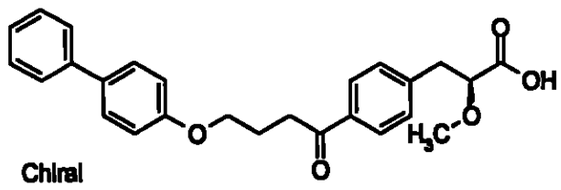
Etapa B

Ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)butiril]fenil}propiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-{4-[4-(4-fenoxifenoxi)-butiril]fenil}-2-metoxipropiónico mediante el procedimiento estándar de hidrólisis C. MS (ES) para $C_{26}H_{26}O_6$ $[M+H]^+$: 435,2.

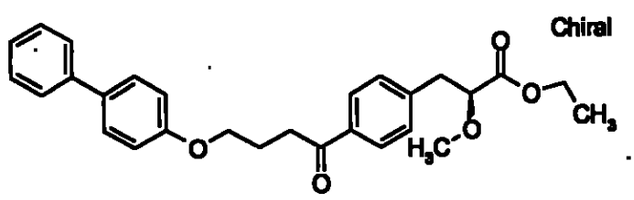
Ejemplo 57

Ácido (2S)-3-[4-(bifenil-4-iloxi)butirilfenil]-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-{4-[4-(4-fenilfenoxi)butiril]fenil}-2-metoxipropiónico



Se disolvió éster etílico del ácido (2S)-3-{4-[4-(bifenil-4-iloxi)but-1-inil]fenil}-2-metoxipropiónico (0,17 mmol) del Ejemplo 40, Etapa C, en 4 ml de metanol. Se añadieron a esta solución 3 ml de una solución de 0,075 g de óxido de mercurio (II) en 12 ml de ácido sulfúrico al 4%. Se agitó la mezcla a 55°C durante 3 horas, se enfrió a temperatura ambiente y se diluyó con 20 ml de una solución saturada de $NaHCO_3$. Se extrajo la mezcla con diclorometano (4 x 20 ml) y se secaron y concentraron las capas orgánicas combinadas ($MgSO_4$). Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 3:1), para obtener un aceite amarillo.

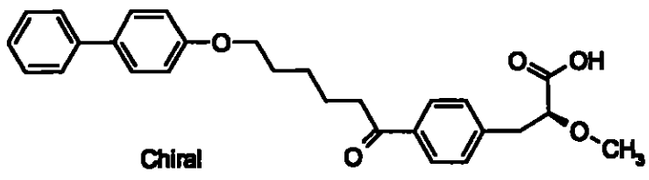
Etapa B

Ácido (2S)-3-[4-(bifenil-4-iloxi)butirilfenil]-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-{4-[4-(4-fenilfenoxi)-butiril]fenil}-2-metoxipropiónico mediante el procedimiento estándar de hidrólisis C. MS (ES) para $C_{26}H_{26}O_5$ $[M+H]^+$: 419,2.

Ejemplo 58

Ácido (2S)-3-{4-[6-(bifenil-4-iloxi)hexanoil]fenil}-2-metoxipropiónico

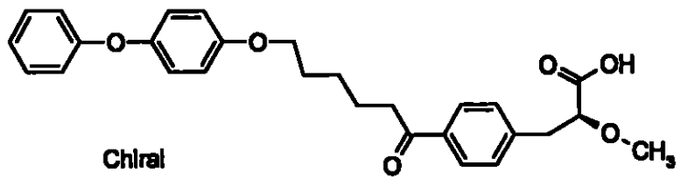


Se trató una solución de trifenilfosfina (0,474 g, 1,8 mmol) en 50 ml THF seco a 0°C con azodicarboxilato de dietilo (1,8 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido 3-[4-(6-hidroxihex-1-inil)fenil]-2-metoxipropiónico (Ejemplo

49, Etapa A) (0,365 g, 1,2 mmol) y 4-fenilfenol (0,307 g, 1,8 mmol) en 10 ml de THF seco y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a vacío y se purificó por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 10:1 a 3:1). Se combinaron y concentraron las fracciones con R_f de 0,48 y 0,45 (hexanos/acetato de etilo 2:1) correspondientes al compuesto acoplado y al fenol de partida, respectivamente. Se disolvió la mezcla en 5 ml de metanol y se trató con una mezcla de 0-712 mg de óxido de mercurio (II) y 12 ml de ácido sulfúrico al 4% en agua. Se agitó la solución a 55°C durante 3 horas, se enfrió a temperatura ambiente, se diluyó con $NaHCO_3$ acuoso saturado (20 ml) y se extrajo con diclorometano (4 x 20 ml). Se lavaron las capas orgánicas combinadas con salmuera (20 ml), se secaron ($MgSO_4$) y se concentraron. Se disolvió el residuo en 6 ml de metanol y 2 ml de NaOH 1N y se agitó durante 2 horas. Se evaporó el metanol a vacío y se diluyó la solución acuosa con salmuera (6 ml) y se lavó con éter dietílico (3 x 15 ml). Se acidificó la capa acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 ml). Se secaron los extractos combinados ($MgSO_4$) y se concentraron para obtener el compuesto del título. MS(ES) para $C_{28}H_{30}O_5[M+H]^+$: 447,2.

Ejemplo 59

<u>Ácido (2S)-2-metoxi-3-{4-[6-(4-fenoxifenoxi)hexanoil]fenil}propiónico</u>

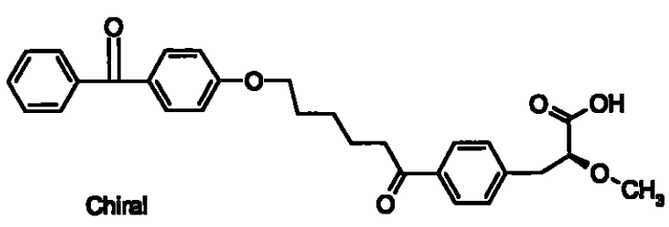


Se trató una solución de trifenilfosfina (1,8 mmol) en 50 ml de THF seco a 0°C con azodicarboxilato de

dietilo (1,8 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido 3-[4-(6-hidroxihex-1-inil)fenil]-2-metoxipropiónico (Ejemplo 49, Etapa A) (1,2 mmol) y 4-fenoxifenol (1,8 mmol) en 10 ml de THF seco y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a vacío y se purificó por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 10:1 a 3:1). Se combinaron y concentraron las fracciones con R_f de 0,48 y 0,45 (hexanos/acetato de etilo 2:1) correspondientes la compuesto acoplado y al fenol de partida, respectivamente. Se disolvió la mezcla en 5 ml de metanol y se trató con una mezcla de 0,712 mg óxido de mercurio (II) y 12 ml de ácido sulfúrico al 4% en agua. Se agitó la solución a 55°C durante 3 horas, se enfrió a temperatura ambiente, se diluyó con $NaHCO_3$ acuoso saturado (20 ml) y se extrajo con diclorometano (4 x 20 ml). Se lavaron las capas orgánicas combinadas con salmuera (20 ml), se secaron ($MgSO_4$) y se concentraron. Se disolvió el residuo en 6 ml de metanol y 2 ml de NaOH 1N y se agitó durante 2 horas. Se evaporó el metanol a vacío y se diluyó la solución acuosa con salmuera (6 ml) y se lavó con éter dietílico (3 x 15 ml). Se acidificó la capa acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 ml). Se secaron los extractos combinados ($MgSO_4$) y se concentraron para obtener el compuesto del título. MS(ES) para $C_{28}H_{30}O_6[M+H]^+$: 463,2.

Ejemplo 60

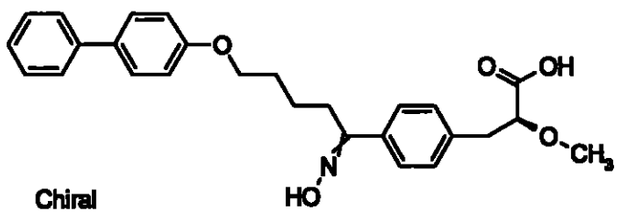
<u>Ácido (2S)-3-{4-[6-(4-benzoilfenoxi)hexanoil]fenil}-2-metoxipropiónico</u>



Se trató una solución de trifenilfosfina (1,8 mmol) en 50 ml de THF seco a 0°C con azodicarboxilato de dietilo (1,8 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido 3-[4-(6-hidroxihex-1-inil)fenil]-2-metoxipropiónico (Ejemplo 49, Etapa A) (1,2 mmol) y 4-hidroxibenzofenona (1,8 mmol) en 10 ml de THF seco y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a vacío y se purificó por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 10:1 a 3:1). Se combinaron y concentraron las fracciones con R_f de 0,48 y 0,45 (hexanos/acetato de etilo 2:1) correspondientes al compuesto acoplado y al fenol de partida, respectivamente. Se disolvió la mezcla en 5 ml de metanol y se trató con una mezcla de 0,712 mg de óxido de mercurio (II) y 12 ml de ácido sulfúrico al 4% en agua. Se agitó la solución a 55°C durante 3 horas, se enfrió a temperatura ambiente, se diluyó con $NaHCO_3$ acuoso saturado (20 ml) y se extrajo con diclorometano (4 x 20 ml). Se lavaron las capas orgánicas combinadas con salmuera (20 ml), se secaron ($MgSO_4$) y se concentraron. Se disolvió el residuo en 6 ml de metanol y 2 ml de NaOH 1N y se agitó durante 2 horas. Se evaporó el metanol a vacío y se diluyó la solución acuosa con salmuera (6 ml) y se lavó con éter dietílico (3 x 15 ml). Se acidificó la capa acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 ml). Se secaron los extractos combinados ($MgSO_4$) y se concentraron, para obtener el compuesto del título. MS(ES) para $C_{29}H_{30}O_6[M+H]^+$: 475,2.

Ejemplo 61

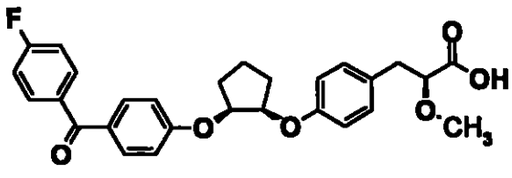
Ácido (2S)-3-{4-[5-(bifenil-4-iloxi)-1-hidroxiiminopentil]fenil}-2-metoxipropiónico



Se mezcló ácido (2S)-3-{4-[5-(bifenil-4-iloxi)pentanoil]fenil}-2-metoxipropiónico del Ejemplo 52 (1 eq) con clorhidrato de hidroxilamina (4 eq), piridina (10 eq) y etanol (2 ml) y se agitó la mezcla de reacción durante la noche. Se evaporó el etanol a vacío y se añadió HCl al 0,5% al residuo a pH = 3. Se extrajo con acetato de etilo y se concentró, para obtener el producto del título como una mezcla de dos oximas. MS(ES) para $C_{27}H_{29}NO_5$ $[M+H]^+$: 448,2,2, $[M-H]^-$: 446,2.

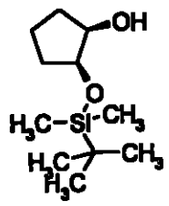
Ejemplo 62

Ácido (2*S*,1'*R**,2'*S**)-3-(4-{2'-[4-(4-fluorobenzoil)fenoxi]ciclopentiloxi}fenil)-2-metoxipropiónico



Etapa A

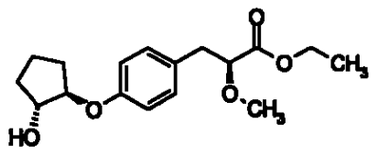
cis-2-(terc-Butildimetilsilaniloxi)ciclopentanol



Se preparó el compuesto del título a partir de meso-1,2-ciclopentanodiol mediante el Procedimiento estándar D para la monoprotección de dioles. Se purificó el residuo por cromatografía en gel de sílice (hexanos/etilo 3:1, R_f 0,55) (50 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 4,04 (dt, 1H, *J*=4,6, 6,2), 3,95-3,89 (m, 1H), 2,59 (d, 1H, *J*=3,8), 1,88-1,49 (m, 6H), 0,91 (s, 9H), 0,09 (s, 6H).

Etapa B

Éster etílico del ácido (2*S*,1'*R*,2'*R*)-3-[4-(2'-hidroxiciclopentiloxi)fenil]-2-metoxipropiónico



Se trató una solución de trifenilfosfina (0,634 g, 2,23 mmol) en 15 ml de THF seco a 0°C con azodicarboxilato de dietilo (0,368 ml, 0,2,45 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido (2S)-2-metoxi-3-hidroxifenilpropiónico (0,5 g, 2,23 mmol) y *cis*-2-(terc-butildimetilsilaniloxi)-ciclopentanol (0,531 g, 0,245 mmol) en 5 ml de THF seco a la solución y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a vacío y se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 6:1). Se recogieron y concentraron las fracciones con R_f de 0,55 (hexanos/acetato de etilo 3:1) correspondientes al compuesto acoplado y al fenol de partida, respectivamente. Se disolvió el residuo en 4 ml de THF y se añadió fluoruro de tetrabutilamonio (2,23 ml, 1 M en THF). Se agitó la solución durante 2 horas a temperatura ambiente, se diluyó con 30 ml de éter dietílico y se lavó con HCl 1N (2 x 20 ml). Se secó la solución orgánica ($MgSO_4$) y se concentró. Se purificó el residuo por cromatografía en gel de sílice

(gel de sílice, hexanos/acetato de etilo 3:1, R_f 0,9) para obtener el producto (60 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,11 (d, 2H, *J*=8,6), 6,80 (d, 2H, *J*=8,9), 4,43-4,40 (m, 1H), 4,23-4,12 (m, 4H); 3,90 (dd, 1H, *J*=7,0, 5,9); 3,35 (s, 3H); 2,95 (d, 2H, *J*=6,7), 2,16-1,60 (m, 6H), 1,22 (t, 3H, *J*=7,0), 0,88 (s, 9H), 0,05 (d, 3H, *J*=2,2).

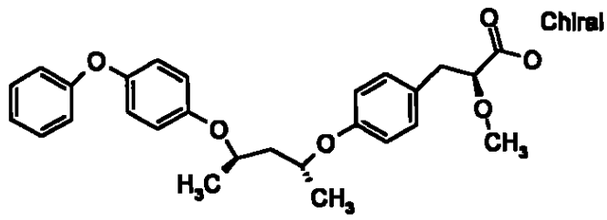
Etapa C

Ácido (2*S*,1'*R**,2'*S**)-3-(4-{2'-[4-(4-fluorobenzoil)fenoxi]ciclopentiloxi}fenil)-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2*S*,1'*R*,2'*R*)-3-[4-(2'-hidroxiciclopentiloxi)fenil]-2-metoxipropiónico y 4-fluoro-4-hidroxibenzofenona mediante el Procedimiento estándar A. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,82-7,67 (m, 4H), 7,18-7,06 (m, 4H), 6,93 (d, 2H, *J*=8,9), 6,76 (d, 2H, *J*=8,6), 4,88-4,74 (m, 2H), 3,97-3,94 (m, 1H), 3,39 (s, 3H); 3,09-2,89 (m, 2H); 2,23-1,98 (m, 6H). MS (ES) para $C_{28}H_{27}FO_6$ $[M+H]^+$: 479,2, $[M+Na]^+$: 501,2.

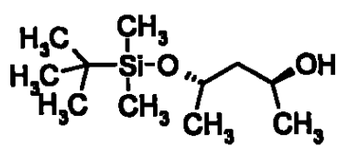
Ejemplo 63

Ácido (2S)-(1'R,3'R)-2-metoxi-3-{4-[1',3'-dimetil-3-(4-fenoxifenoxi)propoxil]fenil}propiónico



Etapa A

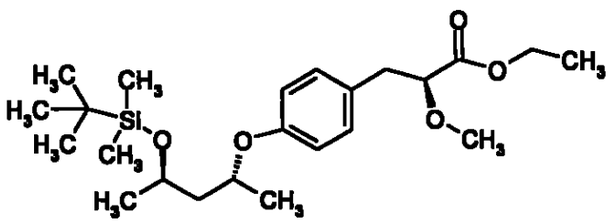
(2*S*,4*S*)-4-(terc-Butildimetilsilaniloxi)pentan-2-ol



Se preparó el compuesto del título partiendo de (2*S*,4*S*)-pentanodiol utilizando el Procedimiento estándar D. MS (ES) para $C_{11}H_{26}O_2Si$ $[M+H]_+$: 219,2.

Etapa B

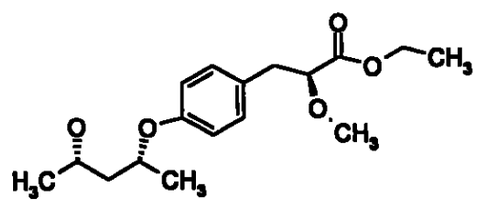
Éster etílico del ácido (2S)-(1'R,3'S)-3-{4-[3'-(*terc*-butildimetilsilaniloxi)-1'-metilbutoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título usando el Procedimiento estándar para el acoplamiento de Mitsounobu B para obtener el producto.

Etapa C

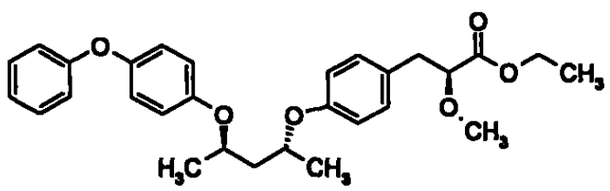
Éster metílico del ácido (2S)-(1'*R*,3'*S*)-3-[4-(3'-hidroxi-1'-metilbutoxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título siguiendo el Procedimiento estándar E para obtener el producto. MS (ES) para $C_{17}H_{26}O_5$ $[M+H]^+$: 328,2.

Etapa D

Éster etílico del ácido (2S)-(1'*R*,2'*R*)-2-metoxi-3-{4-[1'-metil-3'-(4-fenoxifenoxi)butoxi]fenil}propiónico



Se preparó el compuesto del título siguiendo el Procedimiento estándar de acoplamiento de Mitsounobu B para obtener el correspondiente producto. MS (ES) para $C_{29}H_{34}O_6$ $[M+NH_4]^+$: 496,2.

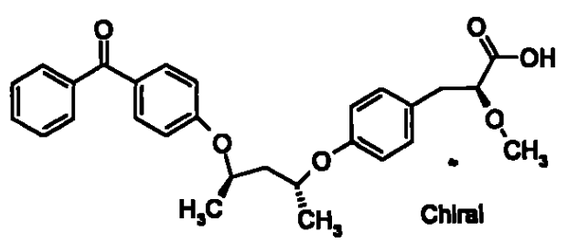
Etapa E

Ácido (2S)-(1'R,3'R)-2-metoxi-3-{4-[1',3'-dimetil-3-(4-fenoxifenoxi)propoxil]fenil}propiónico

Se preparó el compuesto del título mediante el Procedimiento estándar de hidrólisis C del compuesto de la Etapa D para obtener el compuesto final como un sólido gomoso. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,32-7,24 (m, 2H), 7,10-6,75 (m, 11H), 4,70-4,50 (m, 2H), 3,95 (dd, 1H, J=7,3, 4,3), 3,36 (s, 3H), 3,06 (dd, 1H, J=14,5, 4,6), 2,92 (dd, 1H, J=14,2, 7,5), 1,96 (dd, 2H, J=6,7, 5,4), 1,31 (d, 6H, J=6,2).ppm. MS(ES) para $C_{27}H_{30}O_6$ $[M+NH_4]^+$: 468,2, $[M-H]^-$: 449,2.

Ejemplo 64

Ácido (2S)-(1'*R*,3'*R*)-3-{4-[3-(4-benzoilfenoxi)-1',3'-dimetilpropoxil]fenil}2-metoxipropiónico

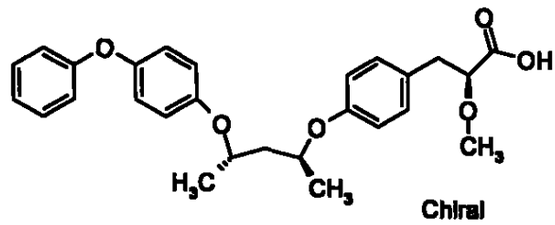


Se preparó el compuesto del título de un modo

análogo al del Ejemplo 63 partiendo del (2*S*,4*S*)-pentanodiol, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 9,24 (s, 1H), 7,75 (t, 1H, J=1,6), 7,70 (t, 1H, J=1,9), 7,69 (dd, 2H, J=12,6, 2,2), 7,59-7,40 (m, 3H), 7,04 (d, 2H, J=8,6), 6,85 (d, 2H, J=9,1), 6,69 (d, 2H, J=8,9), 4,87-4,72 (m, 1H), 4,62-4,47 (m, 1H), 3,94 (dd, 1H, J=7,0, 5,6), 3,37 (s, 3H), 3,05-2,86 (m, 2H), 1,99 (dd, 2H, J=6,7, 5,4), 1,36 (d, 3H, J=6,2), 1,30 (d, 3H, J=6,2).

Ejemplo 65

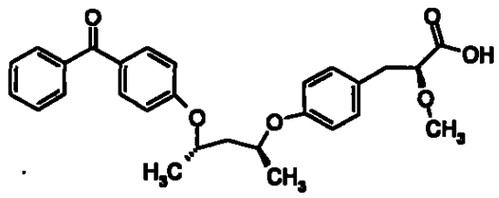
Ácido (2S)-(1'*S*,3'*S*)-2-metoxi-3-{4-[1',3'-dimetil-3-(4-fenoxifenoxi)propoxil]fenil}propiónico



Se preparó el compuesto del título de un modo análogo al del Ejemplo 63 partiendo del (2*R*,4*R*)-pentanodiol, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,33-7,25 (m, 2H), 7,12-6,76 (m, 11H), 4,71-4,49 (m, 2H), 3,95 (dd, 1H, J=7,5, 4,6), 3,36 (s, 3H), 3,05 (dd, 1H, J=14,5, 4,6), 2,93 (dd, 1H, J=14,2, 7,5), 1,96 (dd, 2H, J=7,0, 5,7), 1,31 (d, 6H, J=6,2). MS(ES) para $C_{27}H_{30}O_6$ $[M+NH_4]^+$: 468,2, $[M-H]^-$: 449,2.

Ejemplo 66

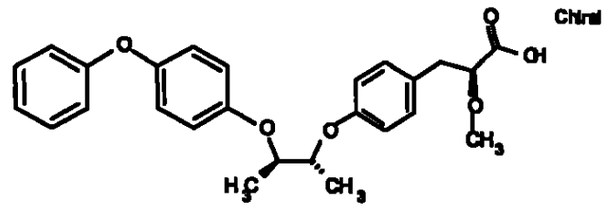
Ácido (2S)-(1'*S*,3'*S*)-3-{4-[3-(4-benzoilfenoxi)-1',3'-dimetilpropoxil]fenil}-2-metoxipropiónico



Se preparó el compuesto del título de un modo análogo al del Ejemplo 63 partiendo del (2*R*,4*R*)-pentanodiol, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,76-7,41 (m, 7H), 7,02 (d, 2H, J=8,6), 6,83 (d, 2H, J=8,9), 6,67 (d, 2H, J=8,6), 4,78 (dd, 1H, J=12,1, 6,2), 4,63-4,47 (m, 1H), 3,99 (dd, 1H, J=6,2, 4,8), 3,41 (s, 3H), 3,08-2,87 (m, 2H), 2,00 (dd, 2H, J=5,6, 12,4), 1,33 (dd, 6H, J=11,6, 6,2). MS(ES) para $C_{28}H_{30}O_6$ $[M+H]^+$: 463,2, $[M-H]^-$: 461,3.

Ejemplo 67

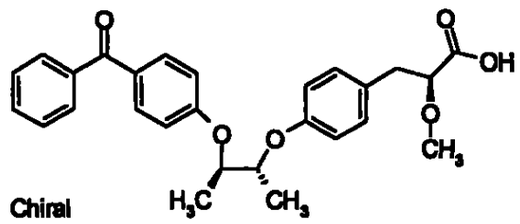
Ácido (2S)-(1'*R*,2'*R*)-2-metoxi-3-{4-[1',2'-dimetil-(4-fenoxifenoxi)etoxil]fenil}propiónico



Se preparó el compuesto del título de un modo análogo al del 63, partiendo del (2*S*,3*S*)-butano-2,3-diol, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,94 (m, 1H), 7,34-7,26 (m, 3H), 7,17-6,83 (m, 10H), 4,59-4,38 (m, 2H), 3,98 (dd, 1H, J=7,5, 4,6), 3,39 (s, 3H), 3,08 (dd, 1H, J=14,2, 4,3), 2,95 (dd, 1H, J=14,2, 7,5), 1,36 (d, 6H, J=6,2). MS(ES) para $C_{26}H_{28}O_6$ $[M+NH_4]^+$: 454,2, $[M-H]^-$: 435,2.

Ejemplo 68

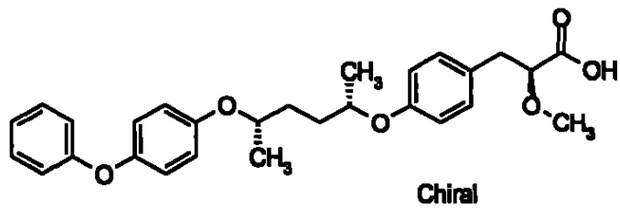
Ácido (2S)-(1'*R*,2'*R*)-3-{4-[1-(4-benzoilfenoxi)-1',2'-dimetiletoxil]fenil}-2-metoxipropiónico



Se preparó el compuesto del título de un modo análogo al del Ejemplo 63, partiendo del (2*S*,3*S*)-butano-2,3-diol, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,77 (t, 3H, J=8,9), 7,74 (s, 1H), 7,60-7,42 (m, 3H), 7,14 (d, 2H, J=8,6), 6,96 (d, 2H, J=8,9), 6,84 (d, 2H, J=8,9), 4,72-4,60 (m, 1H), 4,59-4,47 (m, 1H), 3,98 (dd, 1H, J=7,5, 4,6), 3,39 (s, 3H), 3,08 (dd, 1H, J=14,5, 4,6), 2,95 (dd, 1H, J=14,2, 7,3), 1,42 (d, 3H, J=6,2), 1,37 (d, 3H, J=6,2). MS(ES) para $C_{27}H_{28}O_6$ $[M+H]^+$: 449,2, $[M-H]^-$: 447,2.

Ejemplo 69

Ácido (2S)-(1'*S*,4'*S*)-2-metoxi-3-{4-[1'-metil-4'-(4-fenoxifenoxi)pentiloxi]fenil}propiónico

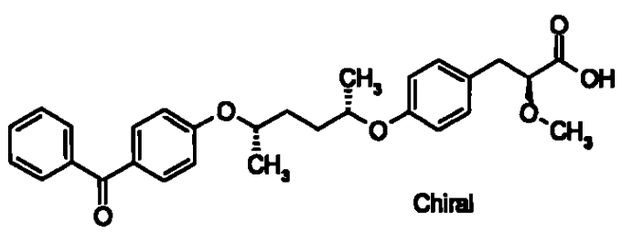


Se preparó el compuesto del título de un modo análogo al del Ejemplo 63 partiendo del (2*R*,5*R*)-hexano-2,5-diol, para obtener el compuesto final. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,3-7,2 (m, 2H), 7,14 (d, 2H, J= 8,6), 7,1-6,8 (m, 9H), 4,4-4,3 (m, 2H), 3,97 (dd, 1H, J=7,6, 4,4), 3,39 (s, 3H), 3,08 (dd, 1H, J=14,2, 4,4), 2,95 (dd, 1H,

J=14,4, 7,6), 2,0-1,7 (m, 4H), 1,31 (d, 6H, J=6,2) ppm.

Ejemplo 70

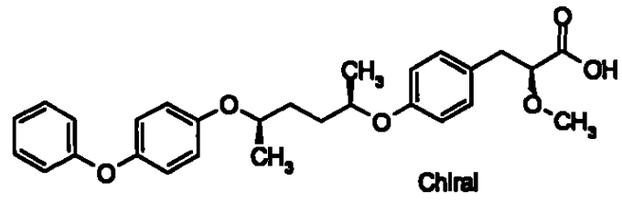
Ácido (2S)-(1'S,4'S)-3-{4-[4-(4-benzoilfenoxi)-1-metil-pentiloxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título de un modo análogo al del Ejemplo 63 partiendo del (2*R*,5*R*)-hexano-2,5-diol, para obtener el compuesto final. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,8-7,7 (m, 4H), 7,6-7,5 (m, 3H), 7,13 (d, 2H, J= 8,6), 6,90 (dd, 2H, J=7,0, 2,0), 6,79 (d, 2H, J=8,6), 4,51 (c, 1H, J=6,0), 4,35 (c, 1H, J= 6,0), 3,98 (dd, 1H, J=7,2, 4,8), 3,39 (s, 3H), 3,08 (dd, 1H, J=14,4, 4,8), 2,95 (dd, 1H, J=14,4, 7,2), 2,0-1,7 (m, 4H), 1,35 (d, 3H, J=6,0), 1,30 (d, 3H, J=6,0) ppm.

Ejemplo 71

Ácido (2S)-(1'*R*,4'*R*)-2-metoxi-3-{4-[1'-metil-4'-(4-fenoxifenoxi)pentiloxi]fenil}propiónico

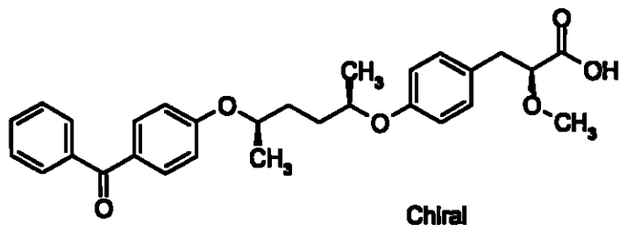


Se preparó el compuesto del título de un modo análogo al del Ejemplo 63 partiendo del (2*S*,5*S*)-hexano-2,5-diol, para obtener el compuesto final. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,3-7,2 (m, 2H), 7,14 (d, 2H, J= 8,4), 7,1-6,7 (m, 9H), 4,4-4,2 (m, 2H), 3,96 (dd, 1H, J=7,4, 4,4), 3,37 (s, 3H), 3,07 (dd, 1H, J=14,4, 4,4), 2,93 (dd, 1H,

J=14,4, 7,4), 2,0-1,6 (m, 4H), 1,30 (d, 6H, J=6,0) ppm.

Ejemplo 72

Ácido (2S)-(1'*R*,4'*R*)-3-{4-[4-(4-benzoilfenoxi)-1-metil-pentiloxi]-fenil}-2-metoxipropiónico

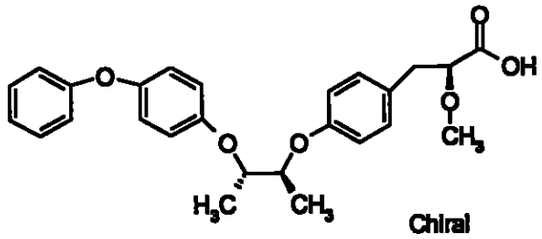


Chiral

Se preparó el compuesto del título de un modo análogo al del Ejemplo 63 partiendo del (2*S*,5*S*)-hexano-2,5-diol, para obtener el compuesto final. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,8-7,5 (m, 3H), 7,5-7,4 (m, 3H), 7,06 (d, 2H, J= 5,6), 6,82 (d, 2H, J=6,0), 6,71 (d, 2H, J=5,8), 4,44 (c, 1H, J=3,6), 4,28 (c, 1H, J= 3,6), 3,88 (dd, 1H, J=9,6, 2,8), 3,29 (s, 3H), 2,98 (dd, 1H, J=9,6, 2,8), 2,86 (dd, 1H, J=9,6, 5,0), 1,9-1,6 (m, 4H), 1,27 (d, 3H, J=4,0), 1,21 (d, 3H, J=4,0) ppm.

Ejemplo 73

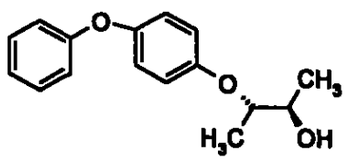
Ácido (2S)-(1'*S*,2'*S*)-2-metoxi-3-{4-[1',2'-dimetil-(4-fenoxifenoxi)etoxil]fenil}propiónico



Chiral

Etapa A

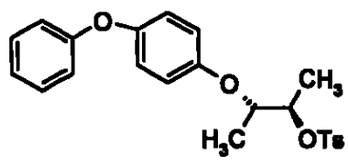
(2R,3S)-3-(4-fenoxifenoxi)butan-2-ol



Se monoprotegió una solución de (2R,3R)-butano-2,3-diol con cloruro de terc-butildimetilsililo usando el Procedimiento estándar D; después de purificar por cromatografía, se acopló el compuesto con 4-fenoxifenol usando el Procedimiento estándar B (en THF) y se desprotegió con fluoruro de tetrabutilamonio como Procedimiento estándar E, para obtener el compuesto del título en forma de aceite. MS (ES) para $C_{16}H_{18}O_3$ $[M+NH_4]^+$: 276,2.

Etapa B

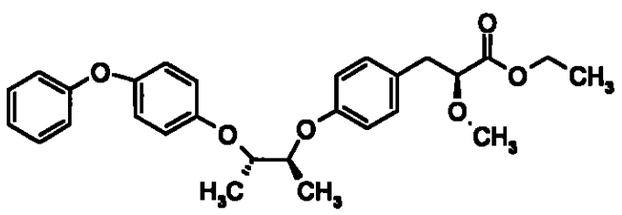
Éster 1-metil-2-(4-fenoxifenoxi)propílico del ácido ((1*R*,2*S*)-toluen-4-sulfónico



A una solución del compuesto de la Etapa A (1 eq) en piridina neta, se añadió cloruro p-toluenesulfónico (1,5 eq) y se agitó la mezcla de reacción a temperatura ambiente a lo largo de dos días. Se apagó la reacción con HCl 1N y se extrajo con acetato de etilo y se lavaron las capas orgánicas con salmuera (3 veces). Se secaron las capas orgánicas y se concentraron a vacío, para obtener un residuo, el cual fue purificado por cromatografía en gel de sílice para obtener el producto del título. MS (ES) para $C_{23}H_{24}O_5S$ $[M+NH_4]^+$: 430,1.

Etapa C

Éster etílico del ácido (2S)-(1'S,2'S)-2-metoxi-3-{4-[1',2'-dimetil(4-fenoxifenoxi)etoxil]fenil}propiónico



Se sometió a reflujo durante la noche una solución de éster 1-metil-2-(4-fenoxifenoxi)propílico del ácido (1R,2S)-toluen-4-sulfónico de la Etapa anterior (1 eq), carbonato de potasio (3 eq) y éster etílico del ácido (2*S*)-3-(4-hidroxifenil)-2-metoxipropiónico (1 eq) en acetonitrilo. Se evaporó la solución a sequedad y se cromatografió para obtener el compuesto del título. MS (ES) para $C_{27}H_{30}O_7$ $[M+ NH_4]^+$: 482,4.

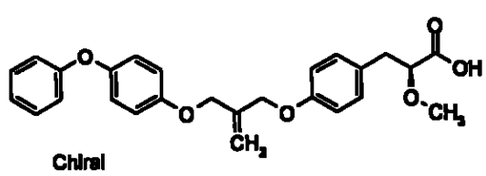
Etapa D

Ácido (2S)-(1'S,2'S)-2-metoxi-3-{4-[1',2'-dimetil-(4-fenoxifenoxi)etoxil]fenil}propiónico

Se preparó el compuesto del título usando el Procedimiento estándar de hidrólisis C, para obtener el producto final en forma de aceite. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,34-7,26 (m, 3H), 7,16-6,83 (m, 10H), 4,58-4,41 (m, 2H), 3,98 (dd, 1H, J=7,3, 4,3), 3,39 (s, 3H), 3,14-2,89 (m, 2H), 1,35 (d, 6H, J=6,2). MS(ES) para $C_{26}H_{28}O_6$ $[M+NH_4]_+$: 454,3, $[M-H]_-$: 435,1.

Ejemplo 74

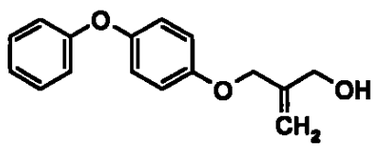
Ácido (2S)-2-metoxi-{4-[2-metilen-3-(4-fenoxifenoxi)propoxil]fenil}propiónico



660 65

Etapa A

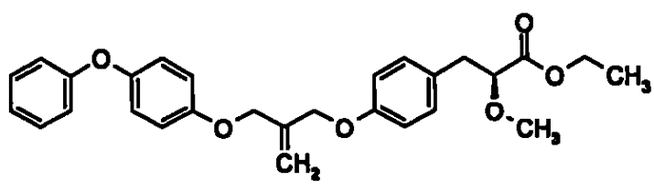
2-(4-Fenoxifenoximetil)prop-2-en-1-ol



Se trató una solución de trifenilfosfina (1 eq) en tolueno a 0°C con azodicarboxilato de dietilo (1 eq) y se agitó durante 20 min. Se añadió luego una solución de 4-fenoxifenol y 2-metilenpropano-1,3-diol en tolueno a la solución y se agitó la mezcla de reacción durante la noche. Se concentró a sequedad y se cromatografió para obtener el compuesto del título.

Etapa B

Éster etílico del ácido (2S)-2-metoxi-{4-[2-metilen-3-(4-fenoxifenoxi)propoxil]fenil}propiónico



Se preparó el compuesto del título usando el las condiciones de acoplamiento estándar de Mitsounobu B.

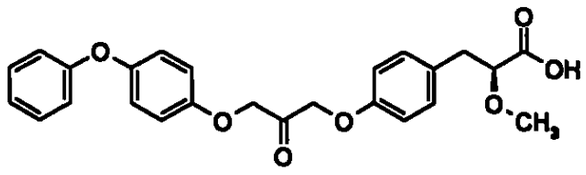
Etapa C

Ácido (2S)-2-metoxi-{4-[2-metilen-3-(4-fenoxifenoxi)propoxil]fenil}propiónico

Se preparó el compuesto del título usando el Procedimiento estándar para hidrólisis C, para obtener el producto final en forma de aceite. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 8,09 (s, 1H), 7,34-6,86 (m, 13H), 5,41 (s, 2H), 4,62 (s, 4H), 3,98 (dd, 1H, J=7,5, 4,6), 3,40 (s, 3H), 3,09 (dd, 1H, J=14,5, 4,6), 2,97 (dd, 1H, J=14,5, 7,5).

Ejemplo 75

Ácido (2S)-2-metoxi-{4-[2-oxo-3-(4-fenoxifenoxi)propoxil]fenil}propiónico

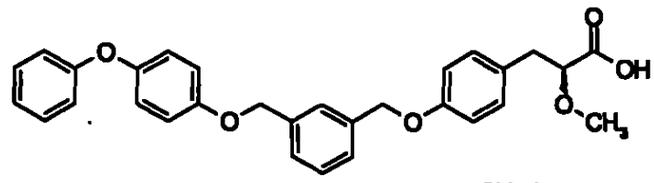


Chiral

Se trató una solución de ácido (2S)-2-metoxi-{4-[2-metilen-3-(4-fenoxifenoxi)propoxil]fenil}propiónico del Ejemplo 74, en diclorometano a -78°C con ozono hasta que la solución se volvió azul. Se lavó con salmuera, se secó y se concentró a sequedad para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,35-6,83 (m, 13H), 4,86 (d, 4H, J=3,0), 3,98 (dd, 1H, J=7,3, 4,3), 3,40 (s, 3H), 3,10 (dd, 1H, J=14,2, 4,0), 2,97 (dd, 1H, J=14,5, 7,3). MS(ES) para $C_{25}H_{24}O_7$ $[M+NH_4]^+$: 454,2, $[M-H]^-$: 435,2.

Ejemplo 76

Ácido (2S)-2-metoxi-3-{4-[3-(4-fenoxifenoximetil)benciloxi]fenil}propiónico

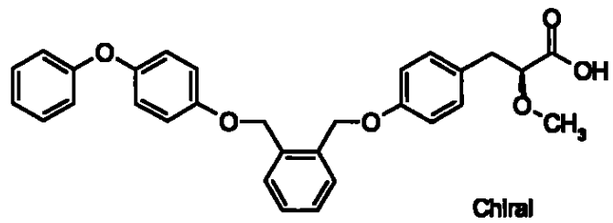


Chiral

Se preparó el compuesto del título de un modo análogo al del Ejemplo 74, partiendo de (3-hidroximetil-fenil)metanol, para obtener el compuesto final. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,50 (s, 1H), 7,40 (s, 2H), 7,28 (d, 2H, J=8,6), 7,17 (d, 2H, J=8,6), 7,1-6,9 (m, 10H), 5,06 (s, 4H), 3,99 (dd, 1H, J=7,2, 4,4), 3,40 (s, 3H), 3,10 (dd, 1H, J=14,4, 4,6), 2,97 (dd, 1H, J=14,2, 7,4) ppm.

Ejemplo 77

Ácido (2S)-2-metoxi-3-{4-[2-(4-fenoxifenoximetil)bencil-oxi]fenil}propiónico

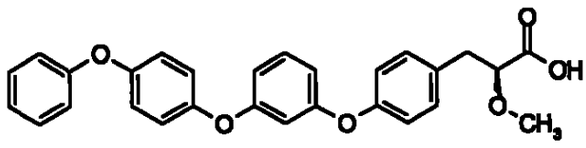


Chiral

Se preparó el compuesto del título de un modo análogo al del Ejemplo 63, partiendo de (2-hidroximetil-fenil)metanol, para obtener el compuesto final. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,5-7,4 (m, 2H), 7,4-7,3 (m, 2H), 7,28 (d, 2H, J=8,0), 7,16 (d, 2H, J=8,6), 7,1-6,9 (m, 9H), 5,14 (s, 4H), 3,95 (dd, 1H, J=7,4, 4,6), 3,37 (s, 3H), 3,07 (dd, 1H, J=14,2, 4,4), 2,94 (dd, 1H, J=14,2, 7,6) ppm.

Ejemplo 78

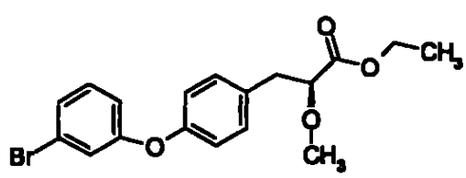
Ácido (2S)-2-metoxi-3-{4-[3-(4-fenoxifenoxi)fenoxi]fenil}propiónico



Chiral

Etapa A

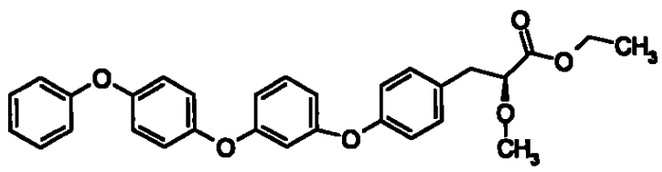
Éster etílico del ácido (2S)-3-[4-(3-bromofenoxi)fenil]-2-metoxipropiónico



Se equipó un tubo de Schlenk hermético secado al horno con un septo de caucho y se enfrió a temperatura ambiente bajo una purga de N_2. Se cargó el tubo con $Pd(OAc)_2$ (2,0% mol), 2-(diterc-butilfosfino)bifenilo (0,03 eq), fosfato de potasio (2 eq), 1,3-dibromobenceno (1 eq) y éster etílico del ácido (2S)-3-(4-hidroxi-fenil)-2-metoxi-propiónico (1,2 eq). Se tapó el tubo con el septo y se purgó con N_2 y se añadió luego tolueno a través del septo. Se selló el tubo con un tapón de rosca de teflón y se agitó la mezcla de reacción a 100°C durante 16 horas. Se eliminó el solvente y se purificó el residuo por cromatografía, para obtener el compuesto del título.

Etapa B

Éster etílico del ácido (2S)-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)fenoxi]fenil}propiónico



Se preparó el compuesto del título usando el mismo procedimiento de acoplamiento descrito anteriormente para la Etapa A con 4-fenoxifenol y éster etílico del ácido (2S)-3-[4-(3-bromofenoxi)fenil]-2-metoxipropiónico.

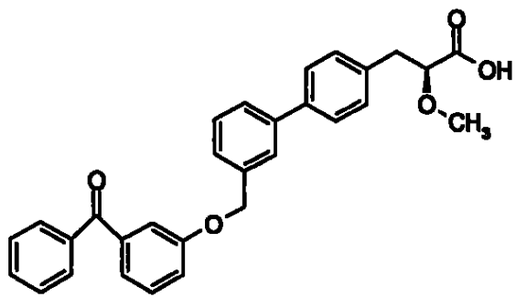
Etapa C

Ácido (2S)-2-metoxi-3-{4-[3-(4-fenoxifenoxi)fenoxi]fenil}propiónico

Se preparó el compuesto del título a partir de la Etapa B usando el Procedimiento estándar para hidrólisis C. MS (ES) para $C_{28}H_{24}O_6$ $[M+Na]^+$: 479.

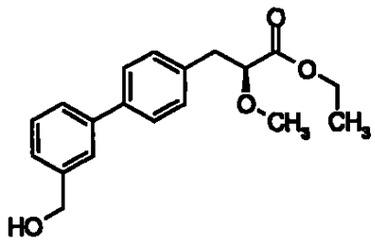
Ejemplo 79

Ácido (2S)3-[3'-(3-benzoilfenoximetil)bifenil-4-il]-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-(3'-hidroximetilbifenil-4-il)-2-metoxipropiónico



Se calentó una solución de éster etílico del ácido (2S) 2-metoxi-3-(4-trifluorometanosulfoniloxi-fenil)propiónico (Ejemplo 1, Etapa A) (150 mg, 0,42 mmol), ácido 3-formilfenilborónico (126 mg, 0,842 mmol) y tetrakis(trifenilfosfina)paladio (0) (15 mg, 0,013 mmol) en 11 ml de una mezcla 20:1 de tolueno/etanol, junto con 2 ml de Na_2CO_3 2N, a 120°C durante 6 horas bajo una atmósfera de nitrógeno. Se enfrió la mezcla de reacción a temperatura ambiente y se diluyó con EtOAc (20 ml). Se lavó con H_2O (3x5ml) y tartrato de sodio (3x5 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío. Se purificó el producto bruto resultante por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 3:1). Se recogieron y concentra-

ron a sequedad las fracciones correspondientes al compuesto deseado (R_f: 0,27). Se disolvió el producto en MeOH enfriado a 0°C y se añadió borohidruro de sodio (3 eq). Se agitó la solución durante 1 h y se diluyó después con acetato de etilo (20 ml). Se lavó con H_2O (3x5ml) y $NaHCO_3$ (3x5 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío. Se purificó el producto bruto resultante por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 2:1). Se obtuvo un aceite incoloro (60 mg, 45%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,55-7,23 (m, 8H), 4,71 (s, 2H), 4,18 (c, 2H, *J*= 7,0), 3,93 (dd, 1H, *J*=7,3, 5,6), 3,35 (s, 3H) 3,05 (s, 1H), 3,02 (s, 1H), 1,25 (t, 3H, *J*=7,25)

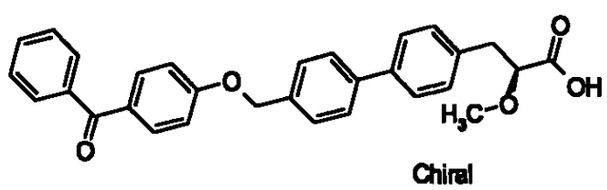
Etapa B

Ácido (2S)-3-[3'-(3-benzoilfenoximetil)bifenil-4-il]-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-(3'-hidroximetil-bifenil-4-il)-2-metoxipropiónico (Etapa A) y 4-hidroxibenzofenona mediante el procedimiento estándar de acoplamiento-hidrólisis de Mitsunobu (Procedimiento estándar A), para producir un sólido oleoso blanco. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,83-7,33 (m, 15H), 7,03 (d, 2H, *J*=8,1), 5,17 (s, 2H), 4,07 (dd, 1H, *J*=6,9, 3,7), 3,40 (s, 3H), 3,16 (dd, 1H, *J*=14,1, 3,6), 3,06 (dd, 1H, *J*=14,1, 7,0).

Ejemplo 80

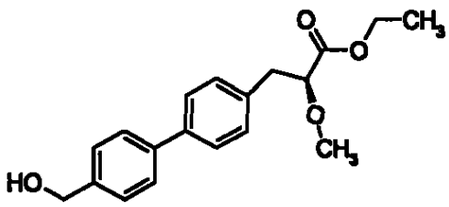
Ácido (2S)-3-[4'-(4-benzoilfenoximetil)bifenil-4-il]-2-metoxipropiónico



Chiral

Etapa A

Éster etílico del ácido (2S)-3-(4'-hidroximetilbifenil-4-il)-2-metoxipropiónico



Se sometió a reflujo una mezcla de éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico del Ejemplo 1, Etapa A, (1 eq), tetrakis(trifenilfosfina)paladio(0) (0,03 eq), carbonato de sodio (1,5 eq) y ácido 4-hidroximetilfenilborónico (2 eq) en tolueno/etanol (20:1) hasta que la reacción se hubo completado por TLC. Se diluyó la mezcla con acetato de etilo, se extrajo y se lavó con agua, $NaHCO_3$, tartrato de sodio y salmuera. Se concentró la capa orgánica a sequedad y se cromatografió para obtener el compuesto del título.

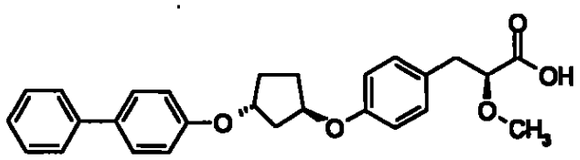
Etapa B

Ácido (2S)-3-[4'-(4-benzoilfenoximetil)bifenil-4-il]-2-metoxipropiónico

Se trató el éster etílico del ácido (2S)-3-(4'-hidroximetilbifenil-4-il)-2-metoxipropiónico de la Etapa A con 4-hidroxibenzofenona según el procedimiento de acoplamiento estándar de Mitsounobu B (THF). Se hidrolizó el producto obtenido tras la cromatografía usando el Procedimiento estándar C para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,86-7,73 (m, 4H), 7,63-7,43 (m, 9H), 7,34-7,29 (m, 2H), 7,05 (d, 2H, J=9,1), 5,18 (s, 2H), 4,06 (dd, 1H, J=7,3, 4,0), 3,42 (s, 3H), 3,20 (dd, 1H, J=14,5, 4,0), 3,06 (dd, 1H, J=14,5, 7,3). MS (ES) para $C_{30}H_{26}O_5$ $[M+H]^+$: 467,2, $[M+Na]^+$: 489,2.

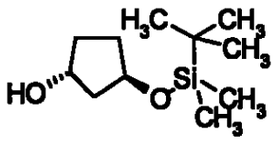
Ejemplo 81

Ácido (2S)-(1'*R**,3'*R**)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico



Etapa A

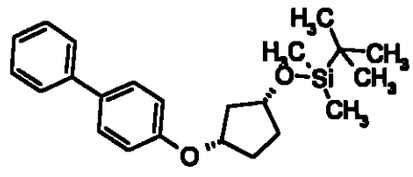
(1*RS*,3*RS*)-3-(*terc*-Butildimetilsilaniloxi)ciclopentanol



A una solución de 1,3-pentanodiol rac. (0,46 g, 4,5 mmol) en 23 ml de THF a 0°C, se añadió hidruro de sodio (0,18 g, 4,5 mmol, dispersión oleosa al 60%). Se agitó la mezcla a 0°C durante 1 h. Se añadió cloruro de *terc*-butildimetilsililo (0,678 g, 4,5 mmol) y se agitó la mezcla durante la noche a temperatura ambiente. Se concentraron los compuestos de la mezcla y se purificaron por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 3:1), para obtener 0,682 g del compuesto del título trans y 0,157 g (6%) del otro isómero cis (1*R**,3*S**)-3-(terc-butildimetilsilaniloxi)ciclopentanol. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 4,48-4,36 (m, 2H), 2,19-1,89 (m, 2H), 1,85-1,79 (m, 2H), 1-58-1,46 (m, 2H), 0,89 (s, 9H), 0,04 (s, 6H).

Etapa B

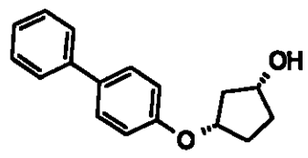
(1*R**,3*S**)-[3-(Bifenil-4-iloxi)ciclopentiloxi]-terc-butildimetilsilano



Se trató una solución de trifenilfosfina (0,195 g, 0,742 mmol) en 5 ml de THF seco a 0°C con azodicarboxilato de dietilo (0,117 ml, 0,742 mmol) y se agitó durante 20 min. Se añadió una solución de (1R*, 3R*)-3-(terc-butildimetilsilaniloxi)ciclopentanol (0,146 g, 0,675 mmol) y 4-fenilfenol (0,126 g, 0,724 mmol) en 5 ml de THF seco a la solución y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la solución a vacío y se purificó por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 6:1, R_f 0,66). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,58-7,29 (m, 7H); 6,93 (d, 2H, J=8,92), 4,76-4,65 (m, 1H), 4,32-4,21 (m, 1H), 2,38 (q, 1H, J=7,0), 2,04-1,94 (m, 2H), 1,87-1,78 (m, 3H), 0,90 (s, 9H), 0,07 (s, 3H), 0,06 (s, 3H).

Etapa C

(1*R**,3*S**)-3-(Bifenil-4-iloxi)ciclopentanol



Se disolvió (1R*,3S*)-[3-(bifenil-4-iloxi)ciclopentiloxi]-terc-butildimetilsilano (0,25 g, 0,67 mmol) en 2 ml de THF y fluoruro de tetrabutilamonio (0,67 ml, 1M en THF) y se agitó a temperatura ambiente durante 2 horas. Se diluyó la reacción con 15 ml de éter dietílico y se lavó con HCl 1N (2 x 15 ml). Se secó la capa orgáni-

ca ($MgSO_4$) y se concentró. Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 3:1, R_f 0,09), para obtener el producto (100 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,58-7,26 (m, 7H), 6,95 (d, 2H, *J*=8,9), 4,92-4,84 (m, 1H), 4,40-4,38 (m, 1H), 2,18-1,92 (m, 7H).

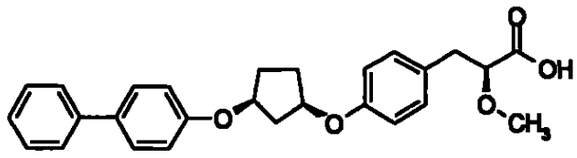
Etapa D

Ácido (2S)-(1'*R**,2'*R**)3-{4-[3-(bifenil-4-iloxi)ciclopentiloxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de (1*R**,3*S**)-3-(bifenil-4-iloxi)ciclopentanol y éster etílico del ácido (2S)-2-metoxi-3-hidroxifenilpropiónico mediante el Procedimiento estándar A. Sólido oleoso. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,57-7,29 (m, 7H), 7,15 (d, 2H, *J*=8,6), 6,94 (d, 2H, *J*=8,9), 6,81 (d, 2H, *J*=8,6), 4,99-4,91 (m, 2H), 3,99 (dd, 1H, *J*=7,3, 4,6), 3,41 (s, 3H), 3,10 (dd, 1H, *J*=14,2, 4,6), 2,96 (dd, 1H, *J*=14,5, 7,3), 2,31 (t, 2H, *J*=4,8), 2,26-1,97 (m, 4H).

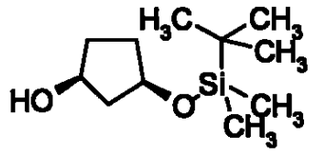
Ejemplo 82

Ácido (2S)-(1'*R**,3'*S**)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico



Etapa A

(1*R**,3S*)-3-(terc-Butildimetilsilaniloxi)ciclopentanol



Se aisló el compuesto del título a partir del Ejemplo 81, Etapa A, con un rendimiento del 6%.

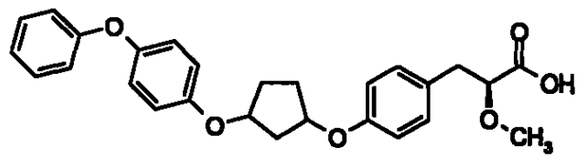
Etapa B

Ácido (2S)-(1'*R**,3'*S**)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título partiendo del compuesto de la Etapa A y siguiendo el mismo procedimiento que en el **Ejemplo 81**, para obtener el producto final. MS (ES) para $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450,2, $[M+Na]^+$: 455,23.

Ejemplo 83

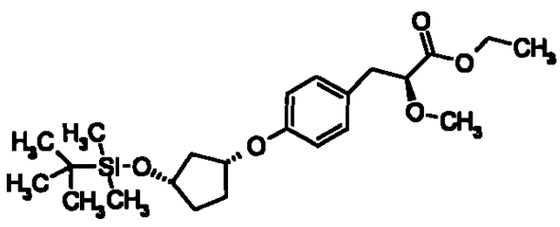
Ácido (2S)-(1'*R**,3'*R**)-2-metoxi-3-{4-[3'-(4-fenoxifenoxi)-1'-ciclopentiloxi]fenil}propiónico



Chiral

Etapa A.

Éster etílico del ácido (2S)-(1*R**,3*S**)-3-{4-[3'-(*terc*-butildimetilsilaniloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico

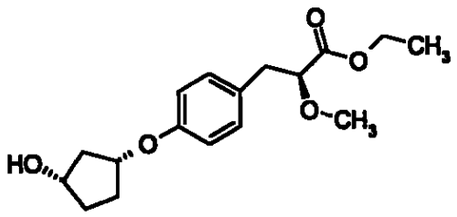


Se trató una solución de trifenilfosfina (0,634 g, 2,23 mmol) en 15 ml de THF seco a 0°C con azodicarboxilato de dietilo (0,2,45 mmol) y se agitó durante 20 min. Se añadió una solución de éster etílico del ácido (2S)-2-metoxi-3-hidroxifenilpropiónico (2,23 mmol) y 1*R**,3*R**-*terc*-butildimetilsilaniloxiciclopentanol (0,245 mmol) en 5 ml de THF seco a la solución y se agitó la

mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a vacío y se purificó el residuo por cromatografía en gel de sílice.

Etapa B

Éster etílico del ácido (2S)-(1*R**,3*S**)-3-[4-(3'-hidroxi-1'-ciclopentiloxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título siguiendo el Procedimiento estándar E, para obtener el producto.

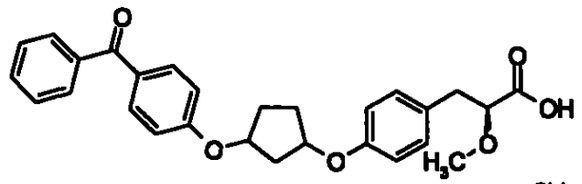
Etapa C

Ácido (2S)-(1'*R**,3'*R**)-2-metoxi-3-{4-[3'-(4-fenoxifenoxi)-1'-ciclopentiloxi]fenil}propiónico

Se trató el éster etílico del ácido (2S)-(1*R**,3*S**)-3-[4-(3'-hidroxi-1'-ciclopentiloxi)-fenil]-2-metoxipropiónico de la Etapa A con 4-fenoxifenol según el procedimiento de acoplamiento estándar de Mitsounobu B (THF). Se hidrolizó el producto obtenido tras la cromatografía usando el procedimiento de hidrólisis estándar C, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,34-7,26 (m, 2H), 7,17-7,04 (m, 3H), 7,00-6,92 (m, 4H), 6,88-6,78 (m, 4H), 4,94-4,89 (m, 2H), 3,99 (dd, 1H, J=7,3, 4,3), 3,41 (s, 3H), 3,10 (dd, 1H, J=14,2, 4,6), 2,96 (dd, 1H, J=14,2, 7,3), 2,28 (t, 2H, J=4,8), 2,21-1,89 (m, 4H). MS (ES) para $C_{27}H_{26}O_6$ $[M+NH_4]^+$: 466,2, $[M+Na]^+$: 471,2.

Ejemplo 84

Ácido (2S)-(1'*R**,3'*R**)-3-{4-[3-(4-benzoilfenoxi)-ciclopentiloxi]fenil}-2-metoxipropiónico

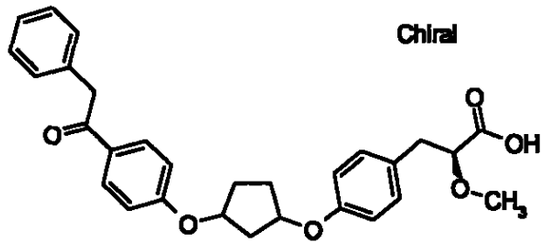


Chiral

Se preparó el compuesto del título de un modo análogo al del Ejemplo 83, partiendo de (1*R**,3*R**)-3-(terc-butildimetilsilaniloxi)ciclopentanol y 4-hidroxibenzofenona. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,83-7,73 (m, 4H), 7,56-7,42 (m, 3H), 7,15 (d, 2H, J=8,3), 6,92 (dd, 2H, J=7,0, 1,9), 6,80 (d, 2H, J=8,6), 5,03-5,01 (m, 1H), 4,96-4,92 (m, 1H), 3,98 (dd, 1H, J=7,3, 4,6), 3,39 (s, 3H), 3,09 (dd, 1H, J=14,5, 4,6), 2,95 (dd, 1H, J=14,2, 7,3), 2,40-1,91 (m, 6H). MS (ES) para $C_{28}H_{28}O_6$ $[M+H]^+$: 461,2, $[M+Na]^+$: 483,2.

Ejemplo 85

Ácido (2S)-(1'R*,3'R*)-2-metoxi-3-{4-[3-(4-fenilacetil-fenoxi)ciclopentiloxi]fenil}propiónico

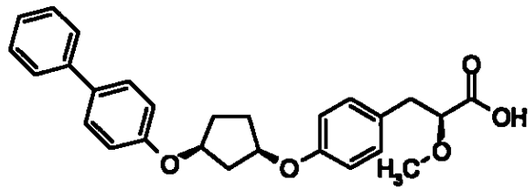


Se preparó el compuesto del título de un modo análogo al del Ejemplo 83, partiendo de (1*R**,3*R**)-3-(terc-butildimetilsilaniloxi)ciclopentanol y 1-(4-hidroxifenil)-2-feniletanona. MS (ES) para $C_{29}H_{30}O_6$ $[M+H]^+$: 475,2, $[M+Na]^+$: 497,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,97

(d, 2H, J=8,9), 7,32-7,23 (m, 5H), 7,15 (d, 2H, J=8,6), 6,91-6,77 (m, 4H), 5,01-4,91 (m, 2H), 4,22 (s, 2H), 3,98 (dd, 1H, J=7,3, 4,6), 3,40 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,6), 2,96 (dd, 1H, J=14,5, 7,3), 2,33-1,92 (m, 6H).

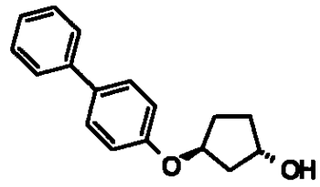
Ejemplo 86

Ácido (2S)-(1'*R*,3'*S*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico



Etapa A

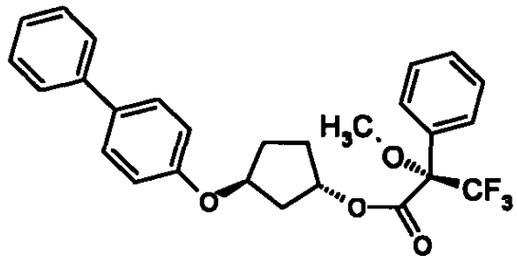
(1S*,3S*)-3-(Bifenil-4-iloxi)ciclopentanol



Se preparó el compuesto del título partiendo de (1*R**,3S*)-3-(terc-butildimetilsilaniloxi)ciclopentanol del Ejemplo 82, Etapa A, y conduciendo una reacción de acoplamiento estándar de Mitsounobu B (tolueno) con 4-fenilfenol. Se desprotegió entonces el producto por el Procedimiento estándar E para obtener el compuesto tras purificar por cromatografía.

Etapa B

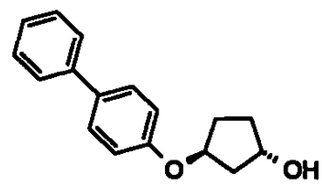
Éster 3'-(bifenil-4-iloxi)-1'-ciclopentílico del ácido (1'S,2S,3'S)-3,3,3-trifluoro-2-metoxi-2-fenilpropiónico



Se agitó una mezcla de (1S*,3S*)-3-(bifenil-4-iloxi)ciclopentanol de la Etapa A (1 eq) con ácido (*S*)-(-)-α-metoxi-α-(trifluorometil)fenilacético (1 eq), DMAP (0,1 eq) y EDCI (1,2 eq) en diclorometano a 36°C durante la noche. Se enfrió la mezcla de reacción y se concentró a sequedad. Se reconstituyó en éter y se lavó con HCl 1N y $NaHCO_3$. Se secó sobre $MgSO_4$ y se concentró a vacío, para obtener un producto bruto, el cual fue purificado por cromatografía en gel de sílice para obtener una mezcla diastereomérica, que fue separada usando HPLC quiral.

Etapa C

(1*S*,3*S*)-3-(Bifenil-4-iloxi)ciclopentanol



A una solución del compuesto de la Etapa C en etanol, se añadió un exceso de NaOH 1N y se agitó la mezcla de reacción a temperatura ambiente durante la noche. Se concentró la solución a vacío y se diluyó con salmuera. Se extrajo con éter y se concentró para obtener el compuesto del título.

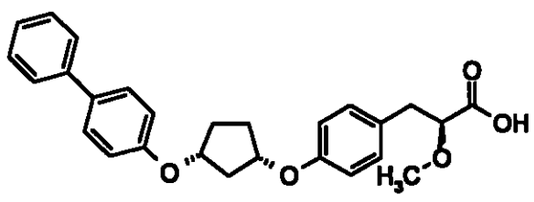
Etapa D

Ácido (2S)-(1'*R*,3'*S*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título usando el Procedimiento estándar para el acoplamiento-hidrólisis de Mitsounobu A en tolueno, para obtener el compuesto final. MS (ES) para $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450,2, $[M+Na]^+$: 455,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,56-7,28 (m, 6H), 7,15-7,08 (m, 3H), 6,95 (d, 2H, J=8,9), 6,84-6,73 (m, 2H), 4,81-4,79 (m, 2H), 3,98 (dd, 1H, J=7,0, 4,3), 3,40 (s, 3H), 3,10 (dd, 1H, J=14,2, 4,0), 2,95 (dd, 1H, J=14,2, 7,3), 2,58-2,44 (m, 1H), 2,19-2,02 (m, 5H).

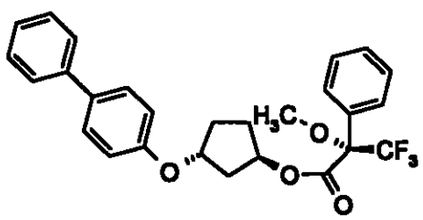
Ejemplo 87

Ácido (2S)-(1'*S*,3'*R*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico



Etapa A

Éster 3'-(bifenil-4-iloxi)-1'-ciclopentílico del ácido (1'R,2S,3'R)-3,3,3-trifluoro-2-metoxi-2-fenilpropiónico



Se agitó una mezcla de (1S*, 3S*)-3-(bifenil-4-iloxi)ciclopentanol de la Etapa A (1 eq) con ácido (*S*)-(-)-α-metoxi-α-(trifluorometil)fenilacético (1 eq), DMAP (0,1 eq) y EDCI (1,2 eq) en diclorometano a 36°C durante

la noche. Se enfrió la mezcla de reacción y se concentró a sequedad. Se reconstituyó en éter y se lavó con HCl 1N y $NaHCO_3$. Se secó sobre $MgSO_4$ y se concentró a vacío, para obtener un producto bruto, el cual fue purificado por cromatografía en gel de sílice para obtener una mezcla diastereomérica, que fue separada por HPLC quiral.

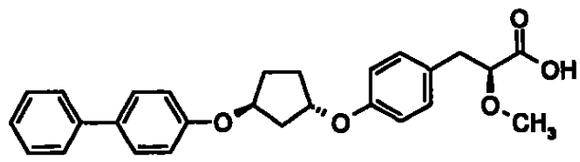
Etapa B

Ácido (2S)-(1'S,3'R)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título usando los mismos procedimientos que en el Ejemplo 86, Etapas C y D, para obtener el compuesto final. MS (ES) para $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450,2, $[M+Na]^+$: 455,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,56-7,28 (m, 6H), 7,15-7,08 (m, 3H), 6,95 (d, 2H, J=8,9), 6,84-6,73 (m, 2H), 4,81-4,79 (m, 2H), 3,98 (dd, 1H, J=7,0, 4,3), 3,40 (s, 3H), 3,10 (dd, 1H, J=14,2, 4,0), 2,95 (dd, 1H, J=14,2, 7,3), 2,58-2,44 (m, 1H), 2,19-2,02 (m, 5H).

Ejemplo 88

Ácido (2S)-(1'*S*,3'*S*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico



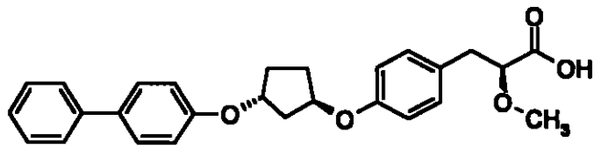
Chiral

Se preparó el compuesto del título a partir de ácido (2S)-(1'*R**,2'*R**)3-{4-[3-(bifenil-4-iloxi)-ciclopentiloxi]fenil}-2-metoxipropiónico de O, Etapa D, el cual fue purificado por HPLC quiral para obtener el enantiómero correspondiente. MS (ES) para $C_{27}H_{28}O_5$ $[M+NH_4]^+$: 450,2, $[M+Na]^+$: 455,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,57-7,29 (m, 7H), 7,15 (d, 2H, J=8,6), 6,94 (d, 2H, J=8,9), 6,81 (d, 2H, J=8,6), 4,99-4,91 (m, 2H), 3,99 (dd, 1H,

J=7,3, 4,6), 3,41 (s, 3H), 3,10 (dd, 1H, J=14,2, 4,6), 2,96 (dd, 1H, J=14,5, 7,3), 2,31 (t, 2H, J=4,8), 2,26-1,97 (m, 4H).

Ejemplo 89

Ácido (2S)-(1'*R*,3'*R*)3-{4-[3'-(bifenil-4-iloxi)-1'-ciclopentiloxi]fenil}-2-metoxipropiónico

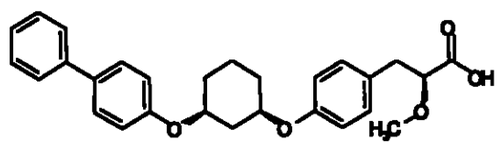


Chiral

Se preparó el compuesto del título a partir de ácido (2S)-(1'*R**,2'*R**)3-{4-[3-(bifenil-4-iloxi)-ciclopentiloxi]fenil}-2-metoxipropiónico del Ejemplo 81, Etapa D, el cual fue purificado por HPLC quiral para obtener el correspondiente enantiómero. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,57-7,29 (m, 7H), 7,15 (d, 2H, J=8,6), 6,94 (d, 2H, J=8,9), 6,81 (d, 2H, J=8,6), 4,99-4,91 (m, 2H), 3,99 (dd, 1H, J=7,3, 4,6), 3,41 (s, 3H), 3,10 (dd, 1H, J=14,2, 4,6), 2,96 (dd, 1H, J=14,5, 7,3), 2,31 (t, 2H, J=4,8), 2,26-1,97 (m, 4H). MS (ES) para $C_{27}H_{28}O_5$ $[M+Na]^+$: 455.

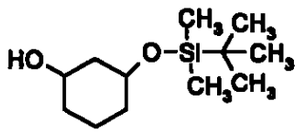
Ejemplo 90

Ácido (2S)-(1'*R*,3'*S*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil}-2-metoxipropiónico



Etapa A

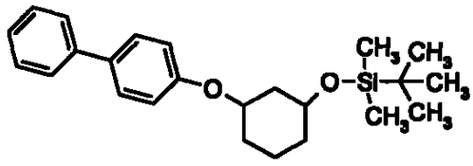
3-(terc-Butildimetilsilaniloxi)ciclohexanol



Se preparó el compuesto del título siguiendo el Procedimiento estándar D para la monoprotección de dioles, para obtener el producto en forma de aceite incoloro.

Etapa B

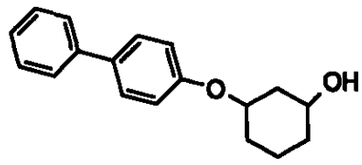
[3-(Bifenil-4-iloxi)ciclohexiloxi]-terc-butildimetilsilano



Se preparó el compuesto del título usando el Procedimiento estándar para el acoplamiento de Mitsounobu B (tolueno), para obtener el producto como un aceite incoloro. MS (ES) para $C_{24}H_{34}O_2Si$: $[M+H]^+$: 383,3.

Etapa C

3-(Bifenil-4-iloxi)ciclohexanol

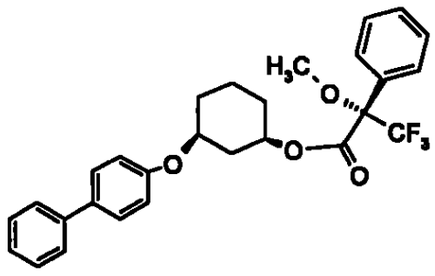


Se preparó el compuesto del título mediante el Procedimiento estándar E para la escisión de los alcoholes protegidos, para obtener una mezcla de los cuatro isómeros de los compuestos. Se purificó la mezcla por cromatografía en gel de sílice, para obtener los dos isómeros correspondientes: (trans) (1*S**,3*S**)-3-(bifenil-4-iloxi)ciclohexanol ^{1}H-RMN ($CDCl_3$, 500,00 MHz): 7,55 (d, J

= 7,3 Hz, 2H); 7,51 (d, J = 8,5 Hz, 2H); 7,41 (t, J = 7,9 Hz, 2H); 7,30 (t, J = 7,3 Hz, 1H); 6,97 (d, J = 8,5 Hz, 2H); 4,74-4,72 (m, 1H); 4,20-4,15 (m, 1H); 2,09-2,04 (m, 1H); 1,86-1,70 (m, 6H); 1,53-1,27 (m, 3H) ppm y (cis) (1R*,3S*)-3-(bifenil-4-iloxi)ciclohexanol ^{1}H-RMN ($CDCl_3$, 500,00 MHz): 7,54 (d, J = 7,6 Hz, 2H); 7,51 (d, J = 8,5 Hz, 2H); 7,41 (t, J = 7,6 Hz, 2H); 7,30 (t, J = 7,3 Hz, 1H); 6,97 (d, J = 8,5 Hz, 2H); 4,39-4,36 (m, 1H); 3,83-3,80 (m, 1H); 2,31 (d, J = 12,3 Hz, 1H); 2,04-1,85 (m, 4H); 1,72-1,34 (m, 10H)ppm.

Etapa D

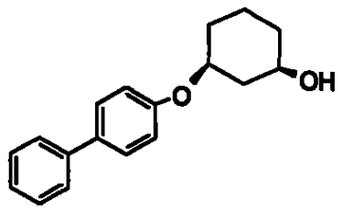
Éster 3-(bifenil-4-iloxi)-1-ciclohexílico del ácido (1*R*,3*S*)-(2S)-3,3,3-trifluoro-2-metoxi-2-fenilpropiónico



Se agitó una mezcla de (1*R**,3*S**)-3-(bifenil-4-iloxi)ciclohexanol de la Etapa C (1 eq) con ácido (*S*)-(-)-α-metoxi-α-(trifluorometil)fenilacético (1 eq), DMAP (0,1 eq) y EDCI (1,2 eq) en diclorometano a 36°C durante la noche. Se enfrió la mezcla de reacción y se concentró a sequedad. Se reconstituyó en éter y se lavó con HCl 1N y $NaHCO_3$. Se secó sobre $MgSO_4$ y se concentró a vacío, para obtener un producto bruto que fue purificado por cromatografía en gel de sílice para obtener una mezcla diastereomérica, la cual fue separada usando HPLC quiral.

Etapa E

(1R,3S)-3-(Bifenil-4-iloxi)ciclohexanol



A una solución del compuesto de la Etapa D en etanol, se añadió un exceso de NaOH 1N y se agitó la mezcla de reacción a temperatura ambiente. Se concentró la solución a vacío y se diluyó con salmuera. Se extrajo con éter y se concentró para obtener el compuesto del título.

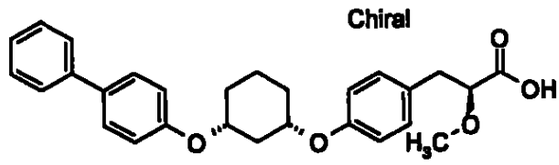
Etapa F

Ácido (2S)-(1'*S*,3'*R*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título usando el Procedimiento estándar para el acoplamiento-hidrólisis de Mitsounobu A en tolueno, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,73-7,28 (m, 7H), 7,12 (dd, 2H, J=10,2, 8,6), 7,00-6,93 (m, 1H), 6,86-6,73 (m, 2H), 4,34-4,19 (m, 2H), 3,98 (dd, 1H, J=7,3, 4,3), 3,39 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,0), 2,94 (dd, 1H, J=14,5, 7,3), 2,67-2,61 (m, 1H), 2,27-2,18 (m, 1H), 1,96-1,93 (m, 1H), 1,71-1,54 (m, 1H), 1,46-1,37 (m, 3H).

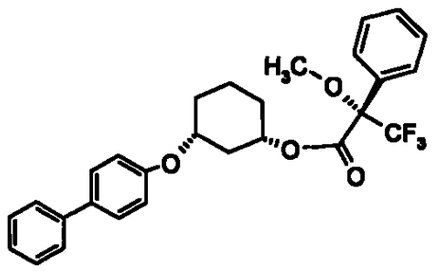
Ejemplo 91

Ácido (2S)-(1'*S*,3'*R*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil}-2-metoxipropiónico



Etapa A

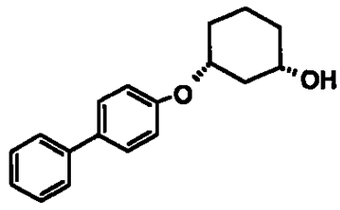
Éster 3-(bifenil-4-iloxi)-1-ciclohexílico del ácido (1*S*,3*R*)-(2S)-3,3,3-trifluoro-2-metoxi-2-fenilpropiónico



Se agitó una mezcla de (1*R**, 3*S**)-3-(bifenil-4-iloxi)ciclohexanol del Ejemplo 90, Etapa C (1 eq) con ácido (*S*)-(-)-α-metoxi-α-(trifluorometil)fenilacético (1 eq), DMAP (0,1 eq) y EDCI (1,2 eq) en diclorometano a 36°C durante la noche. Se enfrió la mezcla de reacción y se concentró a sequedad. Se reconstituyó en éter y se lavó con HCl 1N y $NaHCO_3$. Se secó sobre $MgSO_4$ y se concentró a vacío, para obtener un producto bruto, que fue purificado por cromatografía en gel de sílice para obtener una mezcla diastereomérica, que fue separada usando HPLC quiral.

Etapa B

(1*S*,3*R*)-3-(Bifenil-4-iloxi)ciclohexanol



Se preparó el compuesto usando el mismo procedimiento que en el Ejemplo 90, Etapa E.

Etapa C

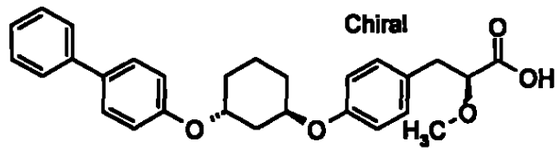
Ácido (2S)-(1'*S*,3'*R*)-3-[4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil)-2-metoxipropiónico

Se preparó el compuesto del título usando el Procedimiento estándar para el acoplamiento-hidrólisis de Mitsounobu A en tolueno, para obtener el compuesto final.

^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,73-7,28 (m, 7H), 7,12 (dd, 2H, J=10,2, 8,6), 7,00-6,93 (m, 1H), 6,86-6,73 (m, 2H), 4,34-4,19 (m, 2H), 3,98 (dd, 1H, J=7,3, 4,3), 3,39 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,0), 2,94 (dd, 1H, J=14,5, 7,3), 2,67-2,61 (m, 1H), 2,27-2,18 (m, 1H), 1,96-1,93 (m, 1H), 1,71-1,54 (m, 1H), 1,46-1,37 (m, 3H).

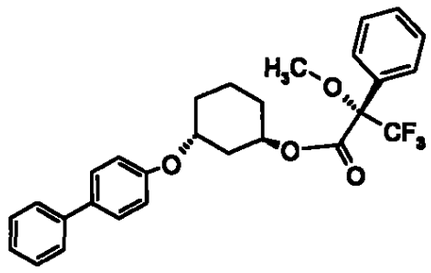
Ejemplo 92

Ácido (2S)-(1'*R*,3'*R*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil}-2-metoxipropiónico



Etapa A

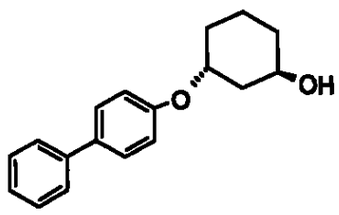
Éster 3-(bifenil-4-iloxi)-1-ciclohexílico del ácido (1R,3*R*)-(2S)-3,3,3-trifluoro-2-metoxi-2-fenilpropiónico



Se agitó una mezcla de (1R*,3R*)-3-(bifenil-4-iloxi)ciclohexanol (trans) del Ejemplo 90, Etapa C, (1 eq) con ácido (*S*)-(-)-α-metoxi-α-(trifluorometil)fenilacético (1 eq), DMAP (0,1 eq) y EDCI (1,2 eq) en diclorometano a 36°C durante la noche. Se enfrió y concentró a sequedad la mezcla de reacción. Se reconstituyó en éter y se lavó con HCl 1N y $NaHCO_3$. Se secó sobre $MgSO_4$ y se concentró a vacío, para obtener un producto bruto que fue purificado por cromatografía en gel de sílice, para obtener una mezcla diastereomérica, que fue separada usando HPLC quiral.

Etapa B

(1*R*,3*R*)-3-(Bifenil-4-iloxi)ciclohexanol



Se preparó el compuesto usando el mismo procedimiento que en el Ejemplo 90, Etapa E.

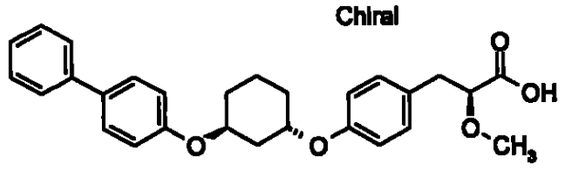
Etapa C

Ácido (2S)-(1'*R*,3'*R*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título usando el Procedimiento estándar para el acoplamiento-hidrólisis de Mitsounobu A en tolueno, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,57-7,27 (m, 7H), 7,13 (d, 2H, J=8,6), 6,96 (dd, 2H, J=6,7, 2,1), 6,83 (d, 2H, J=8,9), 4,75-4,72 (m, 2H), 4,00-3,95 (m, 1H), 3,38 (s, 3H), 3,09 (dd, 1H, J=14,8, 4,3), 2,94 (dd, 1H, J=14,5, 7,5), 2,12-2,05 (m, 3H), 1,80-1,78 (m, 5H).

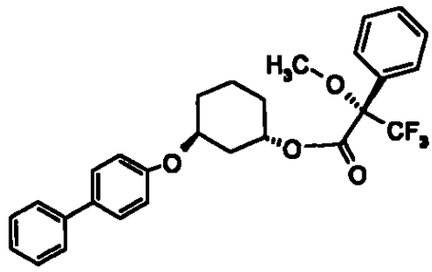
Ejemplo 93

Ácido (2S)-(1'S,3'*S*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil}-2-metoxipropiónico



Etapa A

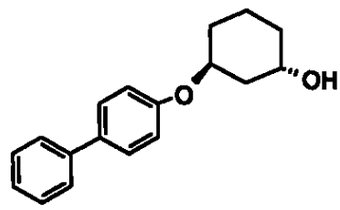
Éster 3-(bifenil-4-iloxi)-1-ciclohexílico del ácido (1*S*,3*S*)-(2S)-3,3,3-trifluoro-2-metoxi-2-fenilpropiónico



Se agitó una mezcla de (1R*,3R*)-3-(bifenil-4-iloxi)ciclohexanol (trans) del Ejemplo 90, Etapa C, (1 eq) con ácido (*S*)-(-)-α-metoxi-α-(trifluorometil)-fenil-acético (1 eq), DMAP (0,1 eq) y EDCI (1,2 eq) en diclorometano a 36°C durante la noche. Se enfrió la mezcla de reacción y se concentró a sequedad. Se reconstituyó en éter y se lavó con HCl 1N y $NaHCO_3$. Se secó sobre $MgSO_4$ y se concentró a vacío, para obtener un producto bruto que fue purificado por cromatografía en gel de sílice para obtener una mezcla diastereomérica, la cual fue separada por HPLC quiral.

Etapa B

(1*S*,3*S*)-3-(Bifenil-4-iloxi)ciclohexanol



Se preparó el compuesto usando el mismo procedimiento que en el Ejemplo 90, Etapa E.

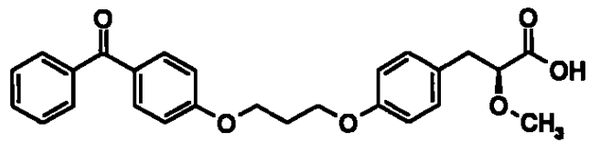
Etapa C

Ácido (2S)-(1'S,3'*S*)-3-{4-[3'-(bifenil-4-iloxi)-1'-ciclohexiloxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título usando el Procedimiento estándar para el acoplamiento-hidrólisis de Mitsounobu A en tolueno, para obtener el compuesto final. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,57-7,27 (m, 7H), 7,13 (d, 2H, J=8,6), 6,96 (dd, 2H, J=6,7, 2,1), 6,83 (d, 2H, J=8,9), 4,75-4,72 (m, 2H), 4,00-3,95 (m, 1H), 3,38 (s, 3H), 3,09 (dd, 1H, J=14,8, 4,3), 2,94 (dd, 1H, J=14,5, 7,5), 2,12-2,05 (m, 3H), 1,80-1,78 (m, 5H).

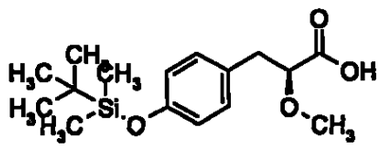
Ejemplo 94

Ácido (2S)-3-{4-[3-(4-benzoilfenoxi)propoxi]-fenil}-2-metoxipropiónico



Etapa A

Ácido (2S)-3-[4-(*terc*-butildimetilsilaniloxi)fenil)-2-metoxipropiónico

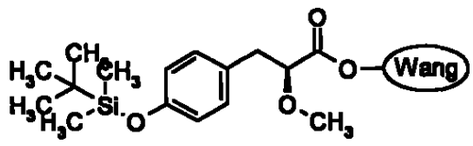


A una solución de ácido (2S)-3-hidroxifenil-2-metoxipropiónico (7,30 g, 37,2 mmol) en 40 ml de DMF seca, se añadieron cloruro de *terc*-butildimetilsililo (11,80 g, 78,2 mmol) e imidazol (5,32 g, 78,2 mmol). Se agitó la solución a temperatura ambiente durante la noche. Se añadió agua (40 ml) y se extrajo la fase acuosa con hexanos (40 ml). Se lavó la capa orgánica con agua (50 ml), se secó ($MgSO_4$) y se concentró. Se disolvió el material bruto en THF (20 ml) y se añadió una solución

saturada de $NaHCO_3$ (20 ml). Se agitó la mezcla resultante durante 2 horas a temperatura ambiente. Se extrajo la capa acuosa con acetato de etilo (40 ml), se acidificó a pH 3 y se extrajo de nuevo con acetato de etilo (3 x 40 ml). Se lavaron las capas orgánicas combinadas con salmuera (60 ml) y se secaron ($MgSO_4$) y se concentraron a un aceite amarillo (11,5 g, 99%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,09 (d, 2H, *J*=8,3), 6,76 (d, 2H, *J*=8,6), 3,97 (dd, 1H, *J*=7,5, 4,3), 3,38 (s, 3H), 3,09 (dd, 1H, *J*=14,5, 4,3), 2,93 (dd, 1H, *J*=14,2, 7,3), 0,97 (s, 9H), 0,18 (6H, s).

Etapa B

Preparación de ácido (2S)-3-[4-(*terc*-butildimetilsilanil-oxi)fenil]-2-metoxipropiónico unido a resina de Wang

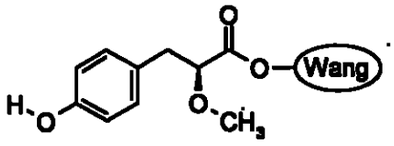


Se llevó a cabo la reacción en una jeringa de polipropileno equipada con una frita de polipropileno. Se suspendió resina de Wang (1 eq, aprox. 1,2 mmol/g resina) en diclorometano (0,05 M) y se añadieron ácido (2S)-3-[4-(*terc*-butildimetilsilaniloxi)fenil]-2-metoxipropiónico (1,5 eq), diisopropilcarbodiimida (2,0 eq) y una cantidad catalítica de dimetilaminopiridina. Se agitó la mezcla a temperatura ambiente durante la noche. Se eliminó el solvente de la reacción y se lavó la resina secuencialmente con CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), metanol y CH_2Cl_2 (2x). Se secó la resina a vacío durante 5 horas. Se suspendió la resina en CH_2Cl_2 (0,05 M) y se trató con anhídrido acético (5 eq) y una cantidad catalítica de dimetilaminopiridina durante 2 horas. Se eliminó el solvente y se lavó la resina secuencialmente con una mezcla 1:1 de ácido acético/CH_2Cl_2 (3x), CH_2Cl_2 (2x), metanol y CH_2Cl_2 (2x) y se secó a vacío durante la noche, para obtener ácido (2S)-3-[4-(*terc*-

ácido (2S)-3-[4-(*terc*-butildimetilsilaniloxi)fenil]-2-metoxipropiónico unido a resina de Wang.

Etapa C

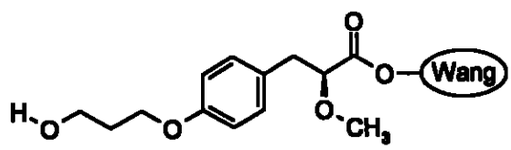
Preparación de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico unido a resina de Wang



Se llevó a cabo la reacción en una jeringa de polipropileno equipada con una frita de polipropileno. A una suspensión de ácido (2S)-3-[4-(*terc*-butildimetilsilaniloxi)fenil]-2-metoxipropiónico unido a resina de Wang (1 eq) en diclorometano (0,05 M), se añadió fluoruro de tetrabutilamonio (aprox. 5 eq). Se agitó la mezcla a temperatura ambiente durante 3 horas. Se eliminó el solvente y se lavó la resina secuencialmente con CH_2Cl_2 (2x), DMF (2x), CH_2Cl_2 (2x), metanol, y CH_2Cl_2 (2x). Se secó la resina a vacío durante la noche para producir ácido (2S) 3-(4-hidroxifenil)-2-metoxipropiónico unido a resina de Wang. La escisión de 20 mg de la resina en TFA/CH_2Cl_2 1:1, seguido de evaporación del solvente, produjo ácido (*S*)-3-(4-hidroxifenil)-2-metoxipropiónico en forma de aceite. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,10 (d, 2H, *J*=8,6), 6,76 (d, 2H, *J*=8,6), 3,99 (dd, 1H, *J*=7,0, 4,6), 3,41 (s, 3H), 3,10 (dd, 1H, *J*=14,5, 4,6), 2,95 (dd, 1H, *J*=14,5, 7,5).

Etapa D

Preparación de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang



Se preparó el compuesto del título a partir de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico unido a resina de Wang mediante el acoplamiento de Mitsunobu (Procedimiento estándar F), para producir ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang. La escisión de 20 mg de la resina en TFA/CH_2Cl_2 1:1, seguido de evaporación del solvente, produjo ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico en forma de aceite. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,16 (d, 2H, *J*=8,6), 6,82 (d, 2H, *J*=8,6), 4,56 (t, 1H, *J*=6,2), 4,09 (2H, dd, *J*=13,2, 5,9), 3,99 (dd, 1H, *J*=6,7, 4,0), 3,90 (1H, t, *J*=5,9), 3,40 (s, 3H), 3,10 (dd, 1H, *J*=14,2, 4,0), 2,96 (dd, 1H, *J*=14,2, 7,3), 2,22 (q, 1H, *J*=5,9), 2,05 (q, 1H, *J*=5,9).

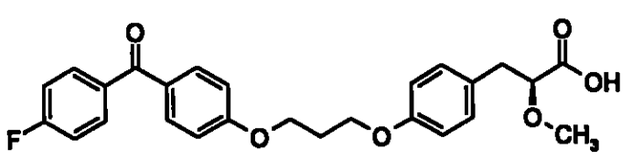
Etapa E

Ácido (2S)-3-{4-[3-(4-benzoilfenoxi)propoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang mediante el procedimiento de acoplamiento-escisión de la resina de Mitsunobu (Procedimiento estándar G), para obtener 1,6 mg de un sólido blanco (6%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,82-7,72 (m, 4H), 7,57-7,43 (m, 3H), 7,14 (d, 2H, *J*=8,8), 6,96 (d, 2H, *J*=8,8), 6,84 (d, 2H, *J*=8,8), 4,25 (t, 2H, *J*=6,0), 4,14 (t, 2H, *J*=6,0), 4,00 (dd, 1H, *J*=6,8, 4,6 Hz), 3,41 (s, 3H), 3,10 (dd, 1H, *J*=14,1, 4,6), 2,97 (dd, 1H, *J*=14,1, 6,8), 2,28 (q, 2H, *J*=6,0).

Ejemplo 95

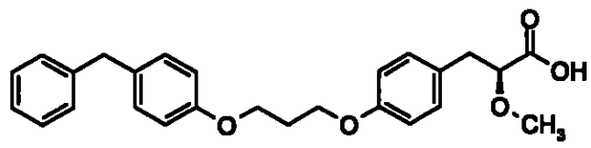
Ácido (2S)-3-(4-{3-[4-(4-fluorobenzoil)fenoxi]propoxi}-fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-hidroxibenzofenona y la escisión de la resina (Procedimiento estándar G) dio lugar a un aceite (7%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,82-7,73 (m, 4H), 7,19-7,10 (m, 4H), 6,96 (d, 2H, *J*=8,9), 6,84 (d, 2H, *J*=8,9), 4,25 (t, 2H, *J*=6,0), 4,15 (t, 2H, *J*=6,0), 4,00 (dd, 1H, *J*=6,7, 4,6), 3,41 (s, 3H), 3,10 (dd, 1H, *J*=14,1, 4,6), 2,97 (dd, dd, *J*=14,1, 6,8), 2,28 (q, 2H, *J*=6,0). MS (ES) para $C_{26}H_{25}FO_6$ $[M+H]^+$: 453,2, $[M+Na]^+$: 475,2.

Ejemplo 96

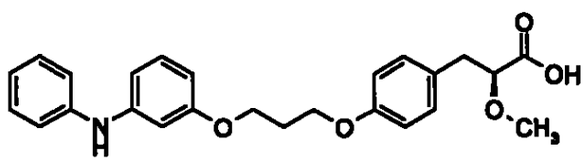
<u>Ácido (2S)-3-{4-[3-(4-bencilfenoxi)propoxi]fenil}-2-metoxipropiónico</u>



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-hidroxidifenilmetano y la escisión de la resina (Procedimiento estándar G) produjo un sólido blanco (5%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,29-7,13 (m, 6H), 7,08 (d, 2H, *J*=8,9), 6,82 (d, 2H, *J*=8,6), 4,12 (t, 4H, *J*=6,2), 3,97 (dd, 1H, *J*=6,6, 4,0), 3,39 (s, 3H), 3,10 (dd, 1H, *J*=14,2, 4,0), 2,95 (dd, 1H, *J*=14,2, 6,6), 2,22 (q, 2H, *J*=6,2).

Ejemplo 97

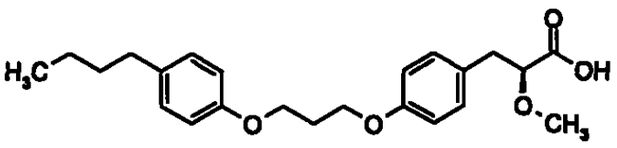
Ácido (2S)-2-metoxi-3-{4-[3-(3-fenilaminofenoxi)-propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 3-hidroxidifenilamina y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso (4%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,31-6,81 (m, 8H), 6,83 (d, 2H, *J*=8,6), 6,65-6,62 (m, 2H), 6,48 (dd, 1H, *J*=8,2, 2,1), 4,12 (t, 4H, *J*=6,2), 3,99 (dd, 1H, *J*=7,0, 4,4), 3,40 (s, 3H), 3,10 (dd, 1H, *J*=14,2, 4,4), 2,95 (dd, 1H, *J*=14,2, 7,0), 2,22 (q, 2H, *J*=6,2).

Ejemplo 98

Ácido (2S)-3-{4-[3-(4-butilfenoxi)propoxi]fenil}-2-metoxipropiónico

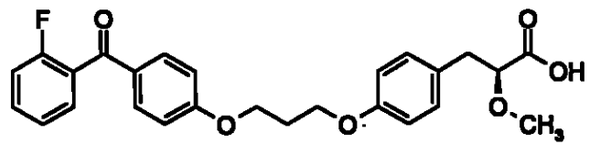


Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-n-butilfenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso (7%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,11 (dd, 4H, *J*=12,7, 8,6), 6,82 (dd, 4H, *J*=8,6, 3,2), 4,12 (t, 4H, *J*=6,2), 3,97 (dd, 1H, *J*=7,7, 4,4), 3,38 (s, 3H),

3,30 (dd, 1H, J=14,5, 4,4), 2,94 (dd, 1H, J=14,5, 7,7), 2,54 (t, 2H, J=7,7), 2,23 (q, 2H, J=6,2), 1,63-1,48 (m, 2H), 1,42-1,24 (m, 2H), 0,91 (t, 3H, J=7,2).

Ejemplo 99

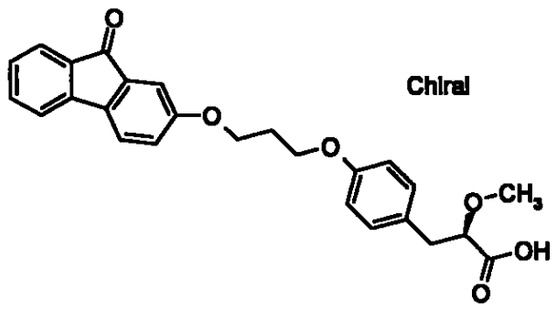
Ácido (2S)-3-{4-{3-[4-(2-fluorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 2-fluoro-4'-hidroxibenzofenona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso (7%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,81 (dd, 2H, J=8,8, 1,3), 7,54-7,45 (m, 2H), 7,28-7,09 (m, 4H), 6,94 (d, 2H, J=8,6), 6,83 (d, 2H, J=8,6), 4,24 (t, 2H, J=6,2), 4,14 (t, 2H, J=6,2), 3,98 (dd, 1H, J=7,0, 4,6), 3,40 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,6), 2,96 (dd, 1H, J=14,2, 7,0), 2,28 (q, 2H, J=6,2).

Ejemplo 100

Ácido (2S)-2-metoxi-3-{4-[3-(9-oxo-9H-fluoren-2-iloxi)-propoxi]fenil}propiónico

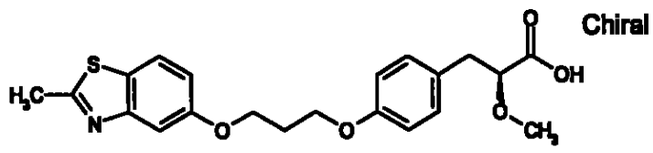


Se preparó el compuesto del título a partir

de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 2-hidroxi-9-fluorenona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,59 (d, 1H, J= 7,0); 7,43-7,37 (m, 3H); 7,26-7,13 (m, 4H); 6,98 (dd, 1H, J= 8,1, 2,4); 6,85 (d, 2H, J= 8,6); 4,17 (q, 4H, J= 5,6); 3,99 (dd, 1H, J= 7,0, 4,6); 3,40 (s, 3H); 3,10 (dd, 1H, J= 14,2, 4,6); 2,96 (dd, 1H, J= 14,2, 7,0); 2,32-2,23 (m, 4H) ppm.

Ejemplo 101

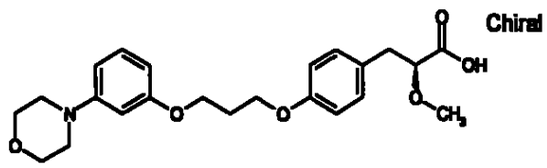
Ácido (2S)-2-metoxi-3-{4-[3-(2-metilbenzotiazol-5-iloxi)-propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxi-propiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 2-metil-5-benzotiazolol y la escisión de la resina (Procedimiento estándar G), para obtener un sólido oleoso. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,65 (d, 1 H, J=8,9), 7,36-7,35 (m, 1 H), 7,16 (d, 2 H, J=8,9), 7,03 (dd, 1 H, J=8,9, 2,4), 6,86 (dd, 2 H, J=6,5, 1,9), 4,22 (t, 2 H, J=5,9), 4,18 (t, 2 H, J=6,2), 4,01 (dd, 2 H, J=6,4, 5,4), 3,43 (s, 3 H), 3,14-2,94 (m, 2 H), 2,87 (s, 3 H), 2,27 (q, 2 H, J=6,2) ppm.

Ejemplo 102

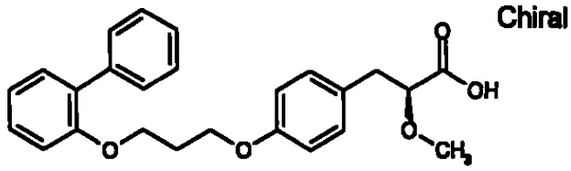
Ácido (2S)-2-metoxi-3-{4-[3-(3-morfolin-4-ilfenoxi)-propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 3-(4-morfolino)-fenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,32-7,23 (m, 1 H), 7,14-7,10 (m, 2 H), 6,84-6,69 (m, 5 H), 4,14 (c, 4 H, J=5,6), 4,02-3,94 (m, 5 H), 3,40 (s, 3 H), 3,33-3,28 (m, 4 H), 3,13-2,91 (m, 2 H), 2,23 (q, 2 H, J=5,9) ppm.

Ejemplo 103

Ácido (2S)-3-{4-[3-(bifenil-2-iloxi)propoxi]fenil}-2-metoxipropiónico

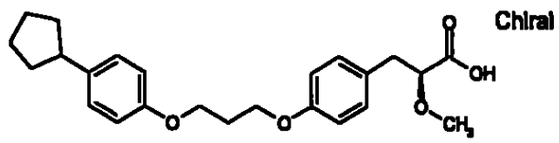


Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 2-fenilfenol y la escisión de la resina (Procedimiento estándar G), para obtener el compuesto del título. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,51-7,43 (m, 2 H), 7,38-7,29 (m, 5 H), 7,15-6,98 (m, 4 H), 6,79-6,72 (m, 2 H), 4,15 (t, 2 H, J = 5,9 Hz),

4,04-3,96 (m, 3 H), 3,39 (s, 3 H), 3,15-2,90 (m, 2 H), 2,15 (q, 2 H, J = 5,9 Hz) ppm.

Ejemplo 104

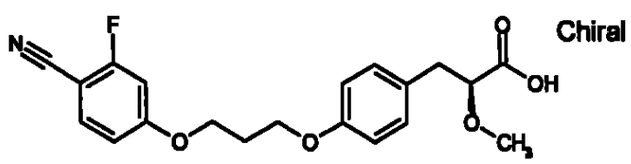
Ácido (2S)-3-{4-[3-(4-ciclopentilfenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-ciclopentilfenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 105

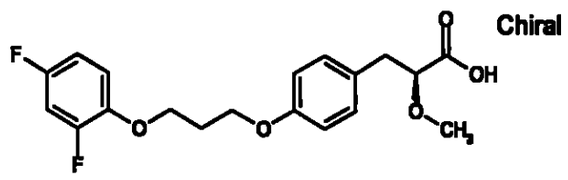
Ácido (2S)-3-{4-[3-(4-ciano-3-fluorofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 2-fluoro-4-hidroxibenzonitrilo y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 106

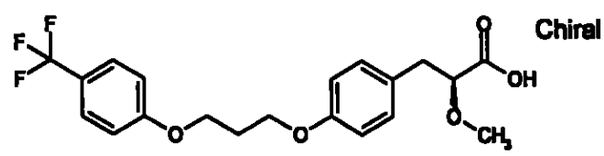
Ácido (2S)-3-{4-[3-(2,4-difluorofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 2,4-difluorofenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 107

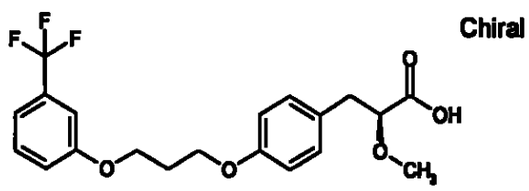
Ácido (2S)-2-metoxi-3-{4-[3-(4-trifluorometilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-trifluorometilfenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 108

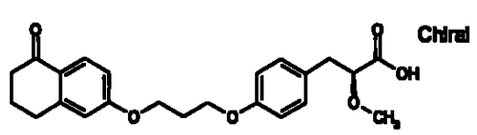
Ácido (2S)-2-metoxi-3-{4-[3-(3-trifluorometilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 3-trifluorometilfenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 109

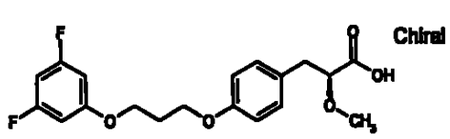
Ácido (2S)-2-metoxi-3-{4-[3-(5-oxo-5,6,7,8-tetrahidronaftalen-2-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 6-hidroxi-1,2,3,4-tetrahidronaftalenona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 110

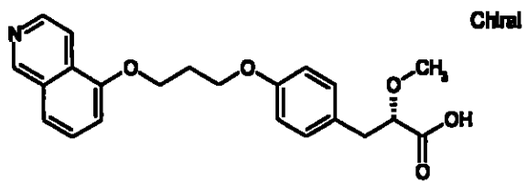
Ácido (2S)-3-{4-[3-(3,5-difluorofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 3,5-difluorofenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 111

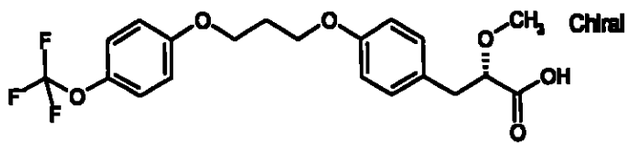
Ácido (2S)-3-{4-[3-(isoquinolin-5-iloxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipro-piónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 5-hidroxiisoqui-nolina y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 112

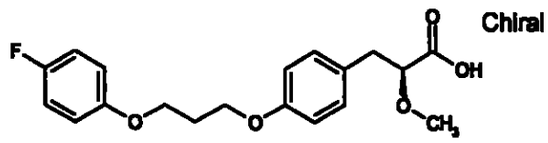
Ácido (2S)-2-metoxi-3-{4-[3-(4-trifluorometoxifenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-trifluorometoxifenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 113

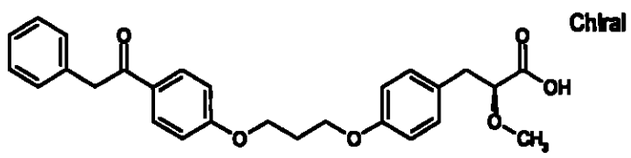
Ácido (2S)-3-{4-[3-(4-fluorofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-fluorofenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 114

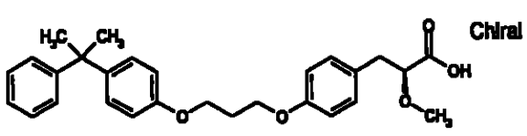
Ácido (2S)-2-metoxi-3-{4-[3-(4-fenilacetilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipro-piónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con bencil-4-hidroxifenilcetona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 115

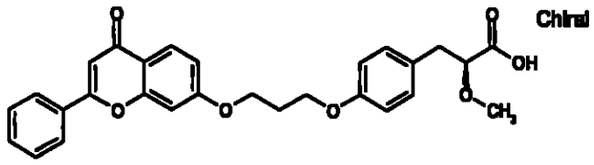
Ácido (2S)-2-metoxi-3-(4-{3-[4-(1-metil-1-feniletil)fenoxi]propoxi}fenil)propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-cumilfenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 116

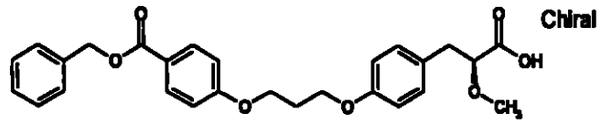
Ácido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-7-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 7-hidroxiflavona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 117

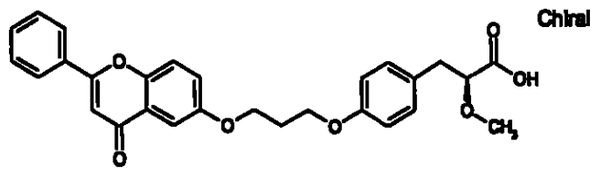
Éster bencílico del ácido 4-{3-[4-(2-carboxi-2-metoxi-etil)fenoxi]propoxi}benzoico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-hidroxibenzoato de bencilo y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 118

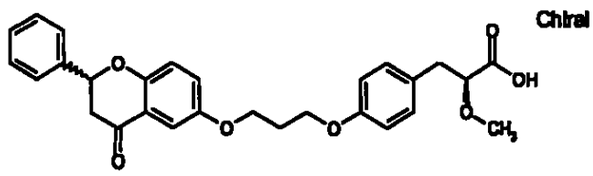
Ácido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenilcroman-6-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 6-hidroxiflavona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 119

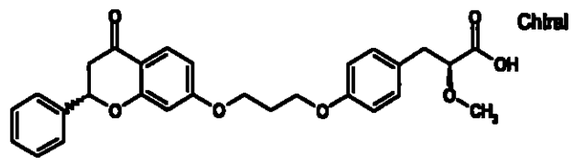
Ácido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenilcroman-6-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 6-hidroxiflavanona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 120

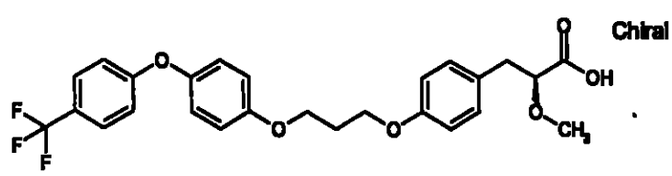
Ácido (2S)-2-metoxi-3-{4-[3-(4-oxo-2-fenilcroman-7-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 7-hidroxiflavanona y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

Ejemplo 121

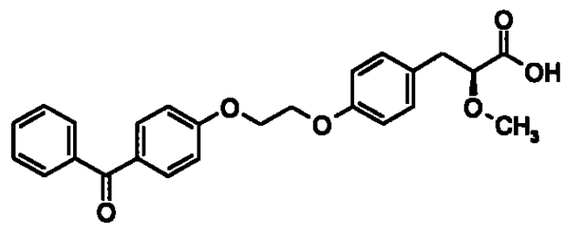
Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-trifluorometilfenoxi)-fenoxi]propoxi}fenil)propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el acoplamiento de Mitsunobu con 4-(4-trifluorometil)fenoxifenol y la escisión de la resina (Procedimiento estándar G) dio un sólido oleoso.

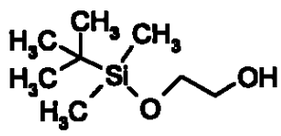
Ejemplo 122

Ácido (2S)-3-{4-[2-(4-benzoilfenoxi)etoxi]fenil}-2-metoxipropiónico



Etapa A

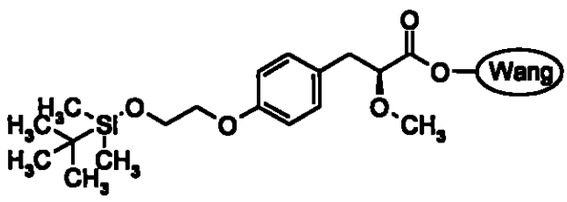
2-(*terc*-butildimetilsilaniloxi)etanol



A una solución de etilenglicol (1,00 g, 16,1 mmol) en THF (80 ml) se añadió NaH (0,65 mg, 16,1 mmol, dispersión al 60% en aceite) a 0°C. Se agitó la reacción durante 1 hora, se añadió cloruro de *terc*-butildimetilsililo (2,35 g, 16,1 mmol) y se dejó calentar a la mezcla de reacción a temperatura ambiente. Después de 3 horas a temperatura ambiente. Se añadió una solución saturada de Na_2CO_3 (80 ml) y se extrajo la capa acuosa con acetato de etilo (3 x 50 ml). Se lavaron las capas orgánicas combinadas con agua (80 ml) y salmuera (80 ml), se secaron sobre $MgSO_4$ y se concentraron a vacío. Se purificó el producto bruto de la reacción por cromatografía en columna de gel de sílice (gel de sílice, hexanos/acetato de etilo, 2:3) para producir 1,93 g (85%) de un aceite amarillo. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 3,74-3,59 (m, 4H), 0,91 (s, 9H), 0,08 (s, 6H).

Etapa B

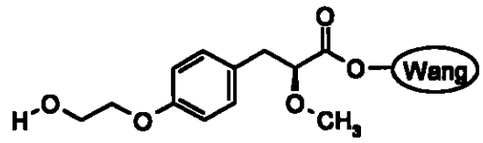
Preparación de ácido (2S)-3-{4-[2-(*terc*-butildimetilsilaniloxi)etoxi]fenil}-2-metoxipropanoico unido a resina de Wang



Se preparó el compuesto del título a partir de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa D) mediante el procedimiento de acoplamiento de Mitsunobu con 2-(*terc*-butildimetilsilaniloxi)etanol (Procedimiento estándar B).

Etapa C

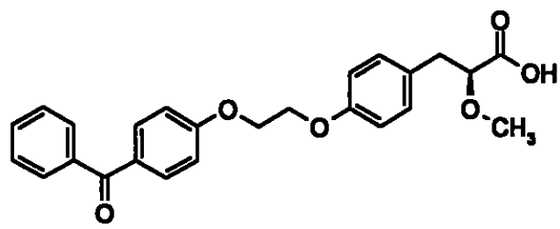
Preparación de ácido (2S)-3-[4-[2-hidroxietoxi]fenil}-2-metoxipropanoic unido a resina de Wang



Se preparó el compuesto del título a partir de ácido 3-{4-[2-(*terc*-butildimetilsilaniloxi)etoxi]fenil}-2-metoxipropanoico unido a resina de Wang cuando se trató con fluoruro de tetrabutilamonio en THF como se describe en el Procedimiento estándar E. La escisión de 20 mg de la resina en TFA/CH_2Cl_2 (1:1), seguido de evaporación del solvente, produjo ácido (2S)-3-[4-[2-hidroxietoxi]fenil}-2-metoxipropanoico en forma de aceite. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,16 (d, 2H, *J*=8,6), 6,85 (d, 2H, *J*=8,9), 4,09-3,93 (m, 5H), 3,41 (s, 3H), 3,11 (dd, 1H, *J*=14,5, 4,0), 2,97 (dd, 1H, *J*=14,5, 7,2).

Etapa D

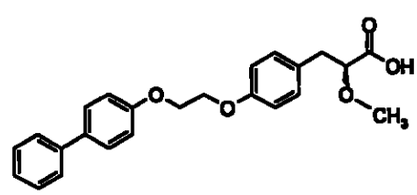
Ácido (2S)-3-{4-[2-(4-benzoilfenoxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico unido a resina de Wang mediante el Procedimiento estándar de acoplamiento de Mitsunobu G. La escisión de la resina dio un sólido oleoso. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,84-7,72 (m, 4H), 7,60-7,41 (m, 3H), 7,18 (d, 2H, J=8,6), 6,99 (d, 2H, J=8,9), 6,87 (d, 2H, J=8,7), 4,43-4,32 (m, 4H), 3,96 (dd, 1H, J=7,5, 4,6), 3,65 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,2), 2,95 (dd, 1H, J=14,2, 7,8)ppm.

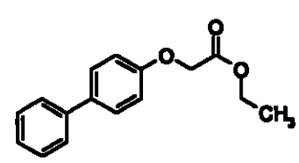
Ejemplo 123

Ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (bifenil-4-iloxi)acético

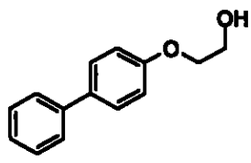


A una solución de 4-fenilfenol (1,02 g, 5,99

mmol) en 10 ml de DMF a -20°C, se añadió hidruro de sodio (0,24 g, 5,99 mmol, dispersión oleosa al 60%) y se agitó la mezcla a 0°C durante 30 min. Se añadió acetato de 2-bromoetilo (0,66 ml, 5,99 mmol) y se agitó la mezcla a temperatura ambiente durante la noche. Se diluyó la solución con agua (50 ml) y se extrajo con éter dietílico (3 x 20 ml). Se lavaron los extractos combinados con agua (4 x 20 ml), se secaron ($MgSO_4$) y se concentraron a vacío. 0,63 g (41 %). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,57-7,50 (m, 4H), 7,45-7,26 (m, 3H), 6,98 (dd, 2H, J=6,4, 2,1), 4,66 (s, 2H); 4,29 (c, 2H, J=7,3), 1,31 (t, 5H, J=7,3) ppm.

Etapa B

2-(Bifenil-4-iloxi)etanol



A una solución de éster etílico del ácido (bifenil-4-iloxi)acético (0,63 g, 2,46 mmol) en tolueno seco (15 ml) a -78°C se añadió DIBAL-H 1M en tolueno (4,92 ml, 4,92 mmol). Se agitó la solución a -78°C durante 1 hora, se calentó hasta la temperatura ambiente y se apagó con una mezcla de una solución de tartrato de sodio en agua y acetato de etilo durante 1 hora. Se separaron las capas y se extrajo después la fase acuosa con acetato de etilo. Se secaron las capas orgánicas combinadas ($MgSO_4$), se concentraron a vacío y se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 4:1, R_f 0,1), 48%. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,58-7,26 (m, 8H); 7,00 (d, 2H, J=8,6), 4,14 (t, 2H, J=4,6), 4,02-3,98 (m, 2H); 2,04 (t, 1H, J=5,4).

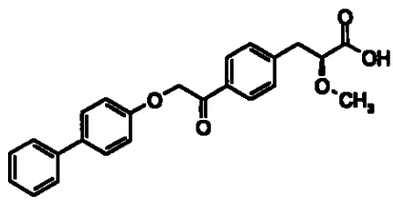
Etapa C

Ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de 2-(bifenil-4-iloxi)etanol y éster etílico del ácido (2S)-2-metoxi-3-hidroxifenilpropiónico utilizando el procedimiento general A (34%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,55-7,49 (m, 4H); 7,43-7,35 (m, 2H); 7,29 (d, 1H, J=7,3); 7,15 (d, 2H, J=8,8); 7,00 (d, 2H, J=8,8); 6,88 (d, 2H, J=8,8); 4,36-4,29 (m, 4H); 3,98 (dd, 1H, J=7,0, 4,4); 3,39 (s, 3H); 3,10 (dd, 1H, J=14,3, 4,4); 2,95 (dd, 1H, J=14,3, 7,3)ppm. MS (ES)para $C_{24}H_{24}O_5$ $[M+NH_4]^+$: 410.

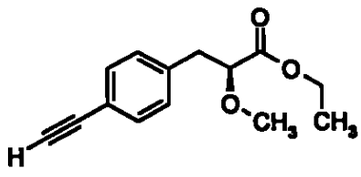
Ejemplo 124

Ácido (2S)-3-{4-[2-(bifenil-4-iloxi)acetil]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S) 3-(4-etinilfenil)-2-metoxipropiónico

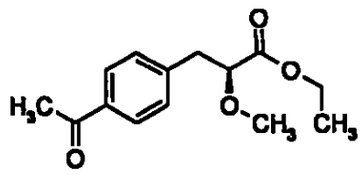


A una solución de éster etílico del ácido (2S)-2-metoxi-3-(4-trifluorometanosulfoniloxifenil)propiónico (0,100 g, 0,29 mmol) (Ejemplo 1, Etapa A) en 10 ml de piperidina desgasificada, se añadió (trimetilsilil)acetileno (99,6 mg, 1,015 mmol), tetrakis(trifenilfosfina)paladio (0) (0,017 g, 0,015 mmol), trifenilfosfi-

na (7,7 mg, 0,029 mmol) y yoduro de cobre (I) (5,5 mg, 0,029 mmol). Se agitó la solución durante 2 horas a 120°C y se enfrió después a temperatura ambiente. Se evaporó el solvente a vacío. Se disolvió el residuo en THF seco y se añadieron 0,4 ml de una solución de fluoruro de tetrabutilamonio (1,0 M en THF) y 0,02 ml de agua. Se agitó la mezcla a temperatura ambiente durante 5 min. Se evaporó el solvente a vacío y se repartió el residuo entre agua (20 ml) y éter dietílico (20 ml). Se separaron las capas y se extrajo la solución acuosa dos veces con 20 ml de éter dietílico. Se lavaron las capas orgánicas combinadas con Na_2CO_3 al 10% (6 x 20 ml) y salmuera (20 ml) y se secaron ($MgSO_4$). La concentración produjo un aceite amarillo (38 mg, 56 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,95 (d, 1H, J=7,3), 7,25 (d, 1H, J=7,3), 4,18 (c, 2H, J=7,0), 3,97 (dd, 1H, J=7,3, 5,6), 3,36 (s, 3H), 3,05 (d, 1H, J=5,3), 3,02 (d, 1H, J=2,4 Hz), 1,22 (t, 3H, J=7,25).

Etapa B

Éster etílico del ácido (2S) 3-(4-acetilfenil)-2-metoxipropiónico

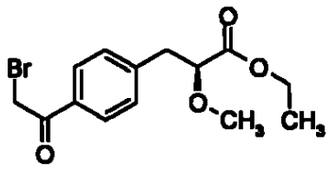


A éster etílico del ácido (2S) 3-(4-etinilfenil)-2-metoxipropiónico (36 mg, 0,15 mmol) (Ejemplo 29, Etapa A), se añadieron 4 ml de ácido fórmico. Se agitó la solución durante 1 hora a 100°C y se enfrió después a temperatura ambiente. Se recogió la mezcla con cloruro de metileno y se lavó la solución con agua, carbonato de sodio y agua, se secó ($MgSO_4$) y se evaporó el solvente a vacío. Se obtuvo un líquido marrón (0,035 g, 95 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,43 (d, 1H, J=7,3), 7,12 (d, 1H, J=7,3), 4,18 (c, 2H, J=7,0), 3,97 (dd, 1H, J=7,3,

5,6), 3,32 (s, 3H), 3,06 (s, 1H), 3,03 (d, 1H, J=2,4 Hz), 2,56 (s, 2H), 1,22 (t, 3H, J=7,25).

Etapa C

Éster etílico del ácido (2S)-3-[4-(2-bromoacetil)fenil]-2-metoxipropiónico



Se añadió bromuro cúprico en polvo (62 mg, 0,28 mmol) por porciones a una solución de éster etílico del ácido (2S)-3-(4-acetilfenil)-2-metoxipropiónico (35 mg, 0,14 mmol) en $CHCl_3$ (5 ml) y acetato de etilo (5 ml). Se agitó la solución durante 1 hora a 65°C y se enfrió después a temperatura ambiente. Se filtró la mezcla y se evaporó el solvente a vacío. Se purificó el residuo por cromatografía (gel de sílice, hexanos/éter etílico 8:2, R_f 0,20), para producir un aceite incoloro (25 mg, 54%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,935 (d, 1H, J=7,3), 7,38 (d, 1H, J=7,3), 4,50 (s, 2H), 4,12 (c, 2H, J=7,0), 3,97 (dd, 1H, J=7,3, 5,6), 3,38 (s, 3H), 3,10 (s, 1H), 3,06 (d, 1H, J=2,4 Hz), 1,22 (t, 3H, J=7,25).

Etapa D

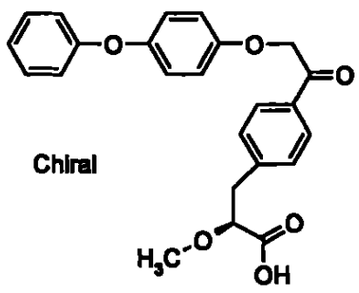
Ácido (2S) 3-[4-[2-(bifenil-4-iloxi)acetil]fenil)-2-metoxipropiónico

Se preparó el compuesto del título a partir de una solución de éster etílico del ácido (2S)-3-[4-(2-bromoacetil)fenil]-2-metoxipropiónico (25 mg, 0,076 mmol) en acetonitrilo (5 ml). Se añadieron 4-fenilfenol (29 mg, 0,152 mmol) y K_2CO_3 (31,5 mg, 0,23 mmol). Se agitó la solución durante 30 min a 80°C y se enfrió después a temperatura ambiente. Se concentró la mezcla a sequedad a vacío y se cromatografió en gel de sílice (hexanos/éter etílico 8:2 a 7:3). Se recogieron las fracciones corres-

pondientes al compuesto acoplado (R_f: 0,27) y se concentraron a sequedad. Se disolvió la mezcla así obtenida en 4 ml de NaOH 1N y 12 ml de metanol y se agitó a temperatura ambiente hasta que la TLC indicó la desaparición la desaparición del material de partida. Se eliminó el metanol a vacío y se diluyó la solución acuosa con 20 ml de salmuera y se lavó con éter dietílico (3 x 15 ml). Se aciduló la fase acuosa con HCl 1N (hasta pH 3), se extrajo con acetato de etilo (3 x 15 ml) y se secó la capa orgánica ($MgSO_4$) y se concentró a vacío. Se obtuvo un aceite incoloro (9,6 mg, 32 %). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,96 (d, 2H, J=8,4), 7,55-7,23 (m, 9H), 6,99 (d, 2H, J=8,8), 5,26 (s, 2H), 4,03 (dd, 1H, J=7,3, 5,6), 3,39 (s, 3H) 3,22 (dd, 1H, J=14,3, 5,5), 3,03 (dd, 1H, J=14,3, 7,2).

Ejemplo 125

Ácido (2S)-2-metoxi-3-{4-[2-(4-fenoxifenoxi)acetil]fenil}propiónico

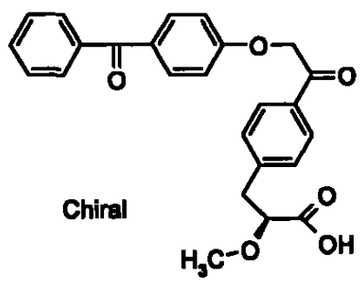


Se preparó el compuesto del título a partir de una solución de éster etílico de ácido (2S)-3-[4-(2-bromoacetil)fenil]-2-metoxipropiónico (0,076 mmol) del Ejemplo 124, Etapa C, en acetonitrilo (5 ml). Se añadieron 4-fenoxifenol (0,152 mmol) y K_2CO_3 (0,23 mmol). Se agitó la solución durante 30 min a 80°C y se enfrió después a temperatura ambiente. Se concentró la mezcla a sequedad a vacío y se cromatografió en gel de sílice (hexanos/éter etílico 8:2 a 7:3). Se recogieron las fracciones

correspondientes al compuesto acoplado (R_f: 0,27) y se concentraron a sequedad. Se disolvió la mezcla así obtenida en 4 ml de NaOH 1N y 12 ml de metanol y se agitó a temperatura ambiente hasta que la TLC indicó la desaparición del material de partida. Se eliminó el metanol a vacío y se diluyó la solución acuosa con 20 ml de salmuera y se lavó con éter dietílico (3 x 15 ml). Se aciduló la fase acuosa con HCl 1N (hasta pH 3), se extrajo con acetato de etilo (3 x 15 ml) y se secó la capa orgánica ($MgSO_4$) y se concentró a vacío. Se obtuvo un aceite incoloro. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,96 (d, 2H, J=8,4), 7,55-7,33 (m, 5H), 7,04-6,83 (m, 6H), 5,24 (s, 2H), 4,08 (dd, 1H, J=7,4, 4,4), 3,40 (s, 3H) 3,22 (dd, 1H, J=14,3, 4,4), 3,15 (dd, 1H, J=14,3, 7,2).

Ejemplo 126

<u>Ácido (2S)-3-{4-[2-(4-benzoilfenoxi)acetil]fenil}-2-metoxipropiónico</u>



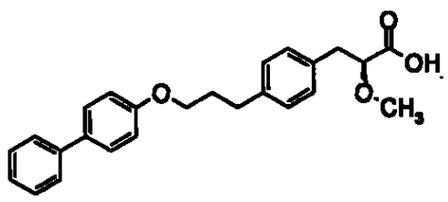
Se preparó el compuesto del título a partir de una solución de éster etílico de ácido (2S)-3-[4-(2-bromoacetil)fenil]-2-metoxipropiónico (0,076 mmol) del Ejemplo 124, Etapa C, en acetonitrilo (5 ml). Se añadieron 4-hidroxibenzofenona (0,152 mmol) y K_2CO_3 (0,23 mmol). Se agitó la solución durante 30 min a 80°C y se enfrió después a temperatura ambiente. Se concentró la mezcla a sequedad a vacío y se cromatografió en gel de sílice (hexanos/éter etílico 8:2 to 7:3). Se recogieron las fracciones correspondientes al compuesto acoplado

712 A

(R_f: 0,27) y se concentraron a sequedad. Se disolvió la mezcla así obtenida en 4 ml de NaOH 1N y 12 ml de metanol y se agitó a temperatura ambiente hasta que la TLC indicó la desaparición del material de partida. Se eliminó el metanol a vacío y se diluyó la solución acuosa con 20 ml de salmuera y se lavó con éter dietílico (3 x 15 ml). Se aciduló la fase acuosa con HCl 1N (hasta pH 3), se extrajo con acetato de etilo (3 x 15 ml) y se secó la capa orgánica ($MgSO_4$) y se concentró a vacío. Se obtuvo un aceite incoloro. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,96-7,71 (m, 6H), 7,57-7,46 (m, 5H), 6,97 (d, 2H, J=8,1), 5,35 (s, 2H), 4,08 (dd, 1H, J=7,4, 4,2), 3,26 (s, 3H) 3,20 (dd, 1H, J=14,1, 4,1), 3,09 (dd, 1H, J=14,1, 7,2).

Ejemplo 127

Ácido (2S)-3-{4-[3-(bifenil-4-iloxi)propil]fenil}-2-metoxipropiónico

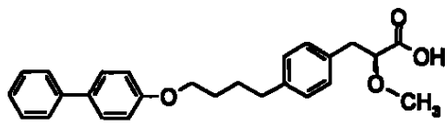


Se preparó el compuesto del título como sigue: se disolvió ácido (2S)-3-{4-[3-(bifenil-4-iloxi)-prop-1-inil]fenil}-2-metoxipropiónico (0, Etapa C) (0,0325 g, 0,08 mmol) en metanol (10 ml). Se añadió paladio al 10% sobre carbono activado (0,004 g, 0,004 mmol) y se saturó la solución con hidrógeno (1 atm) y se agitó durante 5 horas. Se filtró la mezcla a través de una almohadilla de celita y se concentró a vacío. Se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo-ácido acético 50:50:1, R_f 0,23) (85%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,56-7,24 (m, 11H), 6,94 (d, 2H, J=8,8), 4,02-3,95 (m, 3H), 3,38 (s, 3H), 3,11 (dd, 1H, J=14,3, 4,4), 2,98 (dd, 1H, J=14,3, 7,3),

2,79 (t, 2H, J=8,1), 2,16-2,03 (m, 3H).MS (ES)para $C_{25}H_{26}O_4$ $[M+NH_4]^+$: 408,2, $[M+Na]^+$: 413,2.

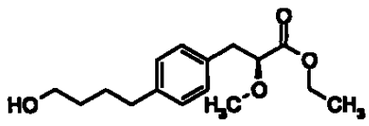
Ejemplo 128

Ácido (2S)-3-{4-[4-(bifenil-4-iloxi)butil]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-[4-(4-hidroxibutil)fenil]-2-metoxipropiónico



Se disolvió éster etílico del ácido (2S)-3-[4-(3-hidroxiprop-1-inil)fenil]-2-metoxipropiónico (0,294 g, 1,06 mmol) en acetato de etilo (50 ml). Se añadió paladio al 10% sobre carbono activado (0,057 g, 0,05 mmol) y se saturó la solución con hidrógeno (1 atm) y se agitó durante 2 horas. Se filtró la mezcla a través de una almohadilla de celita y se concentró a vacío. (100%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,12 (dd, 4H, *J*=11,3, 8,6), 4,17 (c, 2H, *J*=7,0), 3,94 (dd, 1H, *J*=7,0, 6,2), 3,65 (t, 2H, *J*=5,9); 3,35 (s, 3H), 3,00 (s, 1H), 2,97 (s, 1H), 2,61 (t, 2H, *J*=7,3), 1,73-1,60 (m, 4H), 1,22 (t, 3H, *J*=7,0).

Etapa B

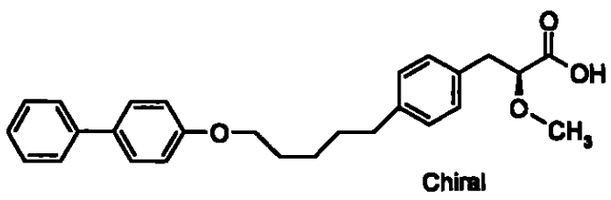
Ácido (2S)-3-{4-[4-(bifenil-4-iloxi)butil]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(4-hidroxibutil)fenil]-2-metoxipropiónico y 4-fenilfenol siguiendo el Procedimiento estándar de acoplamiento-hidrólisis A. ^{1}H-RMN

($CDCl_3$, 200,15 MHz): δ 7,55-7,23 (m, 7H); 7,14 (d, 4H, J=1,1); 6,93 (d, 2H, J=8,4); 4,02-3,96 (m, 3H); 3,37 (s, 3H); 3,11 (dd, 1H, J=14,3, 4,4); 2,97 (dd, 1H, J=14,3, 7,3); 2,66 (t, 2H, J=7,0); 1,83-1,80 (m, 4H). MS (ES)para $C_{26}H_{28}O_4$ $[M+NH_4]^+$: 422,2, $[M+Na]^+$: 427,2.

Ejemplo 129

Ácido (2S)-3-{4-[5-(bifenil-4-iloxi)pentil]fenil}-2-metoxipropiónico

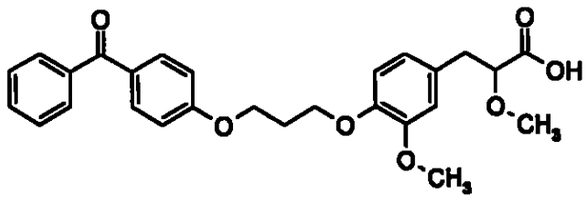


Chiral

Se preparó el compuesto del título como sigue: se disolvió ácido (2S)-3-{4-[5-(bifenil-4-iloxi)-pent-1-inil]fenil}-2-metoxipropiónico del Ejemplo 21 (0,08 mmol) en metanól (10 ml). Se añadió paladio al 10% sobre carbono activado (0,004 g, 0,004 mmol) y se saturó la solución con hidrógeno (1 atm) y se agitó durante 5 horas. Se filtró la mezcla a través de una almohadilla de celita y se concentró a vacío. Se purificó el residuo por cromatografía en columna. MS (ES) para $C_{27}H_{30}O_4$ $[M-H]^-$: 417,3.

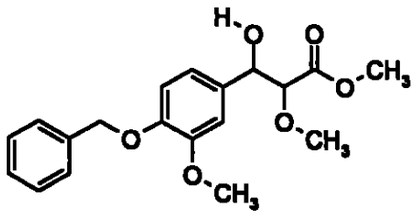
Ejemplo 130

Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-metoxipropiónico



Etapa A

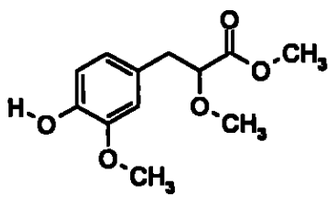
Éster metílico del ácido 3-(4-benciloxi-3-metoxifenil)-3-hidroxi-2-metoxipropiónico



Se añadió una solución de 4-benciloxi-3-metoxibenzaldehído (0,44 g, 1,92 mmol) y metoxiacetato de metilo (0,19 ml, 1,92 mmol) en THF (10 ml) a -78°C por goteo a bis(trimetilsilil)amiduro de sodio (20 ml, 2,11 mmol, 1N en THF) a -78°C. Se agitó la mezcla de reacción durante 3 h y se apagó con HCl 1N (5 ml). Se dejó calentar a la mezcla hasta la temperatura ambiente, se diluyó con agua (15 ml) y se extrajo con acetato de etilo (3 x 15 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$) y se concentraron. Se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo, 1:1), para producir éster metílico de ácido 3-(4-benciloxi-3-metoxifenil)-3-hidroxi-2-metoxipropiónico en forma de aceite (350 mg, 52%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,45-7,20 (m, 5H), 6,9 (s, 1H), 6,8 (a, 2H), 5,1 (s, 2H), 4,90-4,80 (m, 1H), 4,10 (m, 1H), 3,90 (s, 3H), 3,65 (s, 3H), 3,31 (s, 3H), 3,10-2,90 (m, 1H).

Etapa B

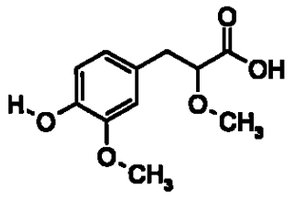
Éster metílico del ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico



Se añadieron anhídrido trifluoroacético (0,62 ml, 4,36 mmol) y trietilamina (0,62 ml, 4,36 mmol) a una solución de éster metílico de ácido 3-(4-benciloxi-3-metoxifenil)-3-hidroxi-2-metoxipropiónico (1,01 g, 2,91 mmol) en cloruro de metileno (30 ml) a 0°C. Se agitó la mezcla resultante durante 4 horas a temperatura ambiente y se concentró a vacío. Se disolvió el residuo en acetato de etilo (30 ml) y se añadió paladio al 10% sobre carbono (0,3 g) a la solución. Se agitó la mezcla bajo presión de hidrógeno (4 atm) durante 16 horas. Se filtró la mezcla a través de Celita y se concentró a vacío. Se purificó el residuo por cromatografía en columna de gel de sílice (gel de sílice, hexanos/acetato de etilo 7:3), para producir éster metílico de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico en forma de aceite (598 mg, 86%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 6,80 (d, 1H, J=7,8), 6,7 (s, 1H), 6,62 (d, 1H, J=7,8), 3,96 (dd, 1H, J=7,8, 4,0), 3,80 (s, 3H), 3,68 (s, 3H), 3,30 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,0), 2,91 (dd, 1H, J=14,2, 7,8).

Etapa C

Ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico

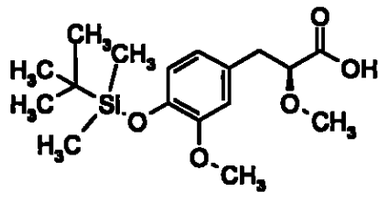


Se añadió una solución acuosa 1N de hidróxido de litio a una solución de éster metílico de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico (280 mg, 1,17 mmol) en THF a temperatura ambiente y se agitó la mezcla de reacción durante la noche. Se extrajo la fase acuosa con acetato de etilo (20 ml), se acidificó a pH 2 y se extrajo con acetato de etilo (3 x 15 ml). Se combinaron estas últimas capas orgánicas y se lavaron con agua (15

ml) y salmuera (10 ml), se secaron ($MgSO_4$), se filtraron y se concentraron a vacío, para producir ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico en forma de aceite (183 mg, 74%). ^{1}H-RMN (250,13 MHz, $CDCl_3$): δ 6,83 (1H, d, *J*=7,8), 6,74 (1H, s), 6,72 (1H, d, *J*=7,8), 3,99 (1H, dd, *J*=7,8, 4,0), 3,85 (s, 3H), 3,40 (s, 3H), 3,09 (1H, dd, *J*=14,2, 4,0), 2,91 (1H, dd, *J*=14,2, 7,8).

Etapa D

Ácido 3-[4-(*terc*-butildimetilsilaniloxi)-3-metoxifenil)-2-metoxipropiónico

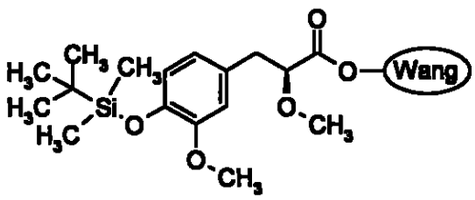


A una solución de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico (1,02 g, 4,87 mmol) en CH_2Cl_2-DMF (20 ml = 10:1) se añadió cloruro de *terc*-butildimetilsililo (1,75 g, 11,68 mmol) e imidazol (0,70 g, 10,24 mmol). Se agitó la solución resultante a temperatura ambiente durante la noche. Se añadió agua (15 ml) y se extrajo la fase acuosa con hexanos (30 ml). Se lavó la capa de hexanos con agua (10 ml), se secó ($MgSO_4$), se filtró y se concentró. Se disolvió el producto bruto en acetato de etilo (10 ml) y se añadió una solución saturada de K_2CO_3 (5 ml). Se agitó la mezcla resultante durante 2 horas a temperatura ambiente. Se extrajo la capa acuosa con acetato de etilo (10 ml), se acidificó a pH 3 y se extrajo de nuevo con acetato de etilo (3 x 10 ml). Se combinaron estas últimas capas orgánicas y se lavaron con salmuera (20 ml), se secaron ($MgSO_4$) y se concentraron a un aceite amarillo (1,2 g, 77%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 6,78-6,67 (m, 3H), 3,96 (dd, 1H, *J*=7,8, 4,0), 3,78 (s, 3H), 3,35 (s, 3H), 3,09 (dd, 1H, *J*=14,2, 4,0),

2,91 (dd, 1H, *J*=14,2, 7,8), 0,98 (s, 9H), 0,13 (6H, s).

Etapa E

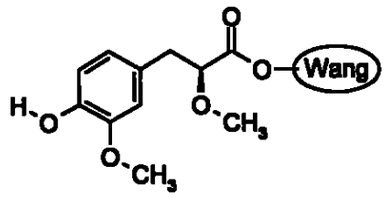
Preparación de ácido 3-[4-(*terc*-butildimetilsilaniloxi)-3-metoxifenil]-2-metoxipropiónico unido a resina de Wang



Se preparó el compuesto del título siguiendo el procedimiento del Ejemplo 95, Etapa B.

Etapa F

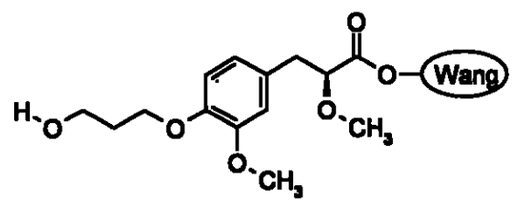
Preparación de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico unido a resina de Wang



Se preparó el compuesto del título siguiendo el procedimiento del Ejemplo 95, Etapa C.

Etapa G

Preparación de ácido 3-[4-(3-hidroxipropoxi)-3-metoxifenil]-2-metoxipropiónico unido a resina de Wang

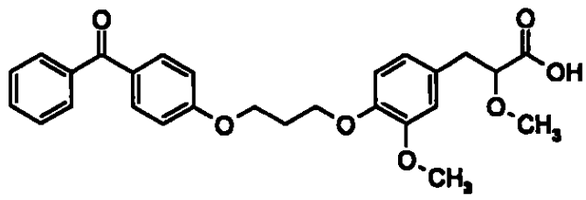


Se preparó el compuesto del título a partir de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico unido a resina de Wang mediante el acoplamiento de Mitsu-

nobu (Procedimiento estándar F), para producir ácido 3-[4-(3-hidroxipropoxi)-3-metoxifenil]-2-metoxipropiónico unido a resina de Wang.

Etapa H

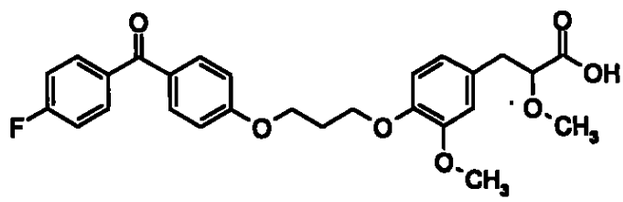
Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-metoxifenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido 3-(4-(3-hidroxipropoxi)-3-metoxifenil)-2-metoxipropiónico unido a resina de Wang mediante el procedimiento de acoplamiento-escisión de la resina de Mitsunobu (Procedimiento estándar G), para producir un sólido oleoso (4%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,81-7,72 (m, 4H), 7,57-7,43 (m, 3H), 6,96 (d, 2H, *J*=8,9), 6,81-6,73 (m, 3H), 4,28 (t, 2H, *J*=6,2), 4,20 (t, 2H, *J*=6,2), 4,01 (dd, 1H, *J*=7,0, 4,6), 3,83 (s, 3H), 3,42 (s, 3H), 3,09 (dd, 1H, *J*=14,5, 4,0), 2,97 (dd, 1H, *J*=14,5, 7,0), 2,33 (q, 2H, *J*=6,2).

Ejemplo 131

Ácido 3-(4-{3-[4-(4-fluorobenzoil)fenoxi]propoxi}-3-metoxifenil)-2-metoxipropiónico

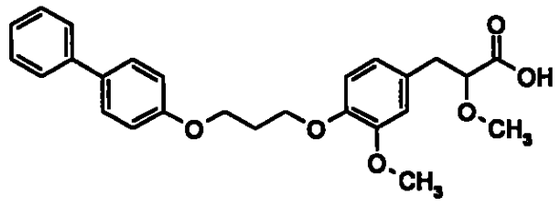


Se preparó el compuesto del título a partir de ácido 3-(4-(3-hidroxipropoxi)-3-metoxifenil)-2-metoxipropiónico unido a resina de Wang mediante el procedi-

miento de acoplamiento-escisión de la resina de Mitsunobu (Procedimiento estándar G), para producir un sólido oleoso (4%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,83-7,74 (m, 4H), 715 (t, 2H, *J*=8,6 Hz), 6,96 (d, 2H, *J*=8,6), 6,85-6,74 (m, 3H), 4,28 (t, 2H, *J*=6,2), 4,20 (t, 2H, *J*=6,2), 4,01 (dd, 1H, *J*=7,0, 4,6), 3,84 (s, 3H), 3,42 (s, 3H), 3,10 (dd, 1H, *J*=14,2, 4,6), 2,97 (dd, 1H, *J*=14,2, 7,0), 2,33 (q, 2H, *J*=6,2).

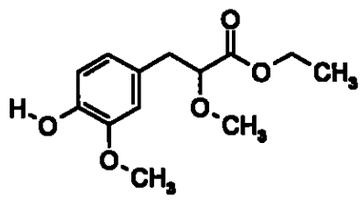
Ejemplo 132

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-metoxifenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico

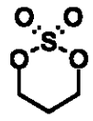


A una solución de ácido 3-[4-(*terc*-butil-dimetilsilaniloxi)-3-metoxifenil]-2-metoxipropiónico (356 mg, 1,05 mmol) en etanol absoluto (8 ml), se añadió ácido sulfúrico concentrado (0,033 ml, 0,63 mmol). Se dejó agitar a la mezcla de reacción a temperatura ambiente durante 17 horas. Se concentró la solución a vacío y se añadieron agua (10 ml) y $NaHCO_3$ sólido para neutralizar el residuo. Se extrajo la fase acuosa con acetato de etilo (2 x 10 ml). Se lavaron las capas orgánicas combinadas

con agua (20 ml) y salmuera (20 ml), se secaron ($MgSO_4$), se filtraron y se concentraron, para producir éster etílico de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico (260 mg, 98%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 6,83 (d, 1H, J=8,1 Hz), 6,76-6,69 (m, 2H), 4,19 (c, 2H, J=7,3 Hz), 3,97-3,90 (m, 1H), 3,87 (s, 3H), 3,36 (s, 3H), 2,96-2,92 (m, 2H), 1,25 (t, 3H, J=7,3 Hz).

Etapa B

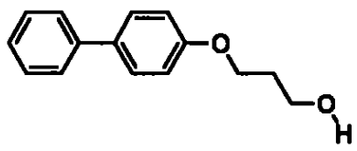
2,2-Dióxido de [1,3,2]dioxatiano



Se añadió a una solución de 1,3-propanodiol (30 g, 394 mmol) en CCl_4 (278 ml cloruro de tionilo (36 ml, 491 mmol) mediante jeringa. Se calentó la mezcla resultante a reflujo durante 1,5 h y se enfrió a 0°C para evaporar el solvente a vacío. Se disolvió el residuo en una mezcla de $CCl_4/CH_3CN/H_2O$ (2:2:3=500 ml) y se enfrió a 0°C. Se añadió tricloruro de rutenio trihidrato (0,556 g, 2,68 mmol), seguido de adición de $NaIO_4$ sólido (14,35 g, 197 mmol). Se agitó la mezcla a temperatura ambiente durante 1 h, se añadió H_2O (1 L) y se extrajo la fase acuosa con éter dietílico (4 x 300ml). Se lavaron las capas orgánicas combinadas con salmuera (2 x 100 ml), se secaron ($MgSO_4$) y se filtraron a través de una almohadilla de gel de sílice, para eliminar las sales de rutenio. Se evaporó el solvente y se añadieron hexanos (200 ml) al aceite resultante. Después de enfriar, precipitó un sólido gris. Se filtró el sólido y se lavó con hexanos. La recristalización a partir de hexanos/éter dio un sólido blanco cristalino (18,15 g, 33%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 4,73 (t, 4H, J=5,6), 2,13 (q, 2H, J=5,6).

Etapa C

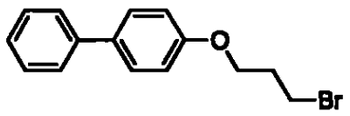
3-(Bifenil-4-iloxi)propan-1-ol



Se agitó una solución de 4-fenilfenol (4,9 g, 29,0 mmol) y *terc*-butóxido de potasio (3,64 g, 30,3 mmol) en THF (100 ml) a temperatura ambiente durante 30 min. Se enfrió al solución a 0°C y se añadió 2,2-dióxido de [1,3,2]dioxatiano (3,6 g, 26,34 mmol) en THF (25 ml). Se agitó la mezcla resultante a temperatura ambiente durante 5 horas y se eliminó el solvente a vacío. Se disolvió el residuo en HCl 6N (15 ml) y se calentó a 100°C durante 16 horas. Se enfrió la mezcla a temperatura ambiente y se extrajo la fase acuosa con acetato de etilo (3 x 30 ml). Se lavaron las capas orgánicas combinadas con H_2O (3 x 25 ml) y salmuera (25 ml), se secaron ($MgSO_4$), se filtraron y se concentraron, para producir 3-(bifenil-4-iloxi)propan-1-ol en forma de sólido blanco (4,16 g, 63%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,49 (m, 4H), 7,45-7,37 (m, 3H), 6,98 (dd, 2H, *J*=6,72, 2,14), 4,17 (t, 2H, *J*=5,9), 3,88 (c, 2H, *J*=5,9), 2,07 (q, 2H, *J*=5,9).

Etapa D

4-(3-Bromopropoxi)bifenilo

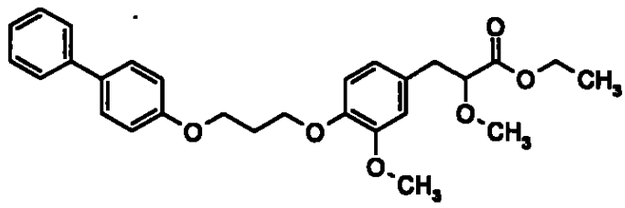


A una solución de 3-(bifenil-4-iloxi)propan-1-ol (1,00 g, 4,38 mmol) en CH_2Cl_2 (20 ml) a 0°C, se añadió trifenilfosfina (1,61 g, 6,14 mmol) y tetrabromuro de carbono (1,81 g, 5,47 mmol). Se dejó calentar a la mezcla de reacción hasta la temperatura ambiente, se agitó du-

rante 1 hora y se extrajo con acetato de etilo (50 ml). Se lavó la capa orgánica con H_2O (3 x 50 ml) y salmuera (3 x 25 ml), se secó ($MgSO_4$), se filtró y se concentró. Se purificó el producto bruto por cromatografía en columna de gel de sílice (gel de sílice, hexanos/acetato de etilo, 9:1), para producir 4-(3-bromopropoxi)bifenilo (1,22 g, 95%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,29 (m, 7H), 6,98 (dd, 2H, J=6,72, 1,88), 4,15 (t, 2H, J=5,92), 3,62 (t, 2H, J=6,44), 2,34 (q, 2H, J=5,92).

Etapa E

Éster etílico del ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-metoxifenil}-2-metoxipropiónico



A una solución de éster etílico de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico (Ejemplo 132, Etapa A) (0,080 g, 0,31 mmol) en acetonitrilo (10 ml), se añadió 4-(3-bromopropoxi)bifenilo (Ejemplo 132, Etapa D) (0,101 g, 0,35 mmol) y carbonato de potasio (0,115 g, 0,945 mmol). Se agitó la suspensión resultante a 85°C durante la noche. Después de enfriar, se diluyó la mezcla de reacción con acetato de etilo (10 ml) y se añadió agua (10 ml). Se lavó la capa orgánica con agua (10 ml) y salmuera (10 ml), se secó ($MgSO_4$) y se concentró. Se purificó el producto bruto por cromatografía en columna de gel de sílice (gel de sílice, hexanos/acetato de etilo, 7:3), para producir éster etílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-metoxifenil}-2-metoxipropiónico (0,086 g, 59%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,26 (m, 7H), 6,98 (d, 2H, J=8,6), 6,87-6,73 (m, 3H), 4,25-4,17 (m, 6H), 3,91 (dd, 1H, J=7,0, 5,6), 3,83

(s, 3H), 3,35 (s, 3H), 2,97-2,93 (m, 2H), 2,31 (q, 2H, J=5,9), 1,24 (t, 3H, J=7,3).

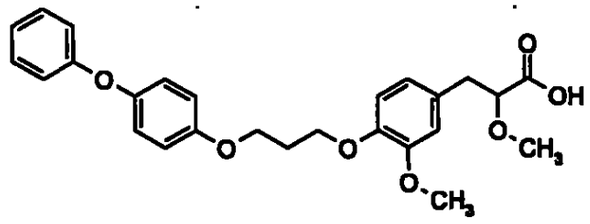
Etapa F

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-metoxifenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-metoxifenil}-2-metoxipropiónico siguiendo el procedimiento de hidrólisis descrito en el Ejemplo 130, Etapa C. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,56-7,25 (m, 7H), 6,97 (d, 2H, J=8,9), 6,89-6,79 (m, 3H), 5,07 (a, 1H), 4,17 (c, 4H, J=5,6), 3,95 (dd, 1H, J=7,5, 3,5), 3,82 (s, 3H), 3,32 (s, 3H), 3,11-2,86 (m, 2H), 2,28 (q, 2H, J=6,2).

Ejemplo 133

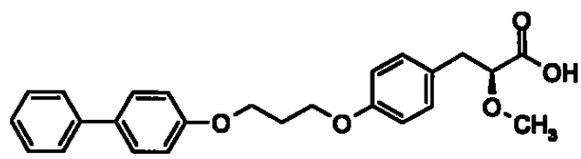
Ácido 2-metoxi-3-{3-metoxi-4-[3-(4-fenoxifenoxi)propoxi]-fenil}propiónico



Se preparó el compuesto del título siguiendo el procedimiento descrito para el Ejemplo 132 (Etapas A-E). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,32-7,24 (m, 2H), 7,06-6,75 (m, 10H), 4,16 (c, 4H, J=6,2), 3,97 (dd, 1H, J=7,8, 4,3), 3,82 (s, 3H), 3,37 (s, 3H), 3,08 (dd, 1H, J=14,2, 4,0), 2,94 (dd, 1H, J=14,5, 7,8); 2,27 (q, 2H, J=6,2).

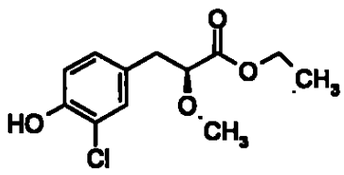
Ejemplo 134

Ácido (2S)-3-(4-[3-(bifenil-4-iloxi)propoxi]-3-clorofenil}-2-metoxipropiónico



Etapa A

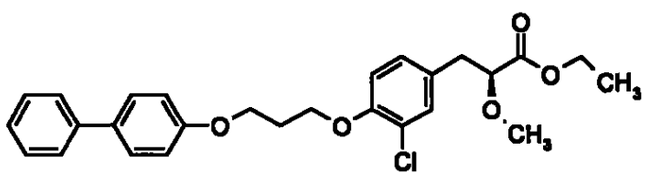
Éster etílico del ácido (2S)-3-(3-cloro-4-hidroxifenil)-2-metoxipropiónico



A una solución de éster etílico de ácido 3-(4-hidroxifenil)-2-metoxipropiónico (0,113 g, 0,5 mmol) en CH_3CN (3 ml) enfriado a 0°C, se añadió N-clorosuccinimida (0,067 g, 0,5 mmol) en varias porciones. Se dejó calentar a la mezcla a temperatura ambiente y se agitó durante 8 horas. Se concentró la mezcla a vacío y se lavó el aceite resultante con CCl_4 (4 ml). Se filtró el precipitado formado y se concentró el filtrado para obtener una mezcla de éster etílico de ácido 3-(3-cloro-4-hidroxifenil)-2-metoxipropiónico y éster etílico de ácido 3-(3,5-dicloro-4-hidroxifenil)-2-metoxipropiónico como un aceite marrón, el cual fue purificado por HPLC dirigida al ultravioleta. Se obtuvo un aceite incoloro (0,020 g, 14%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,18 (d, 1H, *J*=2,15), 7,02 (dd, 1H, *J*=8,32, 2,15), 6,91 (d, 1H, *J*=8,32), 4,18 (c, 2H, *J*=7,25), 3,88 (dd, 1H, *J*=7,24, 5,62), 3,35 (s, 3H), 2,92 (dd, 2H, *J*=6,31, 2,42), 1,24 (t, 3H, *J*=7,2).

Etapa B

Éster etílico del ácido (2S)-3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-clorofenil}-2-metoxipropiónico



Se disolvió éster etílico de ácido 3-(3-cloro-4-hidroxifenil)-2-metoxipropiónico (0,020 g, 0,077 mmol) en CH_3CN (3 ml) y se añadieron 4-(3-bromopropoxi)bifenilo (Ejemplo 132, Etapa D) (0,025 g 0,085 mmol) y K_2CO_3 (0,032 g, 0,23 mmol). Se calentó la mezcla a 85°C y se agitó durante 5 horas. Después de enfriar, se añadió agua (2 ml). Se extrajo la mezcla en EtOAc (3 x 10 ml) y se lavó con H_2O (2 x 5 ml) y salmuera (2 x 5 ml). Se secó la capa orgánica ($MgSO_4$), se filtró y se concentró a vacío. Se purificó el producto bruto por cromatografía en columna de gel de sílice (gel de sílice, hexanos/acetato de etilo 9:1), para producir éster etílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-clorofenil}-2-metoxipropiónico (0,017 mg, 48%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,24 (m, 9H), 7,02-6,89 (m, 3H), 4,28-4,12 (m, 5H), 3,89 (dd, 1H, J=7,24, 5,62), 3,62 (t, 1H, J=6,44), 3,36 (s, 3H), 2,93 (dd, 2H, J=6,31, 2,42), 2,32 (q, 2H, J=5,10), 1,25 (t, 3H, J=7,2).

Etapa C

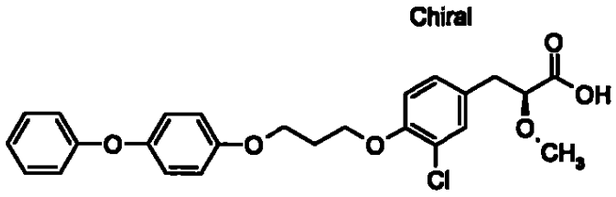
Ácido (2S)-3-{4-[3-(bifenil-4-iloxi)propoxi]-3-cloro-fenil}-2-metoxipropiónico

Se preparó el compuesto del título como sigue: se disolvió éster etílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-clorofenil}-2-metoxipropiónico (0,017 g, 0,037 mmol) en una solución etanólica 0,25 M de NaOH (0,3 ml, 0,075 mmol). Se agitó la mezcla durante 16 horas a temperatura ambiente y se añadió agua. Se extrajo

la capa acuosa con Et_2O (3 x 5 ml). Se acidificó la capa acuosa a pH=1 con HCl 1N y se extrajo con Et_2O (5 x 10 ml). Se secó la capa orgánica ($MgSO_4$) y se concentró a vacío para obtener el compuesto del título en forma de aceite amarillo (0,006 mg, 38%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,25 (m, 9H), 7,0-6,86 (m, 3H), 4,23 (c, 4H, J=6,18), 3,96 (dd, 1H, J=7,24, 4,28), 3,40 (s, 3H), 3,06 (dd, 1H, J=14,5, 4,28), 2,92 (dd, 1H, J=14,5, 7,24), 2,32 (q, 2H, J=5,92).

Ejemplo 135

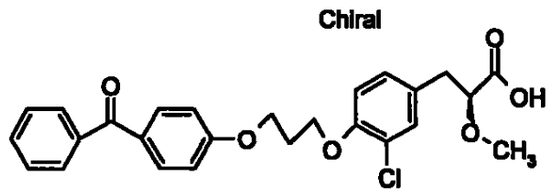
Ácido 3-{3-cloro-4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título del mismo modo que en el Ejemplo 134, pero utilizando 4-(3-bromopropoxi)-1-fenoxibenceno como material para la reacción de acoplamiento.

Ejemplo 136

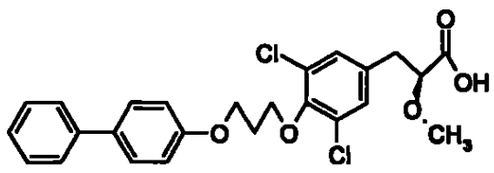
Ácido '3-{4-[3-(4-benzoilfenoxi)propoxi]-3-clorofenil}-2-metoxipropiónico



Se preparó el compuesto del título del mismo modo que en el Ejemplo 134, pero utilizando [4-(3-bromopropoxi)fenil]fenilmetanona como material para la reacción de acoplamiento.

Ejemplo 137

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3,5-diclorofenil}-2-metoxipropiónico



Chiral

Etapa A

Éster etílico del ácido 3-(3,5-dicloro-4-hidroxifenil)-2-metoxipropiónico

A una solución de éster etílico de ácido 3-(4-hidroxifenil)-2-metoxipropiónico (0,113 g, 0,5 mmol) en CH_3CN (3 ml) enfriado a 0°C, se añadió N-clorosuccinimida (0,067 g, 0,5 mmol) en varias porciones. Se dejó que la mezcla se calentara hasta la temperatura ambiente y se agitó durante 8 horas. Se concentró la mezcla a vacío y se lavó el aceite resultante con CCl_4 (4 ml). Se filtró el precipitado formado y se concentró el filtrado, para obtener una mezcla de éster etílico de ácido 3-(3-cloro-4-hidroxifenil)-2-metoxipropiónico y éster etílico de ácido 3-(3,5-dicloro-4-hidroxifenil)-2-metoxi-propiónico como un aceite marrón, que fue purificado por HPLC dirigida a ultravioleta.

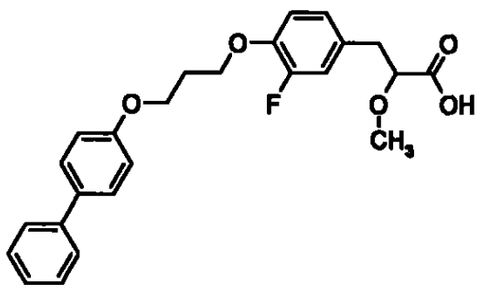
Etapa B

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3,5-diclorofenil}-2-metoxipropiónico

Se preparó el compuesto del título partiendo del compuesto de la Etapa A y utilizando el mismo procedimiento que en 0.

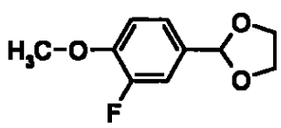
Ejemplo 138

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-fluorofenil}-2-metoxipropiónico



Etapa A

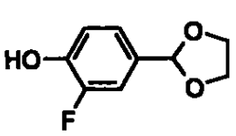
2-(3-Fluoro-4-metoxifenil)-[1,3]-dioxolano



Se calentó una solución de 3-fluoro-4-metoxibenzaldehído (463 mg, 3 mmol), etilenglicol (0,86 ml, 15 mmol) y PPTs (75 mg, 0,3 mmol) en tolueno (15 ml) a reflujo con eliminación azeotrópica de agua durante 6 horas. Se evaporó el solvente y se diluyó el residuo con cloruro de metileno (20 ml), se lavó con agua (2x10 ml) y se secó ($MgSO_4$). La concentración produjo 2-(3-fluoro-4-metoxifenil)-[1,3]-dioxolano como un aceite incoloro (550 mg, 92%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,24-7,15 (m, 2H), 6,92 (t, 1H, J=8,5), 5,71 (s, 1H), 4,10-3,98 (m, 4H), 3,86 (s, 3H).

Etapa B

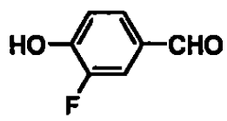
4-[1,3]Dioxolan-2-il-2-fluorofenol



Se calentó una solución de 2-(3-fluoro-4-metoxifenil)-[1,3]-dioxolano (250 mg, 1,26 mmol) y tiometóxido de sodio (106 mg, 1,51 mmol) en *N,N*-dimetilformamida seca (3,5 ml) a 100°C bajo nitrógeno durante 4 horas. Se añadió entonces una solución saturada de cloruro de amonio (15 ml) y se extrajo la capa acuosa con cloruro de metileno (4 x 10 ml). Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 7:3), para producir 4-[1,3]dioxolan-2-il-2-fluorofenol como un aceite marrón claro (120 mg, 52%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,24-7,01 (m, 2H), 6,88 (t, 1H, *J*= 8,4), 6,07 (s_a, 1H), 5,71 (s, 1H), 4,13-3,95 (m, 4H).

Etapa C

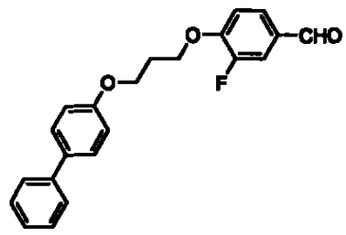
3-Fluoro-4-hidroxibenzaldehído



Se agitó una solución de HCl 1N (1 ml) y 4-[1,3]dioxolan-2-il-2-fluorofenol (250 mg, 1,35 mmol) en THF (2 ml) a temperatura ambiente durante 1 hora. Se diluyó la mezcla con agua y se extrajo con cloruro de metileno (4 x 10 ml). Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 1:1), para producir 3-fluoro-4-hidroxibenzaldehído como un sólido blanco (180 mg, 95%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 9,84 (d, 1H, *J*=2,4), 7,68-7,59 (m, 2H), 7,15 (t, 1H, *J*=8,5), 6,5 (s_a, 1H).

Etapa D

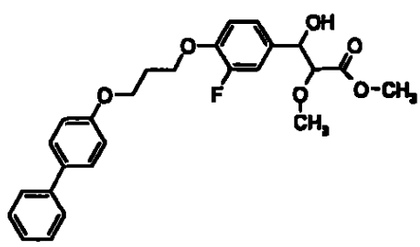
4-[3-(Bifenil-4-iloxi)propoxi]-3-fluorobenzaldehído



Se añadió terc-butóxido de potasio (198 mg, 1,76 mmol), a 0°C, a una solución de 3-fluoro-4-hidroxibenzaldehído (235 mg, 1,68 mmol) en *N,N*-dimetilformamida seca (2 ml). Se agitó la mezcla durante 10 minutos. Se añadió 4-(3-bromopropoxi)bifenilo (Ejemplo 23, Etapa D) (539 mg, 1,84 mmol) y se agitó la reacción durante 24 horas a temperatura ambiente. Se diluyó la mezcla con agua (15 ml) y se extrajo con acetato de etilo (4 x 15 ml). Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío, para producir un sólido que fue lavado con hexanos para producir 4-[3-(bifenil-4-iloxi)propoxi]-3-fluorobenzaldehído como un sólido marrón claro (490 mg, 83%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 9,83 (d, 1H, *J*=2,2), 7,64-7,23 (m, 9H), 7,09 (t, 1H, *J*=8,2), 6,96 (d, 2H, *J*=8,8), 4,32 (t, 2H, *J*=5,9), 4,21 (t, 2H, *J*=5,9), 2,35 (q, 2H, *J*=5,9).

Etapa E

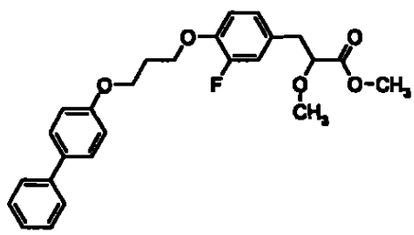
Éster metílico del ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-fluorofenil}-3-hidroxi-2-metoxipropiónico



A una solución de bis(trimetilsilil)amiduro de sodio 1N (0,71 ml, 0,71 mmol) en THF seco (5 ml), se añadió por goteo metoxiacetato de metilo (57 µl, 0,57 mmol) a -78°C. Se agitó la solución durante 1 hora. Se añadió 4-[3-(bifenil-4-iloxi)propoxi]-3-fluorobenzaldehído (220 mg, 0,626 mmol) y se calentó la mezcla a 0°C y se agitó durante 3 horas más. Se apagó la mezcla con HCl 1N (2 ml), se diluyó con agua (20 ml) y se extrajo con diclorometano (4 x 15 ml). Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 7:3), para producir éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-fluorofenil}-3-hidroxi-2-metoxipropiónico como un aceite incoloro (62 mg, 24%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,55-7,25 (m, 8H), 7,15-6,89 (m, 5H), 4,91-4,79 (m, 1H), 4,24-4,18 (m, 4H), 3,92 y 3,81 (2d, 1H, J=5,86 y 5,48), 3,67 y 3,64 (2s, 3H), 3,40 y 3,36 (2s, 3H), 3,01 y 2,94 (2d, 1H, J=5,12 y 5,12), 2,29 (q, 2H, J=5,9).

Etapa F

Éster metílico del ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-fluorofenil}-2-metoxipropiónico



Se añadieron anhídrido trifluoroacético (0,056 ml, 0,395 mmol) y piridina (0,048 ml, 18,9 mmol) a una solución de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-fluorofenil}-3-hidroxi-2-metoxipropiónico (90 mg, 0,197 mmol) en cloruro de metileno (2 ml) a 0°C. Se agitó la mezcla durante 4 horas a temperatura am-

biente y se apagó con HCl 1N (10 ml). Se separaron las capas y se extrajo la acuosa con cloruro de metileno (3 x 20 ml). Se evaporaron las capas orgánicas combinadas y se disolvió el residuo en acetato de etilo (50 ml). Se añadió paladio al 10% sobre carbono (90 mg) a la solución y se agitó la mezcla bajo presión de hidrógeno (5 atm) durante 16 horas, se filtró a través de una almohadilla de celita y se concentró a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 4:1), para producir éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-fluorofenil}-2-metoxipropiónico como un aceite incoloro (40 mg, 46%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,58-7,49 (m, 4H), 7,46-7,37 (m, 2H), 7,34-7,24 (m, 1H), 7,01-6,90 (m, 5H), 4,22 (t, 4H, *J*=5,9), 3,93 (dd, 1H, *J*=7,3, 5,3), 3,73 (s, 3H), 3,37 (s, 3H), 2,97-2,92 (m, 2H), 2,31 (q, 2H, *J*=5,9).

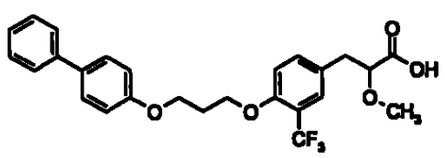
Etapa G

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-fluorofenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-fluorofenil}-2-metoxipropiónico siguiendo el procedimiento estándar E: sólido blanco (38 mg, 98%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,58-7,49 (m, 4H), 7,46-7,37 (m, 2H), 7,34-7,24 (m, 1H), 7,01-6,90 (m, 5H), 4,23 (t, 2H, *J*=5,9), 4,22 (t, 2H. *J*=5,9), 3,97 (dd, 1H, *J*=7,4, 4,4), 3,4 (s, 3H), 3,12-2,89 (m, 2H), 2,31 (q, 2H, *J*=5,9).

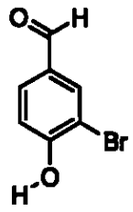
Ejemplo 139

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-trifluorometil-fenil}-2-metoxipropiónico



Etapa A

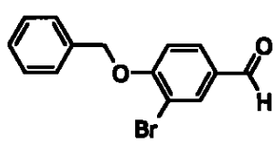
3-Bromo-4-hidroxibenzaldehído



Se añadió una solución de bromo (0,88 ml, 17,18 mmol) en cloroformo (20 ml) por goteo a temperatura ambiente a una solución de 4-hidroxibenzaldehído (2 g, 16,36 mmol) en cloroformo (40 ml) y se agitó la mezcla durante 0,5 horas a temperatura ambiente y 1 hora más a 40°C. Se añadió una solución saturada de $NaHCO_3$ (30 ml) y se separó la capa orgánica. Se extrajo la capa acuosa con cloruro de metileno (3 x 20 ml). Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío. Se cromatografió el residuo (gel de sílice, cloruro de metileno-metanol 98:2), para obtener 3-bromo-4-hidroxibenzaldehído como un sólido blanco (1,1 g, 34%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 9,80 (s, 1H), 8,02 (d, 1H, J=1,8), 7,75 (dd, 1H, J=8,4, 1,8), 7,12 (d, 1H, J=8,4), 6,19 (s, 1H).

Etapa B

4-Benciloxi-3-bromobenzaldehído

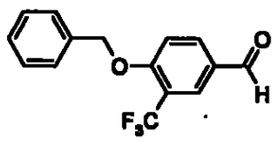


Se añadió lentamente 3-bromo-4-hidroxi-benzaldehído (1,9 g, 9,45 mmol), a 0°C, a una suspensión de NaH al 95% (290 mg, 11,34 mmol) en *N,N*-dimetilformamida seca (45 ml). Se agitó la mezcla durante 0,5 horas. Se

añadió cloruro de bencilo (1,3 ml, 11,34 mmol) y se agitó la reacción a temperatura ambiente durante la noche. Se añadió HCl 1N (40 ml) y se separaron las capas. Se extrajo la capa acuosa con éter dietílico (5 x 50 ml) y se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 9:1), para producir 4-benciloxi-3-bromobenzaldehído como un sólido blanco (2,47 g, 90%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 9,82 (s, 1H), 8,09 (d, 1H, *J*=1,8), 7,76 (dd, 1H, *J*=8,4, 1,8), 7,47-7,32 (m, 5H), 7,02 (d, 1H, *J*=8,4), 5,24 (s, 2H).

Etapa C

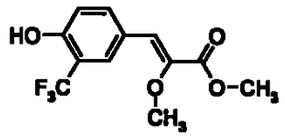
4-Benciloxi-3-trifluorometilbenzaldehído



Se añadió 2,2-difluoro-2-(fluorosulfonil)acetato de metilo (1,25 ml, 9,78 mmol) a una suspensión de CuI seco (745 mg, 3,91 mmol) y 4-benciloxi-3-bromobenzaldehído (570 mg, 1,96 mmol) en *N,N*-dimetilformamida seca (10 ml). Se agitó la mezcla bajo nitrógeno a 120°C durante 6 horas en un tubo sellado. Se enfrió la mezcla de reacción a la temperatura ambiente y se diluyó con agua (20 ml). Se extrajo la capa acuosa con éter dietílico (4 x 20 ml) y se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 9:1), para producir 4-benciloxi-3-trifluorometil-benzaldehído como un sólido blanco (120 mg, 22%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 9,88 (s, 1H), 8,11 (d, 1H, *J*=1,8), 7,98 (dd, 1H, *J*=8,6, 1,8), 7,44-7,31 (m, 5H), 7,14 (d, 1H, *J*=8,6), 5,27 (s, 2H).

Etapa D

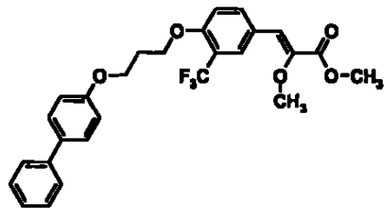
Éster metílico del ácido 3-(4-hidroxi-3-trifluorometilfenil)-2-metoxiacrílico



A una solución de bis(trimetilsilil)amiduro de sodio 1N (0,8 ml, 0,8 mmol) en THF (4 ml), se añadió por goteo metoxiacetato de metilo (0,066 ml, 0,66 mmol) a -78°C. Después de dejar agitar a la mezcla durante 1 hora, se añadió 4-benciloxi-3-trifluorometilbenzaldehído (185 ml, 0,66 mmol) por goteo. Cuando se hubo acabado la adición, se calentó la mezcla a temperatura ambiente y se agitó durante 3 horas más. Se añadió anhídrido trifluoroacético (0,28 ml, 1,98 mmol) y se agitó la mezcla a temperatura ambiente durante 4 horas. Se evaporó el solvente y se disolvió el residuo en acetato de etilo (50 ml). Se añadió paladio al 10% sobre carbono (200 mg) a la solución y se agitó la mezcla bajo presión de hidrógeno (5 atm) durante 16 horas, se filtró a través de una almohadilla de celita y se concentró a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 4:1), para producir éster metílico de ácido 3-(4-hidroxi-3-trifluorometilfenil)-2-metoxiacrílico como un sólido blanco (72 mg, 40%). ^{1}H-RMN ($(CD_3)_2CO$, 200,15 MHz): δ 9,65 (a, 1H), 8,02 (d, 1H, J=1,8), 7,87 (dd, 1H, J=8,4, 1,8), 7,08 (d, 1H, J=8,4), 6,90 (s, 1H), 3,77 (s, 3H), 3,75 (s, 3H).

Etapa E

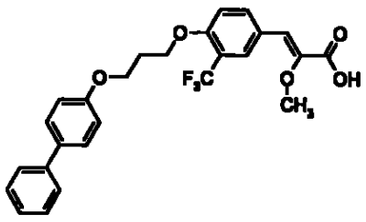
Éster metílico del ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-trifluorometilfenil}-2-metoxiacrílico



Se añadió terc-butóxido de potasio (15 mg, 0,13 mmol) a 0°C a una solución de éster metílico de ácido 3-(4-hidroxi-3-trifluorometilfenil)-2-metoxiacríli-co (35 mg, 0,126 mmol) en *N,N*-dimetilformamida seca (0,6 ml). Se agitó la mezcla durante 0,5 horas y se añadió 4-(3-bromopropoxi)bifenilo (Ejemplo 23, Etapa D) (45 mg, 0,15 mmol). Se agitó la reacción durante 6 horas a temperatura ambiente y se apagó con una solución saturada de cloruro de amonio (10 ml). Se separó la capa acuosa y se extrajo con cloruro de metileno (5 x 10 ml). Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se concentraron a vacío. Se cromatografió el residuo (gel de sílice, hexanos/acetato de etilo 8:2), para producir éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-trifluorometilfenil}-2-metoxiacrílico como un aceite incoloro (35 mg, 57%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,00 (d, 1H, *J*=1,6), 7,89 (dd, 1H, *J*=8,6, 1,6), 7,46-7,26 (m, 7H), 7,05-6,93 (m, 4H), 4,33-4,20 (m, 4H), 3,86 (s, 3H), 3,79 (s, 3H), 2,33 (q, 2H, *J*=5,9).

Etapa F

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-trifluorometil-fenil}-2-metoxiacrílico



Se preparó el compuesto del título a partir de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-trifluorometilfenil}-2-metoxiacrílico (35 mg, 0,072 mmol) siguiendo el Procedimiento estándar E: sólido blanco (31 mg, 92%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,02 (d, 1H, J=1,8), 7,88 (dd, 1H, J=8,6, 1,8), 7,57-7,28 (m, 7H), 7,08-6,96 (m, 4H), 4,35-4,21 (m, 4H), 3,81 (s, 3H), 2,34 (q, 2H, J=5,8).

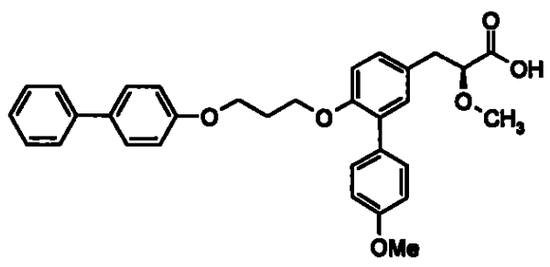
Etapa G

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-trifluorometo-xifenil}-2-metoxipropiónico

Se preparó el compuesto del título como sigue: Se agitó una mezcla de 3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-trifluorometilfenil}-2-metoxiacrílico (20 mg, 0,041 mmol) y magnesio (20 mg, 0,82 mmol) en metanol (1 ml) a temperatura ambiente durante 80 horas. Se apagó la mezcla de reacción con HCl 1N (10 ml). Se extrajo la capa acuosa con cloruro de metileno (5 x 10 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío, para obtener ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-trifluorometoxifenil}-2-metoxipropiónico como un sólido blanco (7 mg, 35%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,57-7,32 (m, 9H), 7,00-6,95 (m, 3H), 4,27-4,19 (m, 4H), 3,97 (dd, 1H, J=7,3, 4,3), 3,41 (s, 3H), 3,16-2,93 (m, 2H), 2,31 (q, 2H, J=5,8).

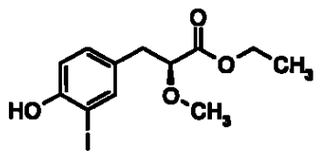
Ejemplo 140

Ácido (2S)-3-{6-[3-(bifenil-4-iloxi)propoxi]-4'-metoxibifenil-3-il}-2-metoxipropiónico



Etapa A

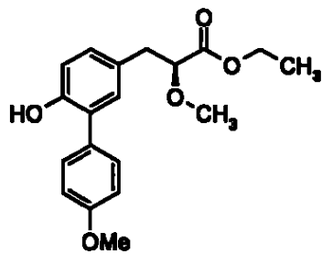
Ácido (4-hidroxi-3-yoduro)-2-metoxidihidrocinámico



Se disolvió ácido (4-hidroxi)-2-metoxi dihidrocinámico (1 g, 4,4 mmol) en 30 ml de CH_3CN y se enfrió a -20°C. Se añadió NIS (0,99 g, 4,43 mmol) y se agitó la mezcla durante 8 horas. Se evaporó el solvente a vacío y se lavó el aceite bruto con CCl_4, con formación de un sólido blanco. Se separó el sólido por filtración y se concentró el filtrado y se purificó por cromatografía en columna (gel de sílice, diclorometano/MeOH 0,5%). Aceite amarillo (924 mg, 60%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,49 (d, 1H, J=2), 7,04 (dd, 1H, J=2, 8,2), 6,80 (d, 1H, J=8,2), 6,03 (s amplio, 1H), 4,17 (c, 2H, J=7,2), 3,88 (dd,1H, J=5,6, 7), 3,33 (s, 3H), 2,88 (dd, 2H, J=2,4, 5,0), 1,21 (t, 3H, J=7,2)

Etapa B

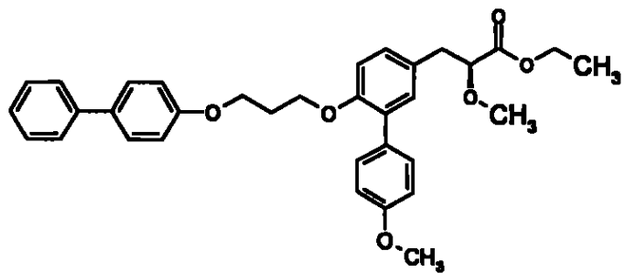
Ácido (2S)-3-(6-hidroxi-4'-metoxibifenil-3-il)-2-metoxi-propiónico



Se calentó una solución de ácido (2S)(4-hidroxi-3-yoduro)-2-metoxidihidrocinámico (197 mg, 0,56 mmol), ácido 4-metoxifenilborónico (170,7 mg, 1,12 mmol) y tetrakis(trifenilfosfina)paladio (0) (8,7 mg, 0,5 mmol) en 11 ml de una mezcla 20:1 de tolueno/etanol, junto con 2 ml de Na_2CO_3 2N a 120°C durante 16 horas bajo una atmósfera de nitrógeno. Se enfrió la mezcla de reacción a temperatura ambiente y se diluyó con acetato de etilo (20 ml). Se lavó con H_2O (3 x 5 ml) y salmuera (3 x 5 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío. Se purificó el producto bruto resultante por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 8:2). Aceite incoloro (123 mg, 67%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,39 (dd, 2H, J=2,1, 6,4), 7,08-7,03 (m, 2H), 6,97 (dd, 2H, J=2,1, 6,7), 6,85 (dd, 1H, J=1,3, 7,5), 5,60 (s, 1H), 4,17 (c, 2H, J=7,0), 3,95 (dd, 1H, J=5,9, 6,4), 3,82 (s, 3H), 3,35 (s, 3H), 2,97 (d, 2H, J=6,4), 1,22 (t, 3H, J=7,2)

Etapa C

Éster etílico del ácido (2S)-3-{6-[3-(bifenil-4-iloxi)-propoxi]-4'-metoxibifenil-3-il}-2-metoxipropiónico



Se preparó éster etílico de ácido 3-{6-[3-(bifenil-4-iloxi)propoxi]-4'-metoxibifenil-3-il}-2-metoxipropiónico siguiendo el Procedimiento estándar B (THF). Se purificó el residuo por cromatografía (gel de sílice, hexanos/acetato de etilo 8:2). Sólido blanco (13 mg, 17%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57 (m, 10H), 7,14 (dd, 2H, J=2,1, 7,8), 6,94-6,87 (m, 4H), 4,24-4,04 (m, 6H), 3,94 (dd,1H, J=5,9, 6,9), 3,81 (s, 3H), 3,36 (s, 3H), 2,99 (d, 2H, J=6,9), 2,18 (q, 2H, J=5,9), 1,22 (t, 3H, J=7,2).

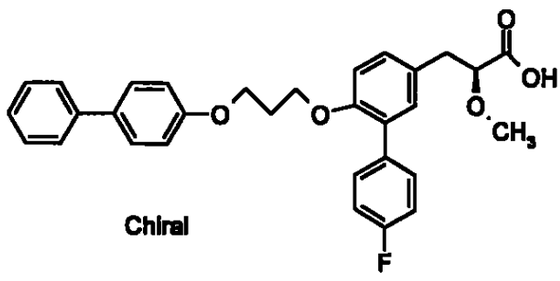
Etapa D

Ácido (2S)-3-{6-[3-(bifenil-4-iloxi)propoxi]-4'-metoxibifenil-3-il}-2-metoxipropiónico

Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 25 (Etapa C). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-6,87 (m, 16 H), 4,15 (t, 2H, J=6,1), 4,07 (t, 2H, J=6,1), 4,01 (dd, 1H, J=7,2, 4,5), 3,80 (s, 3H), 3,41 (s, 3H), 3,13 (dd, 1H, J=4,5, 14,4), 2,99 (dd, 1H, J=7,1, 14,4), 2,21 (q, 2H, J=5,9).

Ejemplo 141

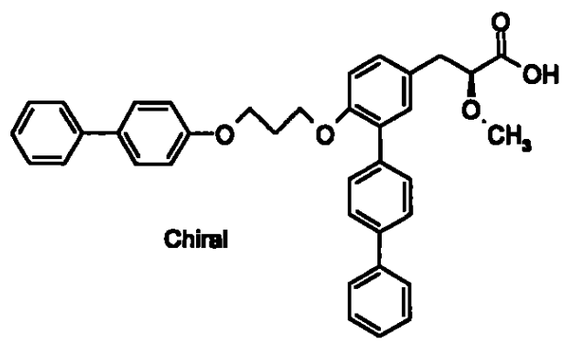
Ácido 3-{6-[3-(bifenil-4-iloxi)propoxi]-4'-fluorobifenil-3-il}-2-metoxipropiónico



Se preparó el compuesto del título como en el Ejemplo 140, con ácido 4-fluorofenilborónico. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-6,87 (m, 16 H), 4,15 (t, 2H, J=5,9), 4,04 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,2, 4,5), 3,41 (s, 3H), 3,13 (dd, 1H, J=4,5, 14,2), 3,00 (dd, 1H, J=7,5, 14,2), 2,17 (q, 2H, J=5,9).

Ejemplo 142

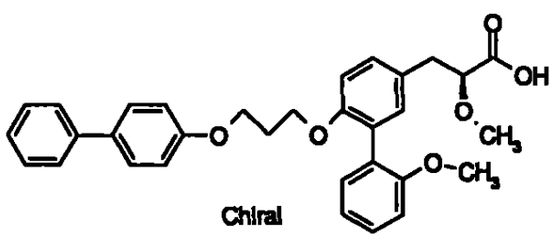
Ácido 3-{6-[3-(bifenil-4-iloxi)propoxi]-[1,1';4',1'']terfenil-3-il}-2-metoxipropiónico



Se preparó el compuesto del título como en el Ejemplo 140, con ácido 4-fenilfenilborónico.

Ejemplo 143

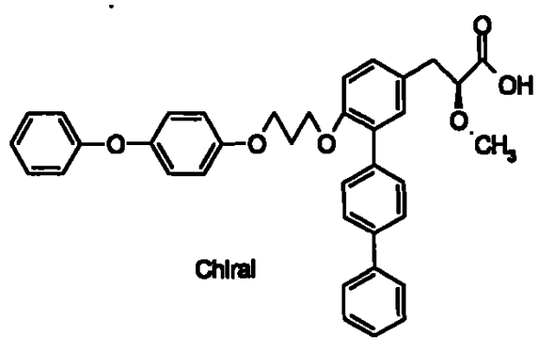
Ácido 3-{6-[3-(bifenil-4-iloxi)propoxi]-2'-metoxibifenil-3-il}-2-metoxipropiónico



Se preparó el compuesto del título como en el Ejemplo 140, con ácido 2-metoxifenilborónico.

Ejemplo 144

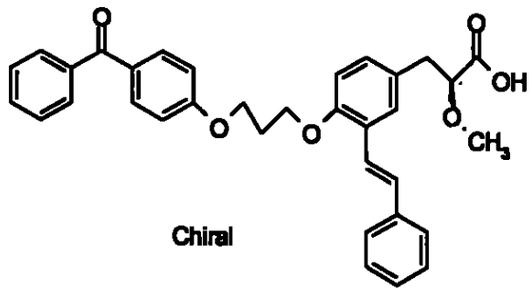
Ácido 2-metoxi-3-{6-[3-(4-fenoxifenoxi)propoxi]-[1,1';-4',1'']terfenil-3-il}propiónico



Se preparó el compuesto del título como en el Ejemplo 140, con ácido 4-difenilborónico.

Ejemplo 145

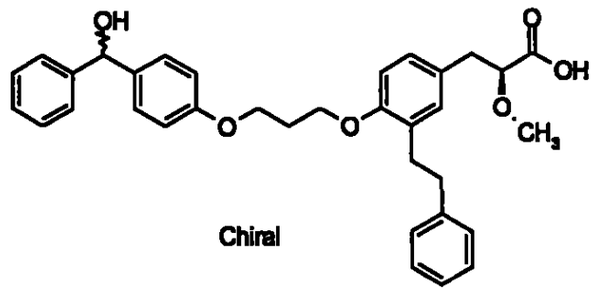
Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-estirilfenil}-2-metoxipropiónico



Se preparó el compuesto del título como en el Ejemplo 140, con ácido trans-2-fenilvinilborónico.

Ejemplo 146

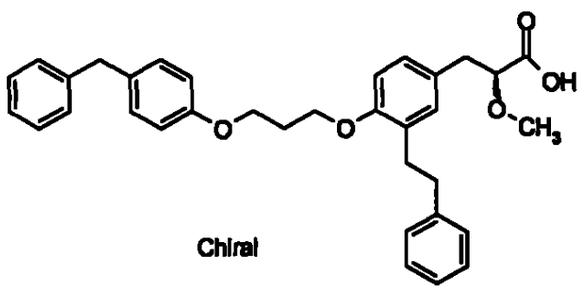
Ácido 3-(4-{3-[4-(hidroxifenilmetil)fenoxi]propoxi}-3-fenetilfenil)-2-metoxipropiónico



Se disolvió una solución de éster etílico de ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-estirilfenil}-2-metoxipropiónico del Ejemplo 145 en etanol y se trató con H_2 bajo presión de balón. Se filtró a través de una almohadilla de celita y se concentró a sequedad. Se trató el compuesto así obtenido mediante el procedimiento estándar de hidrólisis C, para obtener el compuesto del título.

Ejemplo 147

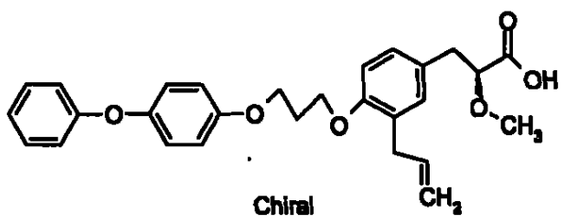
3-{4-[3-(4-Bencilfenoxi)propoxi]-3-fenetilfenil}-2-metoxipropiónico



Se obtuvo el compuesto del título como un producto secundario de la reducción del éster etílico del ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-estirilfenil}-2-metoxipropiónico (del Ejemplo 145) como en el Ejemplo 146 y se hidrolizó según el procedimiento estándar de hidrólisis C, para obtener un producto

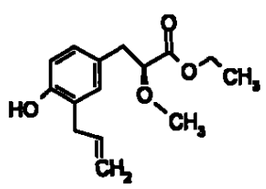
Ejemplo 148

Ácido (2S)-3-{3-alil-4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

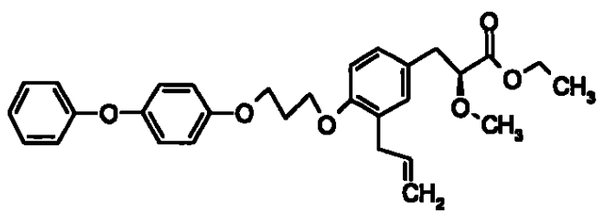
Éster etílico del ácido (2S)-3-(3-alil-4-hidroxifenil)-2-metoxipropiónico



A una solución de éster etílico de ácido 3-(4-hidroxifenil)-2-metoxipropiónico (1 eq) en acetona, se añadieron K_2CO_3 (2 eq) y bromuro de alilo (1,2 eq) y se agitó la mezcla de reacción a 55°C durante la noche. Se apagó con agua y se extrajo con acetato de etilo. Se secó la capa orgánica ($MgSO_4$) y se concentró para obtener éster etílico de ácido 3-(4-aliloxifenil)-2-metoxipropiónico. Se disolvió este producto bruto en Me_2NPh y se calentó a reflujo durante 6 horas y se agitó después a temperatura ambiente durante 3 días. Se sometió de nuevo a reflujo durante 8 horas y se vertió luego en una solución helada de HCl, se extrajo con acetato de etilo y se lavó con agua. Se secó y se concentró para obtener un producto bruto, el cual fue purificado por cromatografía para obtener el compuesto del título.

Etapa B

Éster etílico del ácido (2S)-3-{3-alil-4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se dejó reaccionar éster etílico de ácido (2S)-3-(3-alil-4-hidroxifenil)-2-metoxipropiónico de la Etapa A 4-(3-bromopropoxi)-1-fenoxibenceno según el Procedimiento estándar I, para obtener el compuesto del título.

Etapa C

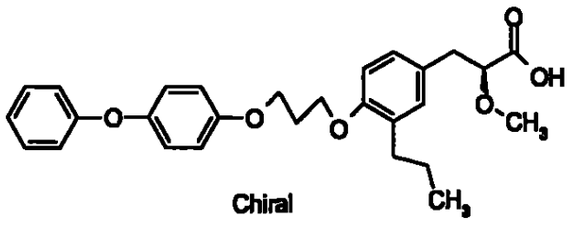
Ácido (2S)-3-{3-alil-4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico

Se hidrolizó éster etílico de ácido (2S)-3-{3-alil-4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-metoxipro-

piónico de la Etapa B según el procedimiento estándar de hidrólisis C, para obtener el producto.

Ejemplo 149

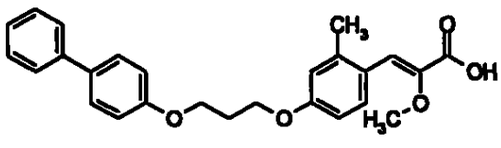
Ácido (2S)-2-metoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]-3-propilfenil}propiónico



Se disolvió una solución de éster etílico de ácido (2S)-3-{3-alil-4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico del Ejemplo 148, Etapa B, en etanol y se trató con H_2 bajo presión de balón. Se filtró a través de una almohadilla de celita y se concentró a sequedad. Se trató el compuesto así obtenido según el procedimiento estándar de hidrólisis C para obtener el compuesto del título.

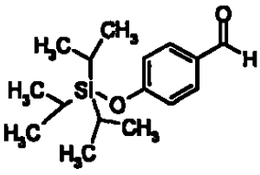
Ejemplo 150

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metilfenil}-2-metoxiacrílico



Etapa A

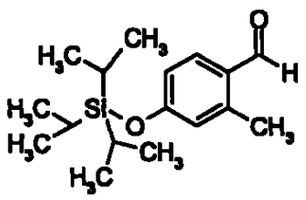
4-Triisopropilsilaniloxibenzaldehído



Se disolvieron 4-hidroxibenzaldehído (3 g, 24,57 mmol), cloruro de triisopropilsililo (5,52 ml, 25,79 mmol) e imidazol (2 g, 29,48 mmol) en 60 ml de DMF y se agitó la solución a temperatura ambiente durante la noche. Se añadió agua (120 ml) a la solución y se extrajo la mezcla con éter dietílico (3 x 50 ml). Se lavaron los extractos combinados con agua (5 x 30 ml), cloruro de amonio saturado (2 x 30 ml) y salmuera (20 ml) y se secaron ($MgSO_4$). La concentración produjo un aceite, que fue purificado por cromatografía (gel de sílice, hexanos/acetato de etilo 20:1, R_f 0,4) (75 %). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 9,85 (s, 1H), 7,75 (d, 2H, J=8,8), 6,95 (d, 2H, J=8,4), 1,31-1,20 (m, 3H), 1,10 (s, 18H).

Etapa B

2-Metil-4-triisopropilsilaniloxibenzaldehído

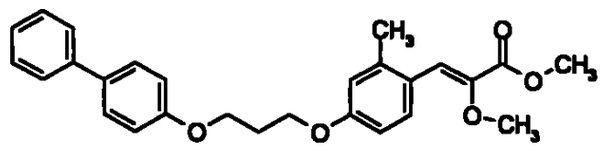


A una solución de trimetiletilendiamina (0,45 ml, 3,48 mmol) en THF (9 ml) a -20°C, se añadió butil-litium 1,6 M en hexanos (2,11 ml, 3,38 mmol). Se agitó la solución a -20°C durante 15 min. Se añadió una solución de 4-triisopropilsilaniloxibenzaldehído (0,922 g, 3,31 mmol) por goteo y se agitó la solución durante 15 min a -20°C. Se añadió butil-litio 1,6 M en hexanos (6,21 ml, 9,93 mmol) por goteo y se mantuvo la solución en el congelador a -20°C durante 26 horas. Se enfrió la solución a -40°C y se añadió yoduro de metilo (3,71 ml, 59,60 mmol). Se dejó llegar a la solución a temperatura ambiente y se agitó después durante 30 min. Se apagó la reacción con cloruro de amonio saturado (20 ml) y se extrajo con acetato de etilo (3 x 30 ml). Se secaron los extractos orgá-

nicos combinados ($MgSO_4$), se concentraron a vacío y se purificaron por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 20:1, R_f 0,085) (49%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 10,1 (s, 1H), 7,69 (d, 1H, J=8,3), 6,80 (dd, 1H, J=8,6, 2,4), 6,72 (s, 1H), ,61 (s, 3H), 1,33-1,19 (m, 3H), 1,12 (s, 18H).

Etapa C

Éster metílico del ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metilfenil}-2- metoxiacrílico



Se añadió 2-metoxiacetato de metilo (0,450 ml, 4,53 mmol) a una solución de NaHDMS (4,74 mmol) en 40 ml de THF enfriado a -78°C. Se agitó la mezcla a -78°C durante 30 min y se añadió luego una solución de 2-metil-4-triisopropilsilaniloxibenzaldehído (1,26 g, 4,3 mmol) en 20 ml de THF por goteo. Se dejó calentar a la solución a 0°C y se agitó durante 2,5 horas. Se apagó la mezcla con HCl 1N (50 ml) a 0°C, se extrajo con diclorometano (3 x 40 ml), se secó ($MgSO_4$) y se concentró a vacío. Se disolvió el residuo en diclorometano (50 ml) y se enfrió a 0°C. Se añadieron a la solución anhídrido trifluoroacético (0,82 ml, 5,84 mmol), N,N-dimetilaminopiridina (0,025 g, 0,21 mmol) y piridina (0,379 ml, 4,59 mmol) y se agitó a temperatura ambiente durante 4 horas. Se eliminaron los volátiles a vacío y se disolvió el residuo en 100 ml de acetato de etilo. Se añadió paladio al 10% sobre carbono activado (0,9 g) y se hidrogenó la mezcla a temperatura ambiente (5 atm H_2) durante 14 horas. Se filtró la solución a través de una almohadilla de celita y se concentró a vacío. Se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 3:1), se

recogieron las fracciones con R_f de 0,08 y se concentraron a vacío (0,249 g que contenían ácido 3-(4-hidroxi-2-metilfenil)-2-metoxiacrílico aprox. 85% puro por RMN). Se añadió el residuo a una solución de 4-(3-bromopropoxi)bifenilo (Ejemplo 23, Etapa D) (0,359 g, 1,23 mmol), yoduro de sodio (0,05 g) y terc-butóxido de potasio (126 mg, 1,12 mmol) en 5 ml de dimetilformamida. Se agitó la solución a temperatura ambiente durante 24 horas, se diluyó con agua y se extrajo con éter dietílico (3 x 30 ml). Se lavaron las capas orgánicas combinadas con agua (5 x 30 ml), se secaron ($MgSO_4$) y se concentraron a vacío. Se purificó el residuo por cromatografía en columna (gel de sílice, hexano:acetato de etilo 6:1, R_f 0,22). (0,18 mg, 10%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,98 (d, 1H, J=8,6), 7,57-7,25 (m, 7H), 7,16 (s, 1H); 6,98 (dd, J=6;7, 2,1), 6,80-6,76 (m, 2H), 4,20 (t, 4H, J=5,9), 3,85 (s, 3H), 3,69 (s, 3H), 2,36 (s, 3H), 2,29 (t, 2H, J=6,2).

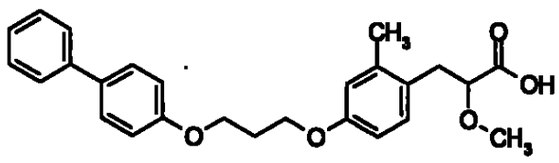
Etapa D

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metilfenil}-2-metoxiacrílico

Se preparó el compuesto del título a partir de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-metil-fenil}-2-metoxiacrílico siguiendo el procedimiento general B. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,97 (d, 1H, J=8,4), 7,55-7,47 (m, 4H), 7,43-7,27 (m, 4H), 6,96 (dd, 2H, J=6,6, 2,2), 6,79-6,75 (m, 2H), 4,19 (t, 4H, J=6,2), 3,69 (s, 3H), 2,35 (s, 3H), 2,27 (t, 2H, J=6,2).

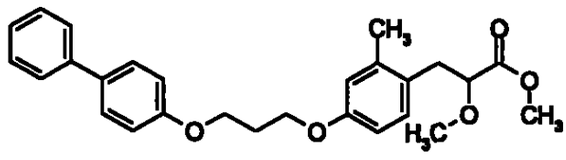
Ejemplo 151

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metilfenil}-2-metoxipropiónico



Etapa A

Éster metílico del ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metilfenil}-2-metoxipropiónico



Se añadieron virutas de magnesio (0,101 g, 4,17 mmol) a una solución de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metilfenil}-2-metoxi-acrílico (Ejemplo 37, Etapa C) (0,09 g, 0,21 mmol) en metanol (2 ml) y éter dietílico (2 ml). Se agitó la mezcla a temperatura ambiente durante la noche y se apagó con HCl 3N hasta pH 7. Se añadió una solución saturada de cloruro de amonio (10 ml) y se extrajo la mezcla con éter etílico (3 x 10 ml). Se secaron los extractos combinados ($MgSO_4$) y se concentraron a vacío. Se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 4,5:1, R_f 0,31) (48%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,57-7,29 (m, 7H), 7,07 (d, 1H, J=8,1); 6,98 (dd, 2H, J=6,7, 2,1), 6,73 (s, 1H); 6,71 (d, 1H, J=11,8); 4,18 (dt, 4H, J=9,7, 6,2), 3,91 (dd, 1H, J=7,3, 6,2), 3,72 (s, 3H), 3,32 (s, 3H), 2,97 (d, 2H, J=6,4), 2,31 (s, 3H); 2,27 (t, 2H, J=6,2).

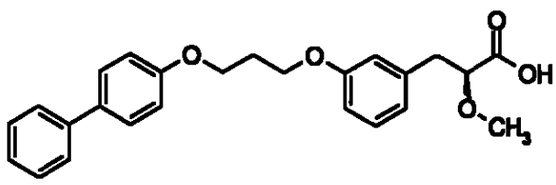
Etapa B

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metilfenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-metilfenil}-2-metoxipropiónico siguiendo el procedimiento general B. (71%). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,55-7,27 (m, 7H); 7,09 (d, 1H, J=8,1); 6,96 (d, 2H, J=9,2); 6,71-6,67 (m, 2H); 4,15 (dt, 4H, J=9,1, 6,2); 3,92 (dd, 1H, J=8,4, 4,4); 3,31 (s, 3H); 3,08 (dd, 1H, J=14,6, 4,4); 2,93 (dd, 1H, J=14,3, 8,4); 2,30 (s, 3H); 2,25 (q, 2H, J=6,2).

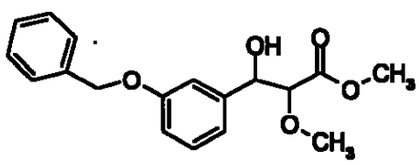
Ejemplo 152

Ácido 3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxi-propiónico



Etapa A

Éster metílico del ácido 3-(3-benciloxifenil)-3-hidroxi-2-metoxipropiónico

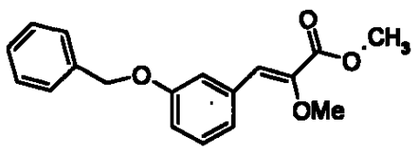


A una solución de NaHMDS (1,1 eq) en THF seco a -78°C, se añadieron por goteo una mezcla de 3-benciloxibenzaldehído (1 eq) y éster metílico del ácido metoxiacético (1,25 eq) en THF y se agitó la mezcla de reacción a esta temperatura a lo largo de 1,5 horas. Se apagó entonces la reacción con HCl 3N y se dejó subir

hasta la temperatura ambiente. Se lavó con salmuera y se extrajo con éter. Se secó la capa orgánica y se concentró a sequedad para obtener, tras cromatografía en gel de sílice, el compuesto del título.

Etapa B

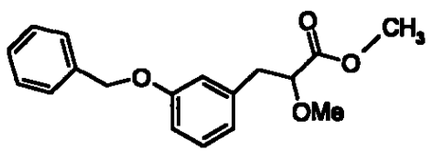
Éster metílico del ácido 3-(3-benciloxifenil)-2-metoxi-acrílico



Se agitó una mezcla de éster metílico de ácido 3-(3-benciloxifenil)-3-hidroxi-2-metoxipropiónico (1 eq), cloruro de mesilo (1 eq), trietilamina (4 eq) y una cantidad catalítica de DMAP (0,1 eq) en diclorometano a temperatura ambiente durante la noche. Se diluyó la mezcla de reacción con éter y se lavó con HCl 1N. Se secó y se concentró a vacío, para obtener un residuo, el cual fue cromatografiado en gel de sílice para obtener el compuesto del título.

Etapa C

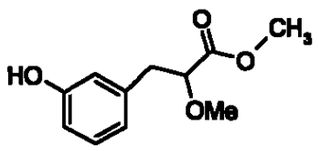
Éster metílico del ácido 3-(3-benciloxifenil)-2-metoxi-propiónico



Se disolvió el compuesto de la Etapa B en metanol y se trató con magnesio. Se puso el matraz en un baño de hielo durante 5 min y se agitó luego la mezcla de reacción a temperatura ambiente durante 4 horas. Se lavó con HCl 3N y se extrajo con éter. Se secó y se concentró a sequedad para obtener el compuesto del título.

Etapa D

Éster metílico del ácido 3-(3-hidroxifenil)-2-metoxipropiónico



Se trató una solución de éster metílico del ácido 3-(3-benciloxifenil)-2-metoxipropiónico en metanol con una cantidad catalítica de Pd-C (0,1 eq) y se burbujeó luego H_2 a través de la mezcla y se agitó durante la noche. Se concentró la mezcla de reacción y se reconstituyó en acetato de etilo, se filtró a través de una almohadilla de celita y se concentró a vacío, para obtener el compuesto del título.

Etapa E

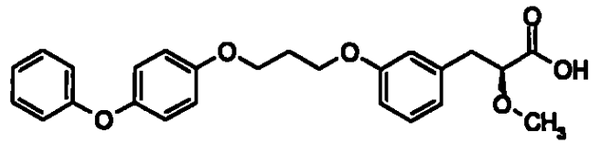
Ácido 3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se agitó una mezcla de éster metílico de ácido 3-(3-hidroxifenil)-2-metoxipropiónico (1 eq) de la Etapa D, carbonato de cesio (3 eq) y 4-(3-bromopropoxi)bifenilo (1 eq) en DMF y en un tubo de 10 ml en un agitador orbital a lo largo de un fin de semana. Se filtró la mezcla a través de una jeringa hidrofóbica y se evaporó en un aparato de velocidad-vacío. Se diluyó después con NaOH 1N-etanol y se agitó durante la noche. Se añadió entonces HCl 3N y se concentró la mezcla de reacción para eliminar el etanol a vacío, se reconstituyó en diclorometano y se filtró a través de una jeringa hidrofóbica. Se evaporó la capa orgánica para obtener el compuesto del título. MS (ES) para $C_{25}H_{26}O_5$ $[M+NH^4]^+$: 424,2, $[M+Na]^+$: 429,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,57-7,17 (m, 9H), 6,98 (dd, 2H, J=6,7, 1,9), 6,84-6,81 (m, 3H), 4,19 (dd, 4H, J=14,0, 6,4), 4,03 (dd, 1H, J=7,3, 4,3), 3,40

(s, 3H), 3,13 (dd, 1H, J=14,2, 4,6), 2,98 (dd, 1H, J=14,0, 7,5), 2,28 (q, 2H, J=5,9)ppm.

Ejemplo 153

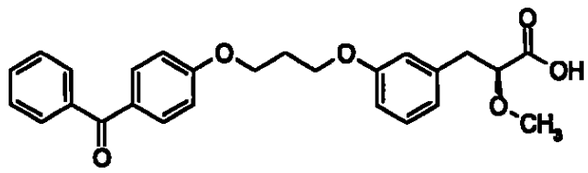
Ácido '2-metoxi-3-{3-[3-(4-fenoxifenoxi)propoxi]fenil}-propiónico



Se preparó el compuesto del título a partir de éster metílico de ácido 3-(3-hidroxifenil)-2-metoxi-propiónico del Ejemplo 152, Etapa D, con 4-(3-bromopropoxi)1-fenoxibenceno de un modo análogo al del Ejemplo 152, Etapa E. MS (ES) para $C_{25}H_{26}O_6$ $[M+NH_4]^+$: 440,2, $[M+Na]^+$: 445,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,33-7,17 (m, 3H), 7,07-6,78 (m, 10H), 4,15 (dt, 4H, J=1,9, 6,2), 4,03 (dd, 1H, J=7,3, 4,3), 3,40 (s, 3H), 3,13 (dd, 1H, J=14,2; 4,6), 2,98 (dd, 1H, J=14,0, 7,5), 2,25 (q, 2H, J=5,9)ppm.

Ejemplo 154

Ácido 3-{3-[3-(4-benzoilfenoxi)propoxi]fenil}-2-metoxi-propiónico

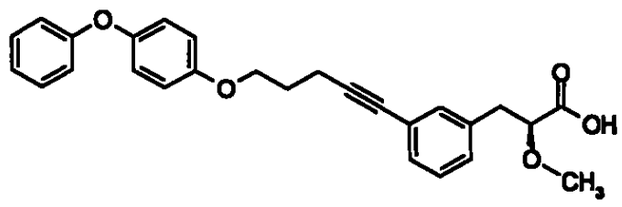


Se preparó el compuesto del título a partir de éster metílico de ácido 3-(3-hidroxifenil)-2-metoxi-propiónico del Ejemplo 152, Etapa D, con [4-(3-bromo-propoxi)fenil]fenilmetanona de un modo análogo al del Ejemplo 152, Etapa E. MS (ES) para $C_{26}H_{26}O_6$ $[M+H]^+$: 435,2, $[M+Na]^+$:457,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,83-7,72 (m, 4H), 7,56-7,42 (m, 3H), 7,21 (dd, 2H, J=9,1, 7,0), 6,97 (d, 2H, J=8,9), 6,82 (d, 1H, J=14,2), 6,82 (s, 2H), 4,25

(t, 2H, J=6,2), 4,16 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,5, 4,3), 3,40 (s, 3H), 3,12 (dd, 1H, J=14,0, 4,3), 2,98 (dd, 1H, J=14,2, 7,5), 2,29 (q, 2H, J=5,9).

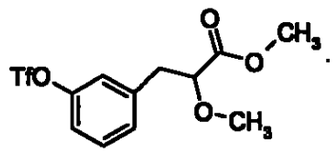
Ejemplo 155

Ácido 2-metoxi-3-{3-[5-(4-fenoxifenoxi)pent-1-inil]fenil}propiónico



Etapa A

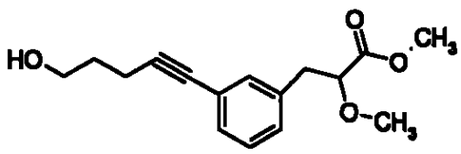
Éster metílico del ácido 2-metoxi-3-(3-trifluorometanosulfoniloxifenil) propiónico



Se preparó el compuesto del título usando el mismo procedimiento que en el Ejemplo 1, Etapa A, partiendo de éster metílico de ácido 3-(3-hidroxifenil)-2-metoxipropiónico.

Etapa B

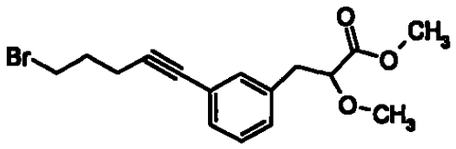
Éster metílico del ácido 3-[3-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de 4-butin-1-ol siguiendo el procedimiento descrito en el Ejemplo 1, Etapa B.

Etapa C

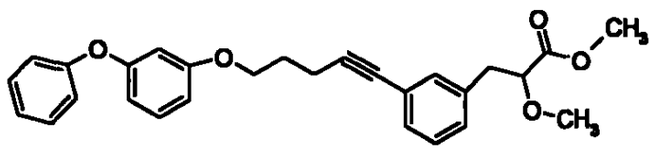
Éster metílico del ácido 3-[3-(5-bromopent-1-inil)fenil]-2-metoxipropiónico



A una solución de éster metílico de ácido 3-[3-(5-hidroxipent-1-inil)fenil]-2-metoxipropiónico y CBr4 disueltos en diclorometano a 0°C, se añadió trifenilfosfina y se agitó la mezcla de reacción a temperatura ambiente a lo largo de 5 horas. Se diluyó entonces la reacción con agua y se extrajo con éter. Se cromatografió para obtener el compuesto del título.

Etapa D

Éster metílico del ácido 2-metoxi-3-{3-[5-(4-fenoxifenoxi)pent-1-inil]fenil}propiónico



Se agitó durante la noche una mezcla de éster metílico de ácido 3-[3-(5-bromopent-1-inil)fenil]-2-metoxipropiónico (1 eq), 4-fenoxifenol (1 eq) y carbonato de cesio (3 eq) en DMF. Se diluyó después en agua y se extrajo con éter, para obtener, después de secar a vacío, el compuesto del título.

Etapa E

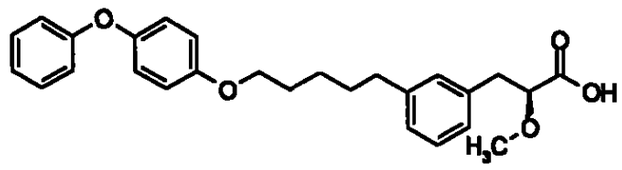
Ácido 2-metoxi-3-{3-[5-(4-fenoxifenoxi)pent-1-inil]fenil}propiónico

Se preparó el compuesto del título siguiendo el Procedimiento estándar de hidrólisis C y partiendo del éster metílico de ácido 2-metoxi-3-{3-[5-(4-fenoxifeno-

xi)pent-1-inil]fenil}propiónico de la Etapa D. MS (ES) para $C_{27}H_{26}O_5$ $[M+NH^4]^+$: 448,2, $[M+Na]^+$:453,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,33-7,17 (m, 7H), 7,07-6,88 (m, 7H), 4,11 (t, 2H, J=6,2), 4,00 (dd, 1H, J=7,5, 4,0), 3,39 (s, 3H), 3,11 (dd, 1H, J=14,0, 4,3), 2,96 (dd, 1H, J=14,5, 7,8), 2,63 (t, 2H, J=7,0), 2,08 (q, 2H, J=6,7).

Ejemplo 156

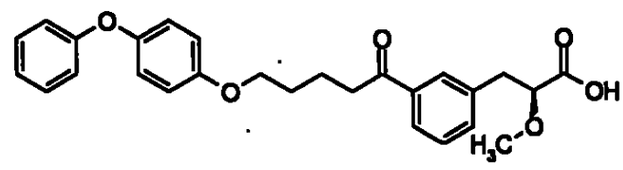
Ácido 2-metoxi-3-{3-[5-(4-fenoxifenoxi)pentil]fenil}propiónico



Se preparó el compuesto del título a partir del ácido 2-metoxi-3-{3-[5-(4-fenoxifenoxi)pent-1-inil]-fenil}propiónico del Ejemplo 155, Etapa E, y se trató con Pd-C (0,1 eq) en acetato de etilo y H_2. Se filtró a través de celita y se concentró para obtener el compuesto. MS (ES) para $C_{27}H_{30}O_5$ $[M+H]^+$: 435,2, $[M+NH_4]^+$:452,2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,34-7,19 (m, 3H), 7,09-6,84 (m, 10H), 4,02 (dd, 1H, J=7,5, 4,6), 3,94 (t, 2H, J=6,5), 3,39 (s, 3H), 3,13 (dd, 1H, J=14,0, 4,3), 3,00 (dd, 1H, J=14,0, 7,5), 2,63 (t, 2H, J=7,8), 1,88-1,45 (m, 6H)ppm.

Ejemplo 157

Ácido 2-metoxi-3-{3-[5-(4-fenoxifenoxi)pentanoil]fenil}-propiónico

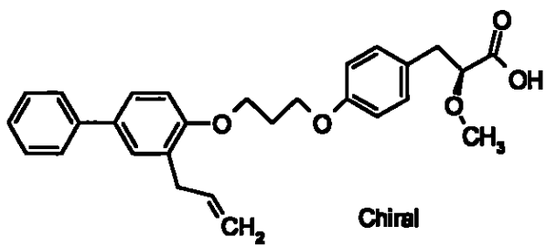


Se preparó el compuesto del título a partir del éster metílico del ácido 2-metoxi-3-{3-[5-(4-fenoxi-fenoxi)pent-1-inil]fenil}propiónico, (Ejemplo 155, Etapa

D) y siguiendo el mismo procedimiento que en el Ejemplo 57 y un procedimiento estándar de hidrólisis C, para obtener el compuesto.

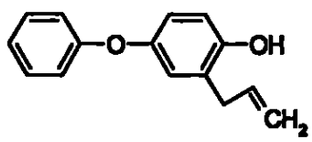
Ejemplo 158

Ácido 3-{4-[3-(3-alilbifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

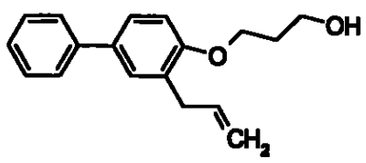
2-Alil-4-fenoxifenol



A una solución de 4-fenilfenol (1 eq) en acetona, se añadieron K_2CO_3 (2 eq) y bromuro de alilo (1,2 eq) y se agitó la mezcla de reacción a 55°C durante la noche. Se apagó con agua y se extrajo con acetato de etilo. Se secó la capa orgánica ($MgSO_4$) y se concentró para obtener 4-aliloxibifenilo. Se disolvió este producto bruto en Me_2NPh y se calentó a reflujo durante 6 horas y se agitó después a temperatura ambiente durante 3 días. Se sometió de nuevo a reflujo durante 8 horas y luego se vertió en una solución helada de HCl 1M, se extrajo con acetato de etilo y se lavó con agua. Se secó y se concentró para obtener un producto bruto, que fue purificado por cromatografía para obtener el compuesto del título.

Etapa B

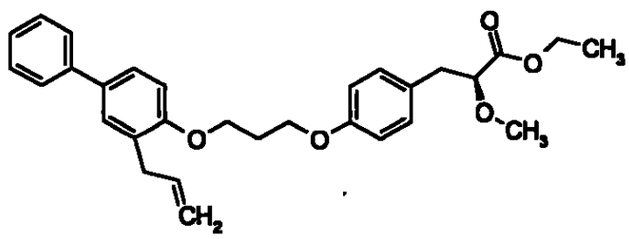
3-(3-Alilbifenil-4-iloxi)propan-1-ol



Se disolvió el producto obtenido en la Etapa A (1,1 eq) en THF y se trató con t-BuOK (1,15 eq) y se dejó que reaccionaran durante 2 horas. Se añadió entonces una solución de 2,2-dióxido de [1,3,2]dioxatiolano (1,0 eq) y se agitó la mezcla de reacción durante la noche, se apagó con HCl 6N y se sometió a reflujo la reacción durante la noche. Se extrajo con acetato de etilo, se lavó con salmuera y se concentró para obtener el compuesto del título.

Etapa C

Éster etílico del ácido 3-{4-[3-(3-alilbifenil-4-iloxi)-propoxi]fenil}-2-metoxipropiónico



Se trató una solución del compuesto de la Etapa B en diclorometano con CBr_4 (1,12 eq) y PPh_3 (1,4 eq) y se dejó que reaccionaran durante 1,5 horas. Se trató el producto aislado después de la cromatografía de esta reacción según el Procedimiento estándar I con éster etílico de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico, para obtener el compuesto del título.

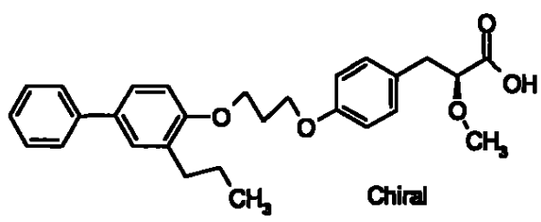
Etapa D

Ácido 3-{4-[3-(3-alilbifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título usando el Procedimiento estándar de hidrólisis C (NaOH).

Ejemplo 159

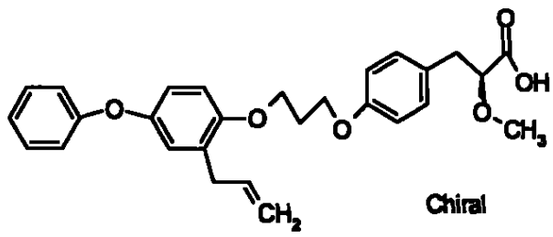
Ácido (2S)-2-metoxi-3-{4-[3-(3-propilbifenil-4-iloxi)propoxi]fenil}propiónico



Se trató el ácido 3-{4-[3-(3-alilbifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico del Ejemplo 158, Etapa D, disuelto en acetato de etilo con Pd(C) al 10% bajo presión de balón durante 6 horas. Se filtró a través de celita y se concentró a sequedad, para obtener el compuesto del título.

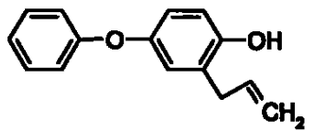
Ejemplo 160

Ácido (2S)-3-{4-[3-(2-alil-4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

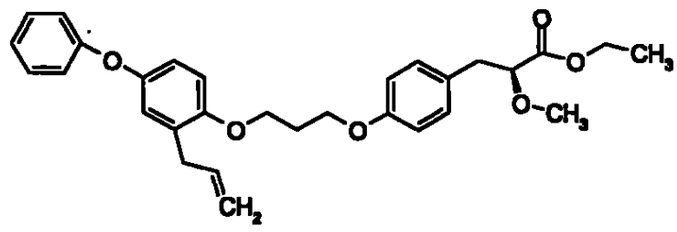
2-Alil-4-fenoxifenol



Se preparó el compuesto del título del mismo modo que en el Ejemplo 158, Etapa A, partiendo de 4-fenoxifenol.

Etapa B

Éster etílico del ácido 2-{4-[3-(2-alil-4-fenoxifenoxi)-propoxi]fenil}-3-metoxipropiónico



Se dejó que reaccionaran éster etílico del ácido 3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico y 2-alil-4-fenoxifenol de la Etapa A según el Procedimiento estándar I para obtener el compuesto del título.

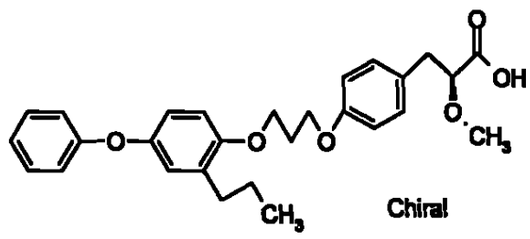
Etapa C

Ácido (2S)-3-{4-[3-(2-alil-4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título usando el Procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título.

Ejemplo 161

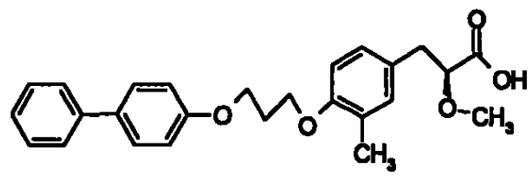
Ácido (2S)-2-metoxi-3-{4-[3-(4-fenoxi-2-propilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido 2-{4-[3-(2-alil-4-fenoxifenoxi)propoxi]fenil}-3-metoxipropiónico del Ejemplo 160, Etapa B, el cual fue tratado en acetato de etilo con Pd(C) y H_2 bajo presión de balón, para obtener, después de filtrar, el correspondiente producto reducido, que fue hidrolizado según el procedimiento estándar C, para obtener el compuesto del título.

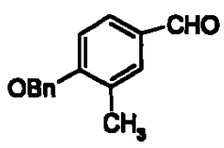
Ejemplo 162

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-metilfenil}-2-metoxipropiónico



Etapa A

4-Benciloxi-3-metilbenzaldehído

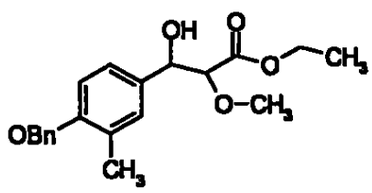


Se trató una mezcla de bromuro de bencilo y 4-hidroxi-3-metilbenzaldehído según el Procedimiento es-

tándar I, para obtener el compuesto del título.

Etapa B

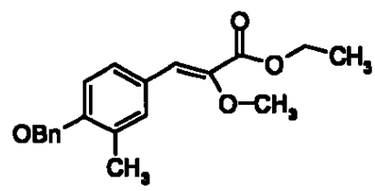
Éster etílico del ácido 3-(4-benciloxi-3-metilfenil)-3-hidroxi-2-metoxipropiónico



A una solución de NaHMDS (1,1 eq) en THF seco a -78°C se añadió una mezcla de 4-benciloxi-3-metil-benzaldehído (1 eq) y éster metílico de ácido metoxiacético (1,25 eq) en THF por goteo y se agitó la mezcla de reacción a esta temperatura a lo largo de 1,5 horas. Se apagó entonces la reacción con HCl 3N y se dejó que subiera hasta la temperatura ambiente. Se lavó con salmuera y se extrajo con éter. Se secó la capa orgánica y se concentró a sequedad, para obtener, tras cromatografía en gel de sílice, el producto del título.

Etapa C

Éster etílico del ácido 3-(4-benciloxi-3-metilfenil)-2-metoxiacrílico

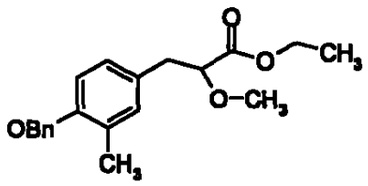


Se agitó una mezcla de éster etílico de ácido 3-(4-benciloxi-3-metilfenil)-3-hidroxi-2-metoxipropiónico (1 eq), cloruro de mesilo (1 eq), trietilamina (4 eq) y una cantidad catalítica de DMAP (0,1 eq) en diclorometano a temperatura ambiente durante la noche. Se diluyó la mezcla de reacción con éter y se lavó con HCl 1N. Se secó

y se concentró a vacío para obtener un residuo, que fue cromatografiado en gel de sílice para obtener el compuesto del título.

Etapa D

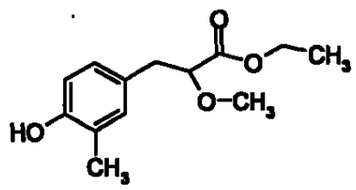
Éster etílico del ácido 3-(4-benciloxi-3-metilfenil)-2-metoxipropiónico



Se disolvió el compuesto de la Etapa C en metanol y se trató con magnesio. Se puso el matraz en un baño de hielo durante 5 min y se agitó entonces la mezcla de reacción a temperatura ambiente durante 4 horas. Se lavó con HCl 3N y se extrajo con éter. Se secó y se concentró a sequedad para obtener el compuesto del título.

Etapa E

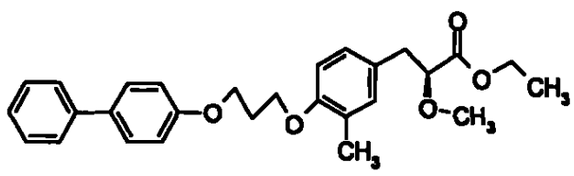
Éster etílico del ácido 3-(4-hidroxi-3-metilfenil)-2-metoxipropiónico



Se trató una solución de éster etílico de ácido 3-(4-benciloxi-3-metilfenil)-2-metoxipropiónico en acetato de etilo con una cantidad catalítica de Pd-C (0,1 eq) y luego se burbujeó H_2 a través de la mezcla y se agitó durante 2 horas. Se filtró la mezcla de reacción a través de una almohadilla de celita y se concentró a vacío para obtener el compuesto del título.

Etapa F

Éster etílico del ácido (2S)-3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-metilfenil}-2-metoxipropiónico



Se trató una mezcla de éster etílico de ácido 3-(4-hidroxi-3-metilfenil)-2-metoxipropiónico de la Etapa E y 4-(3-bromopropoxi)bifenilo según la condición estándar I para obtener el producto del título.

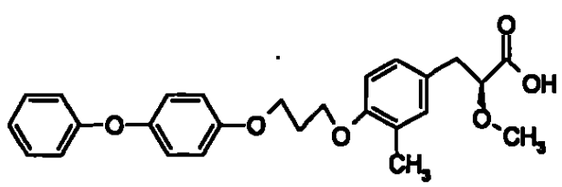
Etapa G

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-3-metilfenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir del compuesto de la Etapa F según el procedimiento estándar de hidrólisis C usando NaOH.

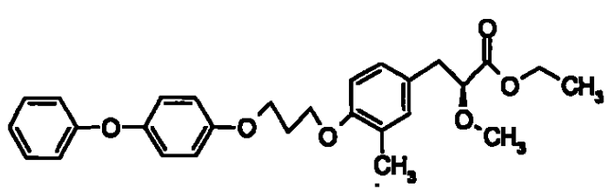
Ejemplo 163

Ácido 2-metoxi-3-{3-metil-4-[3-(4-fenoxifenoxi)propoxi]-fenil}propiónico



Etapa A

Éster etílico del ácido 2-metoxi-3-{3-metil-4-[3-(4-fenoxifenoxi)propoxi]fenil}propiónico



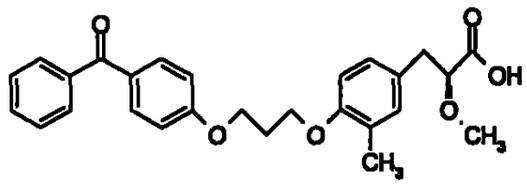
Se trató una mezcla de éster etílico de ácido 3-(4-hidroxi-3-metilfenil)-2-metoxipropiónico del Ejemplo 162, Etapa E, y 4-(3-bromopropoxi)fenoxifenilo según la condición estándar I, para obtener el producto del título.

Etapa B

Se preparó el compuesto del título a partir del compuesto de la Etapa A según el procedimiento estándar de hidrólisis C utilizando NaOH.

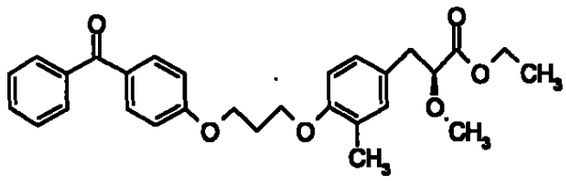
Ejemplo 164

Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-metilfenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-metilfenil}-2-metoxipropiónico



Se trató una mezcla de éster etílico de ácido 3-(4-hidroxi-3-metilfenil)-2-metoxipropiónico del Ejemplo 162, Etapa E, y [4-(3-bromopropoxi)fenil]fenilmetanona según la condición estándar I para obtener el producto del título.

Etapa B

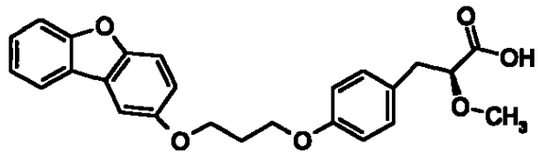
Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-3-metilfenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir

del compuesto de la Etapa A según el procedimiento estándar de hidrólisis C utilizando NaOH.

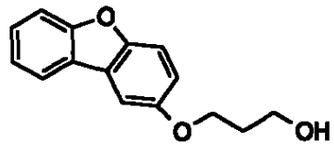
Ejemplo 165

Ácido (2S)-3-{4-[3-(dibenzofuran-2-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

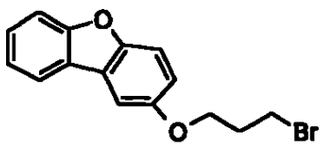
3-(Dibenzofuran-2-iloxi)-propan-1-ol



Se trató una solución de 2-hidroxidibenzofurano, *terc*-butóxido de potasio y 2,2-dióxido de [1,2,3]dioxatiano del mismo modo que en el Ejemplo 132, Etapa C, para obtener el producto del título.

Etapa B

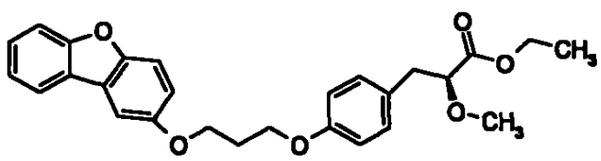
2-(3-Bromopropoxi)dibenzofurano



Partiendo del compuesto de la Etapa A y siguiendo el procedimiento descrito en el Ejemplo 132, Etapa D, obtuvimos el compuesto del título.

Etapa C

Éster etílico del ácido 3-{4-[3-(dibenzofuran-2-iloxi)-propoxi]fenil}-2-metoxipropiónico



Se dejó reaccionar a una mezcla de 2-(3-bromopropoxi)di-benzofurano y éster etílico de ácido (2S)-3-(4-hidroxife-nil)-2-metoxipropiónico según el procedimiento estándar I, para obtener el compuesto del título.

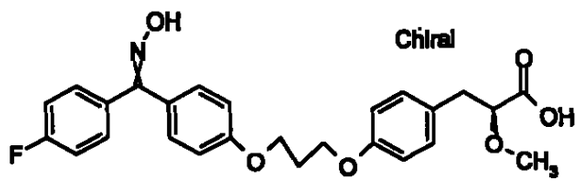
Etapa D

Ácido (2S)-3-{4-[3-(dibenzofuran-2-iloxi)propoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de Etapa C utilizando el procedimiento estándar de hidrólisis C (NaOH).

Ejemplo 166

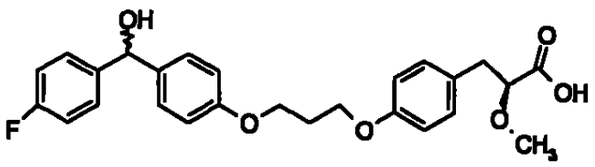
Ácido (2S)-3-[4-(3-{4-[(4-fluorofenil)hidroxiiminometil]-fenoxi}propoxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-(4-{3-[4-(4-fluorobenzoil)fenoxi]-propoxi}fenil)-2-metoxipropiónico (Ejemplo 95) y se trató en las mismas condiciones que en el Ejemplo 61, para obtener el compuesto del título.

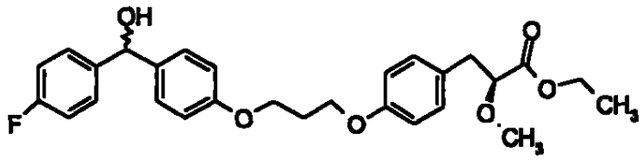
Ejemplo 167

Ácido (2S)-3-[4-(3-{4-[(4-fluorofenil)hidroximetil]fenoxi}propoxi)fenil]-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-[4-(3-{4-[(4-fluorofenil)-hidroximetil]fenoxi}propoxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-(4-{3-[4-(4-fluorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico (Ejemplo 95), que fue disuelto en metanol y se trató a 0°C con $NaBH_4$ (2 eq) durante para 6 horas. Se lavó con agua y se extrajo con diclorometano para obtener, tras purificación por cromatografía, el compuesto del título.

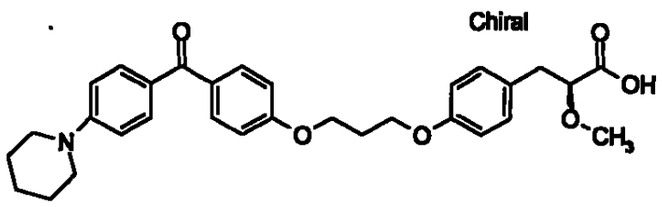
Etapa B

Ácido (2S)-3-[4-(3-{4-[(4-fluorofenil)hidroximetil]fenoxi}propoxi)fenil]-2-metoxipropiónico

Se preparó el compuesto del título a partir de la Etapa A por el procedimiento estándar de hidrólisis C (NaOH).

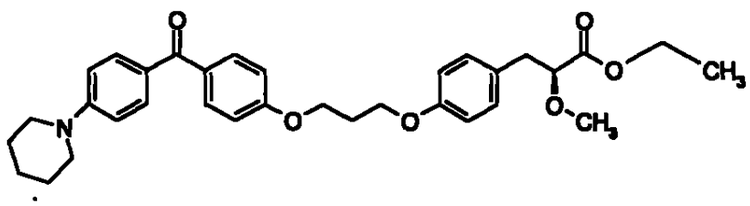
Ejemplo 168

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-piperidin-1-il-benzoil)fenoxi]propoxi}fenil)propiónico



Etapa A

Éster etílico del ácido (2S)-2-metoxi-3-(4-{3-[4-(4-piperidin-1-ilbenzoil)fenoxi]propoxi}fenil)propiónico



A una solución de éster etílico de ácido (2S)-3-(4-{3-[4-(4-fluorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico (Ejemplo 95) en DMSO, se añadió piperidina (3 eq) y se calentó la mezcla de reacción a 140°C durante 2 días. Se extrajo la reacción con acetato de etilo y se lavó (varias veces) con agua. Se concentró a sequedad y se cromatografió para obtener el compuesto del título.

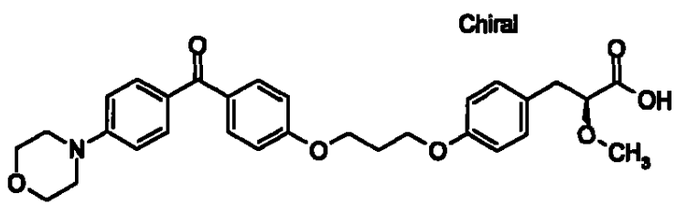
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-piperidin-1-il-benzoil)fenoxi]propoxi}fenil)propiónico

Se preparó el compuesto del título a partir de la Etapa A por el procedimiento estándar de hidrólisis C (LiOH). MS (ES) para $C_{31}H_{35}NO_6$ $[M+H]^+$: 518.

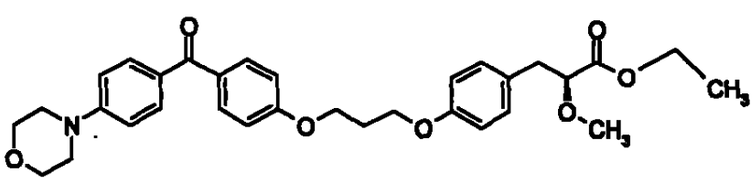
Ejemplo 169

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-morfolin-4-ilbenzoil)-fenoxi]propoxi}fenil)propiónico



Etapa A

Éster etílico del ácido (2S)-2-metoxi-3-(4-{3-[4-(4-morfolin-4-ilbenzoil)fenoxi]propoxi}fenil)propiónico



A una solución de éster etílico de ácido (2S)-3-(4-{3-[4-(4-fluorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico (Ejemplo 95) en DMSO, se añadió morfolina (3 eq) y se calentó la mezcla de reacción a 140°C durante 2 días. Se extrajo la reacción con acetato de etilo y se lavó (varias veces) con agua. Se concentró a sequedad y se cromatografió para obtener el compuesto del título.

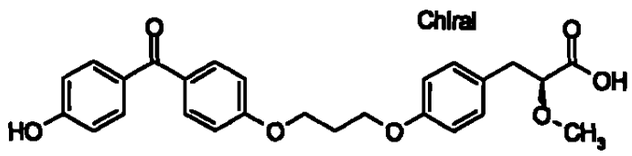
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-morfolin-4-ilbenzoil)-fenoxi]propoxi}fenil)propiónico

Se preparó el compuesto del título a partir de la Etapa A mediante el procedimiento estándar de hidrólisis C (LiOH). MS (ES) para $C_{30}H_{33}NO_7$ $[M+H]^+$: 520.

Ejemplo 170

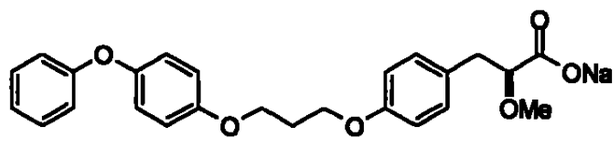
Ácido (2S)-3-{4-{3-[4-(4-hidroxibenzoil)fenoxi]propoxi}-fenil)-2-metoxipropiónico



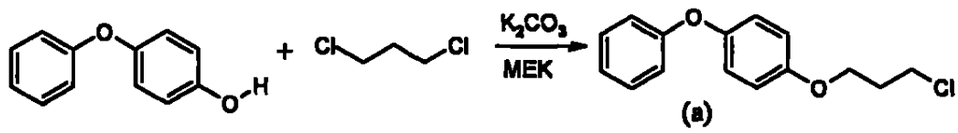
Se calentó una solución de ácido (2S)-3-(4-{3-[4-(4-fluorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico (85 mg) (Ejemplo 95) y KOH (100mg) en clorobenceno (0,3 ml) con agua (1 ml) en un tubo sellado a 200°C durante 3 días. Se extrajo con acetato de etilo, se secó y se concentró a sequedad para obtener un producto bruto, que fue purificado por cromatografía para obtener el compuesto del título. MS (ES) para $C_{26}H_{26}O_7$ $[M+H]^+$: 451.

Ejemplo 171

Sal sódica del ácido 2S-2-metoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propanoico



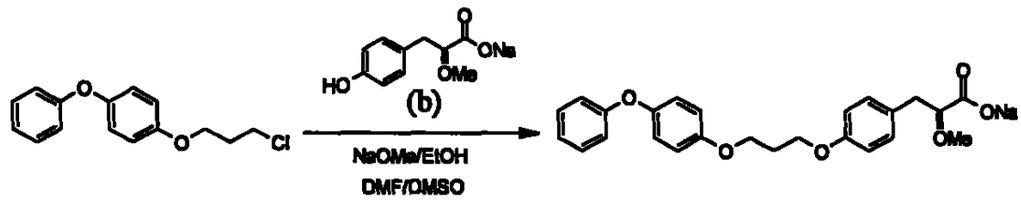
Etapa 1: 1-Cloro-3-(4-fenoxifenil)propano (a)



Se disolvió el compuesto de 4-fenoxifenol (81,03g, 435,15 mmol) en 810 ml de metiletilcetona ("MEK") a temperatura ambiente bajo nitrógeno. Se añadió carbonato de potasio en polvo (577,16 g, 4.176,27 mmol), seguido de 1,3-dicloropropano (300,00 g, 2,655,1 mmol), y se calentó la solución resultante a reflujo durante 15,5

horas. Se enfrió la solución a temperatura ambiente, se filtró y se lavó con 750 ml de MEK. Se concentró el filtrado a vacío para obtener un líquido bruto de color naranja. Se disolvió el líquido bruto en 260 ml de MeOH absoluto a temperatura ambiente y se agitó durante 5 minutos, enfriándolo luego en un baño de hielo/aceto-na/agua durante 1,5 horas. Se separó por filtración el precipitado blanco y se lavó con 480 ml de MeOH absoluto frío. Se recogió el sólido blanco y se secó a vacío a 30°C durante 16 horas, para obtener aproximadamente 81,87 g del compuesto (a).

Etapa 2: Sal sódica del ácido 2S-2-metoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propanoico

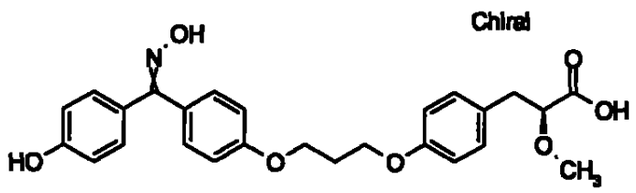


Se disolvió el compuesto (b) (10,9g, 50 mmol) en 50 ml de etanol absoluto a temperatura ambiente. Se añadió metóxido de sodio (4,05g, 75 mmol) de una sola vez y se calentó la solución resultante a reflujo durante 30 minutos. Se enfrió la solución a 40°C y se añadió el compuesto (a) (15,72g, 75 mmol) de una sola vez, seguido de 50 ml de DMF y 50 ml de DMSO. Se calentó la solución roja transparente a reflujo durante 30 minutos y se enfrió a temperatura ambiente. Se eliminó el etanol a vacío a 60°C y se añadió una mezcla de 100 ml de agua y 100 ml de MTBE. Se evaporó la capa orgánica superior y se desechó. Se añadió MTBE fresco (100 ml) y se produjo cristalización. Se agitó la suspensión bifásica a temperatura ambiente durante 30 minutos, se filtró y se lavó con 250 ml de MTBE. Se secó el sólido blanco a vacío a 60°C durante 16 horas, para obtener aproximadamente 15,34 g del com-

puesto del título.

Ejemplo 172

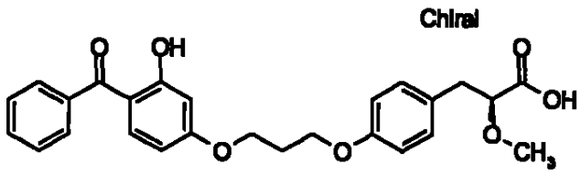
Ácido (2S)-3-[4-(3-{4-[hidroxiimino(4-hidroxifenil)metil]fenoxi}propoxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-(4-{3-[4-(4-hidroxibenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico (Ejemplo 170) y se trató en las mismas condiciones que en el Ejemplo 61, para obtener el compuesto del título. MS (ES) para $C_{26}H_{27}NO_7$ $[M-H]^-$: 464.

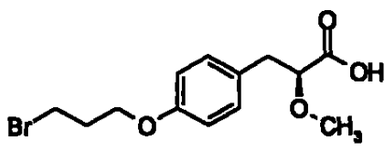
Ejemplo 173

Ácido (2S)-3-{4-[3-(4-benzoil-3-hidroxifenoxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico

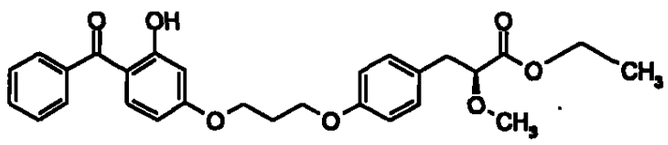


Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(3-hidroxipropoxi)-

fenil]-2-metoxipropiónico del Ejemplo 171, Etapa B, y siguiendo el procedimiento descrito en el Ejemplo 132, Etapa D, obtuvimos el compuesto del título.

Etapa B

Éster etílico del ácido 3-{4-[3-(4-benzoil-3-hidroxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se dejó reaccionar a una mezcla de éster etílico del ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico de la Etapa A y 2,4-dihidroxibenzofenona según el Procedimiento estándar I, para obtener el compuesto del título.

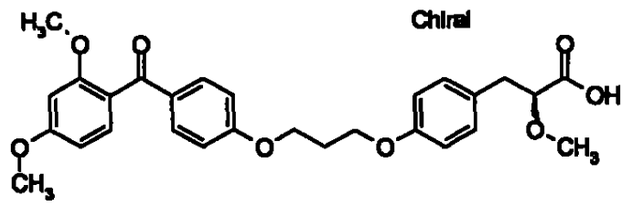
Etapa C

Ácido (2S)-3-{4-[3-(4-benzoil-3-hidroxifenoxi)propoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de la Etapa B mediante el procedimiento estándar de hidrólisis C (LiOH). MS (ES) para $C_{26}H_{26}O_7$ $[M-H]^-$: 449.

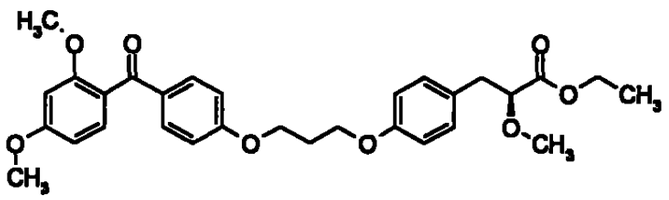
Ejemplo 174

Ácido (2S)-3-(4-{3-[4-(2,4-dimetoxibenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

Éster etílico del ácido 3-{4-{3-[4-(2,4-dimetoxibenzoil)-fenoxi]propoxi}fenil)-2-metoxipropiónico



Se dejó reaccionar a una mezcla de éster etílico del ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico de 0, Etapa A, y 2,4-dimetoxi-4'-hidroxibenzofenona según el Procedimiento estándar I, para obtener el compuesto del título.

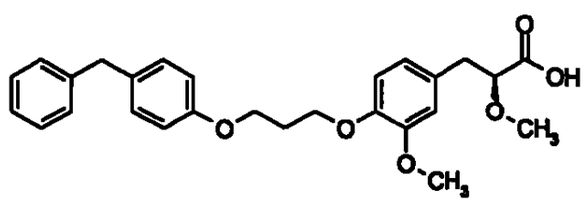
Etapa B

Ácido (2S)-3-(4-{3-[4-(2,4-dimetoxibenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se preparó el compuesto del título a partir de la Etapa A mediante el procedimiento estándar de hidrólisis C (LiOH). MS (ES) para $C_{28}H_{30}O_8$ $[M-H]^-$: 493.

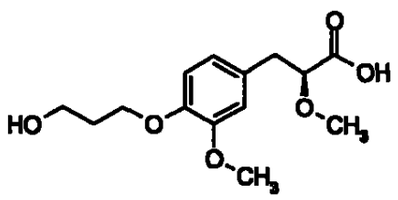
Ejemplo 175

Ácido 3-{4-[3-(4-bencilfenoxi)propoxi]-3-metoxifenil}-2-metoxipropiónico



Etapa A

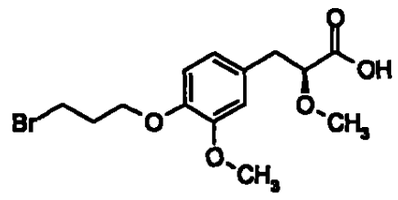
Ácido 3-[4-(3-hidroxipropoxi)-3-metoxifenil]-2-metoxipropiónico



Se trató una mezcla de éster etílico del ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico (Ejemplo 130, Etapa A) y 3-(terc-butildimetilsilaniloxi)propan-1-ol según las condiciones de acoplamiento estándar de Mitsounobu B utilizando DIAD y tolueno. Se trató el producto así obtenido según el Procedimiento estándar E para la escisión de alcoholes protegidos, para obtener el producto del título.

Etapa B

Ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido 3-[4-(3-hidroxipropoxi)-3-metoxifenil]-2-metoxipropiónico y siguiendo el procedimiento descrito en el Ejemplo 132, Etapa D, obtuvimos el compuesto del título.

Etapa C

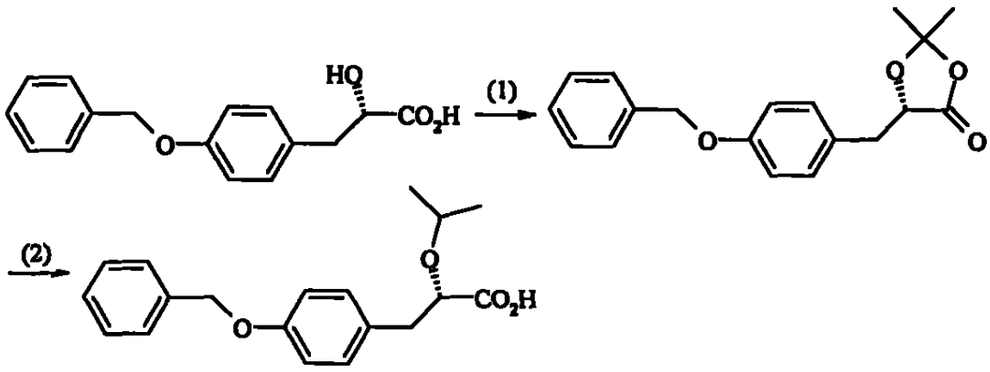
Ácido 3-{4-[3-(4-bencilfenoxi)propoxi]-3-metoxifenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxi-

propiónico y 4-bencilfenol siguiendo el Procedimiento estándar J. MS (ES) para $C_{27}H_{30}O_6$ $[M+NH_4]^+$: 468, $[M+Na]^+$: 473.

Ejemplo 176

Ácido (*S*)-3-(4-benciloxifenil)-2-isopropoxipropiónico



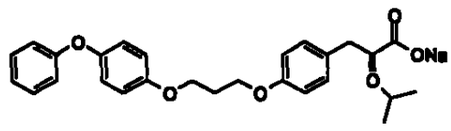
Etapa 1: Se calentó a reflujo una solución que contenía ácido (*S*)-5-(4-benciloxibencil)-2,2-dimetil[1,3]dioxolan-4-ona-(*S*)-3-(4-benciloxifenil)-2-hidroxipropiónico (2,0 g, 7,34 mmol), 2,2-dimetoxipropano (18,63 g, 0,179 mol) y *p*-toluensulfonato de piridinio (0,92 g, 3,66 mmol) en cloroformo (80 ml) durante 40 minutos bajo N_2. Se enfrió la reacción, se diluyó con agua y se extrajo con CH_2Cl_2. Se secó la capa orgánica (Na_2SO_4) y se eliminó el solvente a vacío, para obtener un producto bruto, el cual fue purificado por cromatografía instantánea usando hexanos:acetona 10:1, para obtener aproximadamente 2,01g (88%) de (*S*)-5-(4-benciloxibencil)-2,2-dimetil[1,3]dioxolan-4-ona. ^1H RMN (400 MHz, $CDCl_3$) δ 7,43-7,29 (m, 5H), 7,17 (d, 2H, *J* = 8,80 Hz), 6,91 (d, 2H, *J* = 8,80 Hz), 5,04 (s, 2H), 4,61 (dd, 1H, *J* = 6,36 Hz, *J* = 4,40 Hz), 3,12 (dd, 1H, *J* = 14,67 Hz, *J* = 4,40 Hz), 2,99 (dd, 1H, *J* = 14,67 Hz, *J* = 6,36 Hz), 1,49 (s, 3H), 1,36 (s, 3H). MS (ES^+) *m/z* masa exacta calculada para $C_{19}H_{20}O_4$ (M + NH_4) 330. Encontrado *m/z* 330.

Etapa 2: Ácido (*S*)-3-(4-benciloxifenil)-2-isopropoxipropiónico

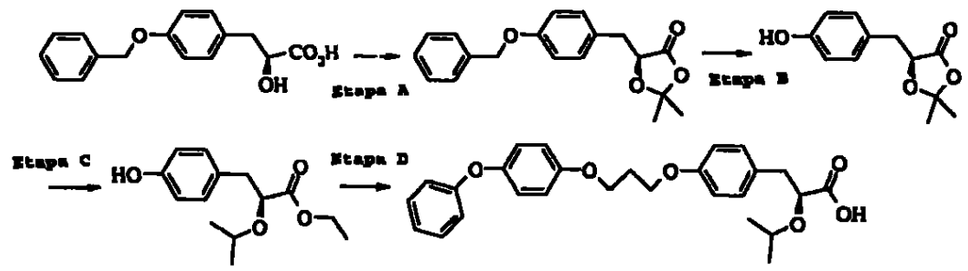
Se trató por goteo una solución a -78°C de (*S*)-5-(4-benciloxibencil)-2,2-dimetil[1,3]dioxolan-4-ona (0,20 g, 0,64 mmol) y trietilsilano (0,223 g, 1,92 mmol) en CH_2Cl_2 (8 ml) con una solución 1 molar de $TiCl_4$ en CH_2Cl_2 (0,64 ml, 0,64 mmol) bajo N_2. Se agitó la solución a -78 °C durante 15 minutos y se apagó luego con agua. Se extrajo la mezcla con EtOAc y se secó la capa orgánica (Na_2SO_2). Se filtró la capa orgánica se eliminó el solvente a vacío para obtener un producto bruto, que fue purificado por cromatografía instantánea utilizando hexanos:acetona 5:1, para obtener 0,171 g (85%) ácido (*S*)-3-(4-benciloxifenil)-2-isopropoxipropiónico. ^1H RMN (400 MHz, DMSO-d_6) δ 12,50 (s amplio, 1H), 7,42-7,27 (m, 5H), 7,12 (d, 2H, *J* = 8,80 Hz), 6,88 (d, 2H, *J* = 8,80 Hz), 5,02 (s, 2H), 3,96 (dd, 1H, *J* = 7,83 Hz, *J* = 4,89 Hz), 3,47 (hp, 1H, *J* = 5,87 Hz), 2,83 (dd, 1H, *J* = 13,69 Hz, *J* = 4,89 Hz), 2,71 (dd, 1H, *J* = 13,69 Hz, *J* = 8,31 Hz), 1,02 (d, 2H, *J* = 5,87 Hz), 0,86 (d, 2H, *J* = 5,87 Hz). IR (KBr) 3012, 2977, 2931, 1767, 1722, 1610, 1511, 1380, 1240, 1116, 1020. HRMS (TOF ES^-) *m/z* masa exacta calculada para $C_{19}H_{21}O_4$ (M-1) 313,1440. Encontrado *m/z* 313,1434.

Ejemplo 176A

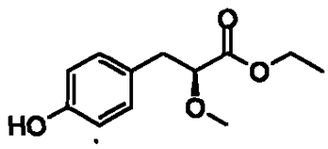
Sal sódica del ácido 2S-2-isopropoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propanoico



Esquema

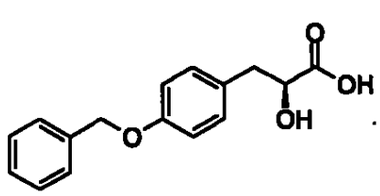


Éster etílico del ácido (*S*)-3-(4-hidroxifenil)-2-metoxi-propiónico etilo



Se trató por goteo una solución de ácido (*S*)-3-(4-hidroxifenil)-2-metoxipropiónico (20 g, 100 mmol) en etanol 3A (140 ml) con ácido sulfúrico concentrado (5,7 ml)) y se agitó a temperatura ambiente durante la noche. Se concentró la solución y se añadió agua (110 ml). Se añadió bicarbonato de sodio para llevar el pH a 7-8. Se extrajo la mezcla con acetato de etilo (3 x 50 ml). Se lavaron las capas orgánicas combinadas con una solución de NaCl al 20% (50 ml), se secaron ($MgSO_4$), se filtraron y se concentraron a un aceite dorado (18 g, 80%). ^{1}H-RMN ($CDCl_3$): 7,1 (d, 2H); 6,7(d, 2H); 4,2(m, 2H); 3,9(m, 1H); 3,6(s, 3H); 2,95(m, 2H); 1,25(t, 3H). MS (ES): 223,2 (M-1).

Ácido (*S*)-3-(4-benciloxifenil)-2-hidroxipropiónico



Se trató ácido (*S*)-2-hidroxi-3-(4-hidroxifenil)propiónico (121 g, 0,664 mol) (Wang y col., *Tetrahedron Lett.* 1998, 39, 5501) en EtOH absoluto (2L) con carbonato de potasio (184 g, 1,33 mol) y cloruro de bencilo 169 g, 1,34 mol). Se calentó la mezcla a reflujo durante la noche y se concentró a aproximadamente la mitad del volumen a vacío. Se añadió NaOH acuoso 5N (100 ml) y se agitó la mezcla a temperatura ambiente durante la noche y luego se concentró. Se acidificó el residuo con HCl concentrado. Se recogió el sólido amarillo por filtración y se secó durante la noche a vacío a 50°C. Se calentó el producto bruto en isopropanol (1,8 L) a reflujo durante aproximadamente 30 minutos, se enfrió a temperatura ambiente y se agitó durante aproximadamente 16 horas. Se filtró la suspensión y se secó a vacío a 70°C durante la noche para obtener el compuesto del título como un sólido blanco (137 g, 76%).

Etapa A: (*S*)-5-(4-benciloxibencil)-2,2-dimetil[1,3]dioxolan-4-ona

Se calentaron ácido (*S*)-3-(4-benciloxifenil)-2-hidroxipropiónico (2,0 g, 7,34 mmol), 2,2-dimetoxipropano (18,63 g, 0,179 mol) y *p*-toluensulfonato de piridinio (0,92 g, 3,66 mmol) en cloroformo (80 ml) a reflujo durante 40 minutos bajo N_2. Se enfrió la mezcla, se diluyó con agua y se extrajo con CH_2Cl_2. Se secó la capa orgánica (Na_2SO_4) y se concentró a vacío para obtener un producto bruto, que fue purificado por cromatografía instantánea utilizando hexanos:acetona 10:1, para obtener el compuesto del título (2,01 g, 88%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,43-7,29 (m, 5H), 7,17 (d, 2H, *J* = 8,80 Hz), 6,91 (d, 2H, *J* = 8,80 Hz), 5,04 (s, 2H), 4,61 (dd, 1H, *J* = 6,36 Hz, *J* = 4,40 Hz), 3,12 (dd, 1H, *J* = 14,67 Hz, *J* = 4,40 Hz), 2,99 (dd, 1H, *J* = 14,67 Hz, *J* = 6,36 Hz), 1,49 (s, 3H), 1,36 (s, 3H). MS (ES^+) *m/z* calc. para $C_{19}H_{20}O_4$ ($M+NH_4$) 330. Encontrado *m/z* 330.

Etapa B: (*S*)-5-(4-hidroxibencil)-2,2-dimetil[1,3]dioxolan-4-ona

Se combinó (*S*)-5-(4-benciloxibencil)-2,2-dimetil-[1,3]dioxolan-4-ona (1,0 g, 3,2 mmol) con Pd 10%/C (0,75 g) en EtOAc (40 ml) y se purgó con N_2 y luego con H_2 y se agitó después bajo un balón de hidrógeno durante 3 horas. Se añadió sulfato de sodio y se filtró la mezcla a través de Celita. Se eliminó el solvente a vacio para obtener el compuesto del título (0,747 g, 100%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,11 (d, 2H, *J* = 8,31 Hz), 6,76 (d, 2H, *J* = 8,31 Hz), 4,93 (s amplio, 1H), 4,61 (dd, 1H, *J* = 6,36 Hz, *J* = 4,40 Hz), 3,11 (dd, 1H, *J* = 14,67 Hz, *J* = 4,40 Hz), 2,98 (dd, 1H, *J* = 14,67 Hz, *J* = 5,86 Hz), 1,49 (s, 3H), 1,36 (s, 3H). MS (ES^-) *m/z* masa calc. para $C_{12}H_{14}O_4$ (M-1) 221. Encontrado *m/z* 221.

Etapa C: Éster etílico del ácido (*S*)-3-(4-hidroxifenil)-2-isopropoxipropiónico

Se trató una solución a 0°C de (*S*)-5-(4-hidroxibencil)-2,2-dimetil[1,3]dioxolan-4-ona (0,20 g, 0,90 mmol) y trietilsilano (1,05 g, 9,02 mmol) en CH_2Cl_2 (10 ml) por goteo con $TiCl_4$ (0,90 ml, 0,90 mmol, CH_2Cl_2 1M) bajo N_2. Se agitó la solución a 0°C durante aproximadamente 15 min y se calentó hasta la temperatura ambiente. Después de aproximadamente 45 minutos, se apagó la mezcla con agua y se extrajo con EtOAc. Se secó la capa orgánica (Na_2SO_2), se filtró y se concentró a vacío, para obtener un producto bruto (0,32 g). Se combinó este material con etanol (25 ml) y H_2SO_2 conc. (1 ml) y se agitó durante 17 horas a temperatura ambiente bajo N_2. Se concentró la mezcla y se repartió entre EtOAc y agua. Se secó la capa orgánica (Na_2SO_2), se filtró, y se concentró a vacio. Se purificó el producto bruto por cromatografía instantánea utilizando hexanos:acetona 5:1, para obtener el compuesto del título (0,158 g, 70%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,11 (d, 2H, *J* = 8,31 Hz), 6,76 (d, 2H, *J* = 8,31 Hz), 4,79 (s

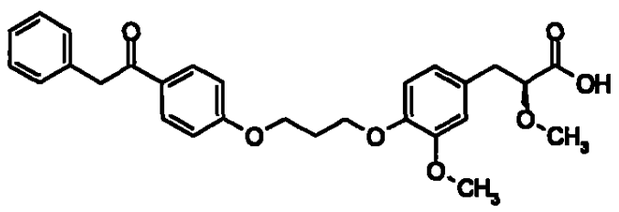
amplio, 1H), 4,20-4,12 (m, 2H), 3,99 (dd, 1H, *J* = 8,56 Hz, *J* = 4,89 Hz), 3,49 (hp, 1H, *J* = 6,36 Hz), 2,94-2,83 (m, 2H), 1,23 (t, 3H, *J* = 6,85 Hz), 1,14 (d, 3H, *J* = 6,36 Hz), 0,96 (d, 3H, *J* = 6,36 Hz). MS (ES^-) *m/z* calc. para $C_{14}H_{20}O_4$ (M-1) 251. Encontrado *m/z* 251.

Etapa D: Ácido (*S*)-2-isopropoxi-3-{4-[3-(4-fenoxifenoxi)-propoxi]fenil}propiónico

Se completó la síntesis de sal sódica del ácido 2S-2-isopropoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propanoico según los procedimientos descritos en el Ejemplo 171. ^1H RMN (400 MHz, $CDCl_3$): δ 0,96 (d, 3 H, *J*= 5,9 Hz), 1,09 (d, 3 H, *J*= 6,3 Hz), 2,22 (cuarteto, 2 H, *J* = 5,9 Hz), 2,82 (dd, 1 H, *J* = 9,3 Hz, 13,7 Hz), 3,01 (dd, 1 H, *J* = 2,5 Hz, 13,7 Hz), 3,43 (c, 1 H, *J* = 5,9 Hz), 4,01 (dd, 1 H, *J* = 3,4 Hz, 8,8 Hz), 4,11 (c, 4 H, *J* = 6,4 Hz), 6,80 (d, 2 H, *J*= 8,3 Hz), 6,88 (d, 2 H, *J*= 8,8 Hz), 6,90-7,00 (m, 4 H), 7,01-7,05 (m, 1 H), 7,17 (d, 2 H, *J*= 8,3 Hz), 7,28 (d, 2 H, *J*= 8,8 Hz). MS: 451,2 (MH^+).

Ejemplo 177

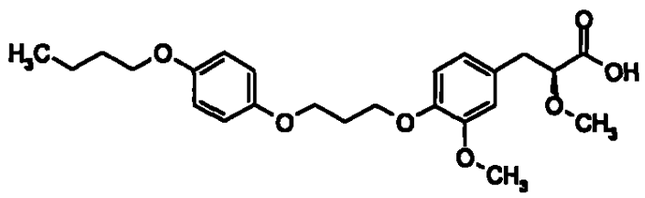
Ácido 2-metoxi-3-{3-metoxi-4-[3-(4-fenilacetilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxi-propiónico (Ejemplo 175, Etapa B) y 1-(4-hidroxifenil)-2-feniletanona siguiendo el Procedimiento estándar J. MS (ES) para $C_{28}H_{30}O_7$ $[M+H]^+$: 479.

Ejemplo 178

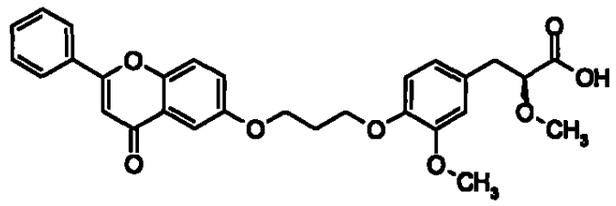
Ácido 3-{4-[3-(4-butoxifenoxi)propoxi]-3-metoxifenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxi-propiónico (Ejemplo 175, Etapa B) y 4-butoxifenol siguiendo el Procedimiento estándar J. MS (ES) para $C_{24}H_{32}O_7$ $[M+Na]^+$: 455.

Ejemplo 179

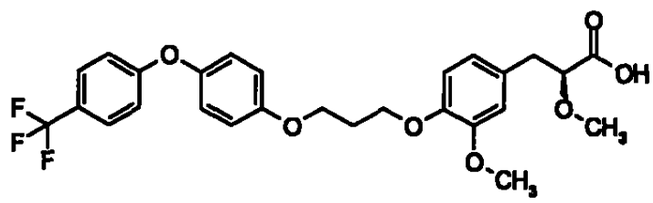
Ácido 2-metoxi-3-{3-metoxi-4-[3-(4-oxo-2-fenil-4H-cromen-6-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxi-propiónico (Ejemplo 175, Etapa B) y 6-hidroxi-2-fenil-cromen-4-ona siguiendo el Procedimiento estándar J. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 8,0-7,9 (m, 2H), 7,6-7,5 (m, 5H), 7,30 (dd, 1H, J=9,0, 3,0), 6,9-6,8 (m, 4H), 4,3-4,2 (m, 4H), 4,00 (dd, 1H, J=7,2, 4,6), 3,83 (s, 3H), 3,41 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,6), 2,96 (dd, 1H, J=14,2, 7,2), 2,33 (q, 2H, J=6,2) ppm.

Ejemplo 180

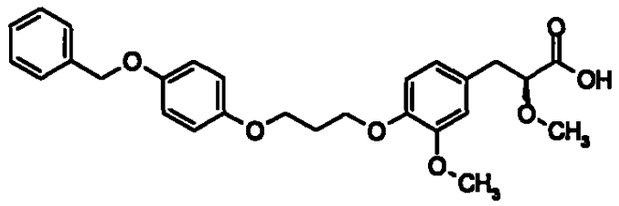
Ácido 2-metoxi-3-(3-metoxi-4-{3-[4-(4-trifluorometilfenoxi)fenoxi]propoxi}fenil)propiónico



Se preparó el compuesto del título a partir de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxipropiónico (Ejemplo 175, Etapa B) y 4-(4-trifluorometilfenoxi)fenol siguiendo el Procedimiento estándar J. MS (ES) para $C_{27}H_{27}F_3O_7$ $[M+Na]^+$: 543.

Ejemplo 181

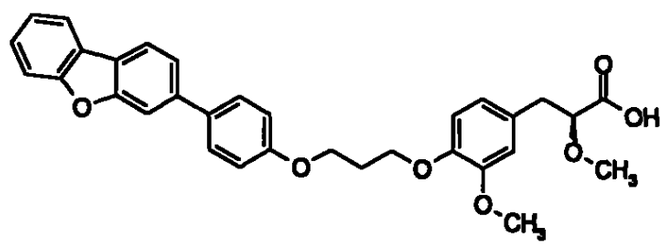
Ácido 3-{4-[3-(4-benciloxifenoxi)propoxi]-3-metoxifenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxipropiónico (Ejemplo 175, Etapa B) y 4-benciloxifenol siguiendo el Procedimiento estándar J. MS (ES) para $C_{27}H_{30}O_7$ $[M+Na]^+$: 489.

Ejemplo 182

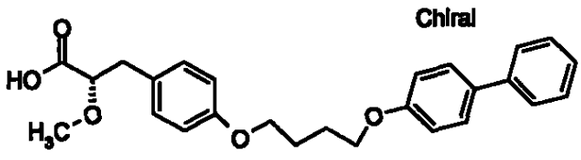
Ácido 3-{4-[3-(4-dibenzofuran-3-ilfenoxi)propoxi]-3-metoxifenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxipropiónico (Ejemplo 175, Etapa B) y 4-dibenzofuran-3-ilfenol siguiendo el Procedimiento estándar J. MS (ES) para $C_{32}H_{30}O_7$ $[M+NH_4]^+$:544, $[M+Na]^+$: 549.

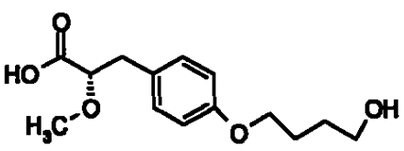
Ejemplo 183

Ácido (2S)-3-{4-[4-(bifenil-4-iloxi)butoxi]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-[4-(4-hidroxibutoxi)fenil]-2-metoxipropiónico

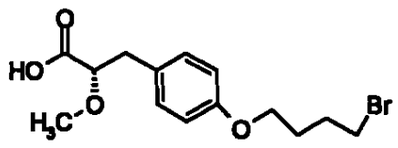


Se trató una mezcla de éster etílico del ácido 3-(4-hidroxifenil)-2-metoxipropiónico y 3-(terc-butildimetilsilaniloxi)butan-1-ol según las condiciones de acoplamiento estándar de Mitsounobu B utilizando DIAD y

THF. Se trató el producto así obtenido según el Procedimiento estándar E para la escisión de alcoholes protegidos, para obtener el producto del título.

Etapa B

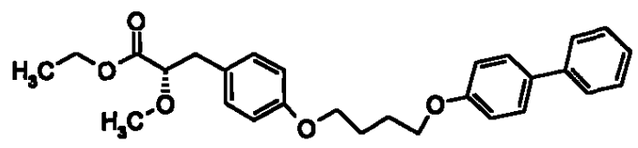
Éster etílico del ácido (2S)-3-[4-(4-bromobutoxi)fenil]-2-metoxipropiónic



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(4-hidroxibutoxi)-fenil]-2-metoxipropiónico y siguiendo el procedimiento descrito en el Ejemplo 132, Etapa D, obtuvimos el compuesto del título.

Etapa C

Éster etílico del ácido (2S)-3-{4-[4-(bifenil-4-iloxi)butoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(4-bromobutoxi)fenil]-2-metoxipropiónico (Etapa B) y 4-fenilfenol según el Procedimiento estándar I, para obtener el producto.

Etapa D

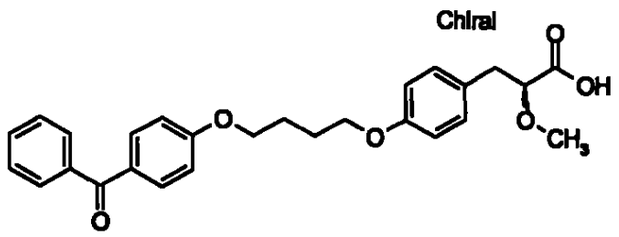
Ácido (2S)-3-{4-[4-(bifenil-4-iloxi)butoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir del éster etílico del ácido (2S)-3-{4-[4-(bifenil-4-iloxi)butoxi]fenil}-2-metoxipropiónico de la Etapa C según el procedimiento estándar de hidrólisis C (LiOH). ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,57-7,49 (m, 4H); 7,45-7,37 (m,

2H); 7,32-7,11 (m, 3H); 6,97 (d, 2H, J= 8,9); 6,84 (d, 2H, J= 8,9); 4,11-3,93 (m, 5H); 3,40 (s, 3H); 3,10 (dd, 1H, J= 14,0, 4,3); 2,96 (dd, 1H, J= 14,5, 7,0); 1,99-1,97 (m, 4H) ppm.

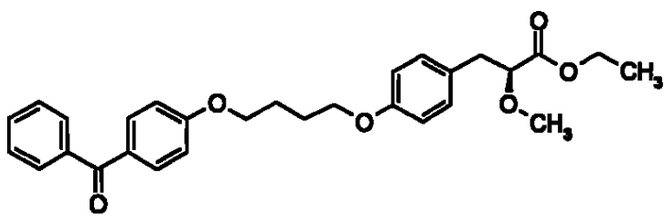
Ejemplo 184

Ácido (2S)-3-{4-[4-(4-benzoilfenoxi)butoxi]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-{4-[4-(4-benzoilfenoxi)butoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico del ácido (2S)-3-[4-(4-bromobutoxi)fenil]-2-metoxipropiónico (Ejemplo 183, Etapa B) y 4-hidroxibenzofenona según el Procedimiento estándar I, para obtener el producto.

Etapa B

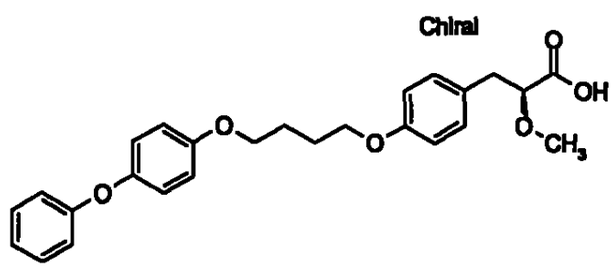
Ácido (2S)-3-{4-[4-(4-benzoilfenoxi)butoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir del éster etílico de ácido (2S)-3-{4-[4-(4-benzoilfenoxi)butoxi]fenil}-2-metoxipropiónico de la Etapa A según el procedimiento estándar de hidrólisis C (LiOH). ^{1}H-RMN

(200,15 MHz, $CDCl_3$): 7,81 (d, 2H, J=8,9), 7,75 (dd, 2H, J=8,3, 1,4), 7,6-7,4 (m, 3H), 7,15 (d, 2H, J=8,6), 6,81 (d, 2H, J=8,3), 4,2-3,9 (m, 5H), 3,37 (s, 3H), 3,08 (dd, 1H, J=14,2, 4,3), 2,94 (dd, 1H, J=14,2, 7,5), 2,1-1,9 (m, 4H) ppm.

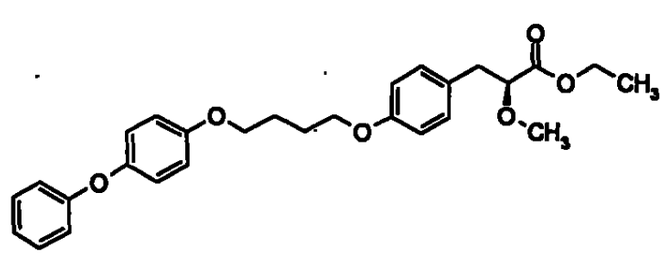
Ejemplo 185

Ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)butoxi]fenil}propiónico



Etapa A

Éster etílico del ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)butoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(4-bromobutoxi)fenil]-2-metoxipropiónico (Ejemplo 183, Etapa B) y 4-fenoxifenol según el Procedimiento estándar I, para obtener el producto.

Etapa B

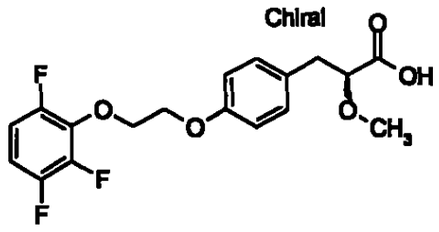
Ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)butoxi]fenil}propiónico

Se preparó el compuesto del título a partir

del éster etílico del ácido (2S)-2-metoxi-3-{4-[4-(4-fenoxifenoxi)butoxi]fenil}propiónico de la Etapa A según el procedimiento estándar de hidrólisis C (LiOH). ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,4-7,2 (m, 2H), 7,15 (d, 2H, J=8,6), 7,1-6,7 (m, 9H), 4,0-3,9 (m, 5H), 3,34 (s, 3H), 3,08 (dd, 1H, J=14,0, 4,0), 2,93 (dd, 1H, J=14,0, 7,8), 2,1-1,9 (m, 4H) ppm.

Ejemplo 186

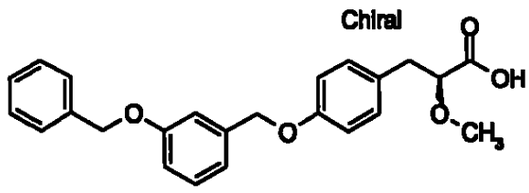
Ácido (2S)-2-metoxi-3-{4-[2-(2,3,6-trifluorofenoxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxifenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa C) mediante el acoplamiento-escisión de Mitsounobu (Procedimiento estándar G) con 2-(2,3,6-trifluorofenoxi)etanol, para obtener el producto deseado. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,15 (d, 2H, J=8,6), 6,9-6,8 (m, 4H), 4,51 (t, 2H, J=4,0), 4,27 (t, 2H, J=4,8), 3,97 (dd, 1H, J=7,2, 4,3), 3,39 (s, 3H), 3,09 (dd, 1H, J=14,5, 4,5), 2,95 (dd, 1H, J=14,5, 7,5) ppm.

Ejemplo 187

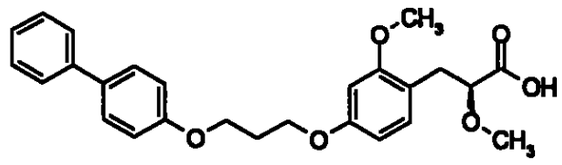
Ácido (2S)-3-[4-(3-benciloxibenciloxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxifenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa C) mediante el acoplamiento-escisión de Mitsounobu (Procedimiento estándar G) con (3-benciloxifenil)metanol, para obtener el producto deseado. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,5-7,2 (m, 5H), 7,2-6,8 (m, 8H), 5,07 (s, 2H), 5,01 (s, 2H), 3,99 (dd, 1H, J=7,0, 4,6), 3,40 (s, 3H), 3,10 (dd, 1H, J=14,2, 4,3), 2,96 (dd, 1H, J=14,5, 7,2) ppm.

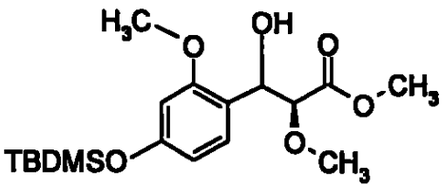
Ejemplo 188

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metoxifenil}-2-metoxipropiónico



Etapa A

Éster metílico del ácido 3-[4-(terc-butildimetilsilanil-oxi)-2-metoxifenil]-3-hidroxi-2-metoxipropiónico

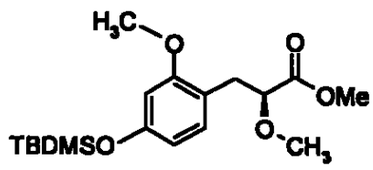


Se añadió por goteo una solución de 4-*terc*-butildimetilsilaniloxi-2-metoxibenzaldehído (1 eq) y metoxiacetato de metilo (1,25 eq) en THF (10 ml) a -78°C a bis(trimetilsilil)amiduro de sodio (1,25 eq, 1N en THF) a -78°C. Se agitó la mezcla de reacción durante 3 h y se apagó con HCl 1N (5 ml). Se dejó calentar a la mezcla hasta la temperatura ambiente, se diluyó con agua (15 ml) y se extrajo con acetato de etilo (3 x 15 ml). Se secaron

las capas orgánicas combinadas ($MgSO_4$) y se concentraron. Se purificó el residuo mediante columna de gel de sílice para obtener el compuesto del título.

Etapa B

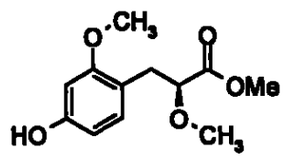
Éster metílico del ácido 3-[4-(terc-butildimetilsilanil-oxi)-2-metoxifenil]-2-metoxipropiónico



Se agitó una mezcla de éster metílico de ácido 3-[4-(terc-butildimetilsilaniloxi)-2-metoxifenil]-3-hidroxi-2-metoxipropiónico (1 eq), cloruro de mesilo (1 eq), trietilamina (4 eq) y una cantidad catalítica de DMAP (0,1 eq) en diclorometano a temperatura ambiente durante la noche. Se diluyó la mezcla de reacción con éter y se lavó con HCl 1N. Se secó y se concentró a vacío para obtener un residuo, que fue cromatografiado en gel de sílice para obtener un compuesto, el cual fue disuelto en metanol, tratado con Mg (20 eq) y agitado hasta observar el desprendimiento de gas. Se enfrió a 0°C y se agitó durante 4 horas. Se eliminó el solvente y se lavó el residuo reconstituido en éter con HCl 1N y salmuera y se concentró para obtener el producto del título.

Etapa C

Éster metílico del ácido 2-(4-hidroxi-2-metoxibencil)butírico



Se trató el éster metílico de ácido 3-[4-(terc-butildimetilsilaniloxi)-2-metoxifenil]-2-metoxipro-

piónico de la Etapa B según el Procedimiento estándar E para la escisión del grupo sililo protegido y se obtuvo el producto.

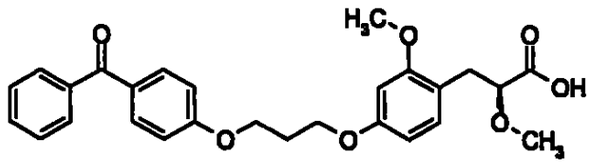
Etapa D

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-metoxifenil}-2-metoxipropiónico

Se hizo reaccionar una mezcla en solución del éster metílico de ácido 2-(4-hidroxi-2-metoxibencil)butírico de la Etapa C y 3-(bifenil-4-iloxi)propan-1-ol según las condiciones estándar de acoplamiento de Mitsounobu B (DIAD/tolueno), para obtener el correspondiente producto acoplado, que dio lugar al compuesto del título mediante el procedimiento estándar de hidrólisis C (NaOH). MS(ES) para $C_{26}H_{28}O_6$ $[M+NH_4]^+$: 454.

Ejemplo 189

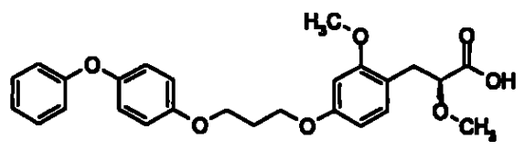
Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-2-metoxifenil}-2-metoxipropiónico



Se dejó reaccionar a una mezcla en solución del éster etílico de ácido 2-(4-hidroxi-2-metoxibencil)butírico del Ejemplo 188, Etapa C, y [4-(3-hidroxipropoxi)fenil]fenilmetanona según las condiciones de acoplamiento estándar de Mitsounobu B (DIAD/tolueno), para obtener el correspondiente producto acoplado, el cual, mediante el procedimiento estándar de hidrólisis C (NaOH), dio lugar al compuesto del título. MS (ES) para $C_{27}H_{28}O_7$ $[M+H]^+$: 465.

Ejemplo 190

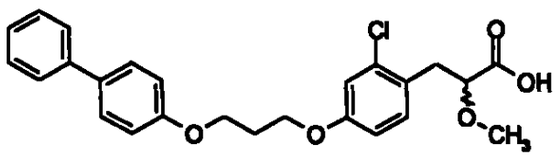
Ácido 2-metoxi-3-{2-metoxi-4-[3-(4-fenoxifenoxi)propoxi]-fenil}propiónico



Se dejó reaccionar a una mezcla en solución del éster etílico de ácido 2-(4-hidroxi-2-metoxibencil)-butírico del Ejemplo 188, Etapa C, y 3-(4-fenoxifenoxi)-propan-1-ol según las condiciones de acoplamiento estándar de Mitsounobu B (DIAD/tolueno), para obtener el correspondiente producto acoplado, el cual, mediante el procedimiento estándar de hidrólisis C (NaOH) dio el compuesto del título. MS (ES) para $C_{26}H_{28}O_7$ $[M+Na]^+$: 475.

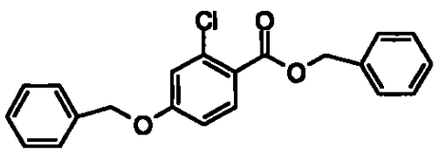
Ejemplo 191

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-clorofenil}-2-metoxipropiónico



Etapa A

Éster bencílico del ácido 4-benciloxi-2-clorobenzoico

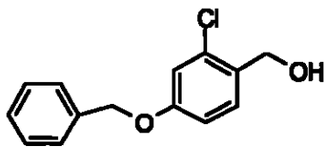


Se calentó una mezcla en solución de ácido 2-cloro-4-hidroxibenzoico (1 eq) con bromuro de bencilo (2 eq) y K_2CO_3 (3 eq) en acetonitrilo a 85°C. Se filtró entonces y se concentró a sequedad para obtener, tras cro-

matografía en gel de sílice, el compuesto del título.

Etapa B

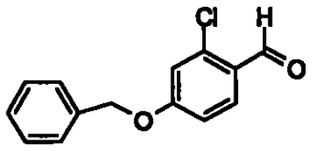
(4-Benciloxi-2-clorofenil)metanol



Se agitó una mezcla del éster bencílico del ácido 4-benciloxi-2-clorobenzoico de la Etapa A con DIBAL-H 1M en tolueno (2,2 eq) en THF a temperatura ambiente durante 3 horas. Se apagó con una solución saturada de tartrato y se extrajo con acetato de etilo. Se concentró a sequedad y se purificó por cromatografía para obtener el compuesto del título.

Etapa C

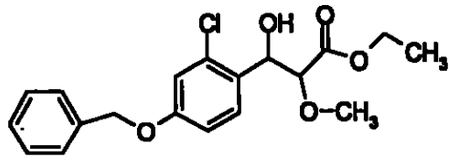
4-Benciloxi-2-clorobenzaldehído



A una solución de (4-benciloxi-2-clorofenil)-metanol en diclorometano, se añadió MnO_2 (10 eq) y se agitó la mezcla de reacción durante la noche. Se filtró a través de una almohadilla de celita y se purificó por cromatografía en gel de sílice, para obtener el producto del título.

Etapa D

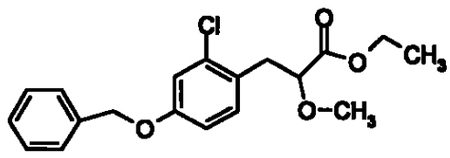
Éster etílico del ácido 3-(4-benciloxi-2-clorofenil)-3-hidroxi-2-metoxipropiónico



Se añadió por goteo una solución de 4-benciloxi-2-cloro-benzaldehído (1 eq) y metoxiacetato de metilo (1,25 eq) en THF (10 ml) a -78°C a bis(trimetilsilil)amiduro de sodio (1,25 eq, 1N en THF) a -78°C. Se agitó la mezcla de reacción durante 3 h y se apagó con HCl 1N (5 ml). Se dejó calentar a la mezcla a la temperatura ambiente, se diluyó con agua (15 ml) y se extrajo con acetato de etilo (3 x 15 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$) y se concentraron. Se purificó el residuo en columna de gel de sílice para obtener el compuesto del título.

Etapa E

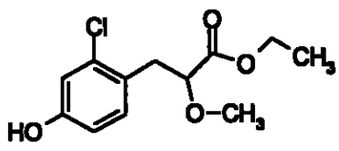
Éster etílico del ácido 3-(4-benciloxi-2-clorofenil)-2-metoxipropiónico



Se agitó una mezcla de éster etílico de ácido 3-(4-benciloxi-2-clorofenil)-3-hidroxi-2-metoxipropiónico (1 eq), cloruro de mesilo (1 eq), trietilamina (4 eq) y una cantidad catalítica de DMAP (0,1 eq) en diclorometano a temperatura ambiente durante la noche. Se diluyó la mezcla de reacción con éter y se lavó con HCl 1N. Se secó y se concentró a vacío para obtener un residuo, que fue cromatografiado en gel de sílice para obtener un compuesto, que fue disuelto en metanol y tratado con Mg (20 eq), y se agitó hasta observar desprendimiento de gas. Se enfrió a 0°C y se agitó durante 4 horas. Se eliminó el solvente y se reconstituyó el residuo en éter, se lavó con HCl 1N y salmuera y se concentró para obtener el producto del título.

Etapa F

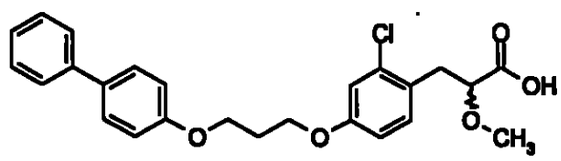
Éster etílico del ácido 3-(2-cloro-4-hidroxifenil)-2-metoxipropiónico



Se trató el éster etílico de ácido 3-(4-benciloxi-2-clorofenil)-2-metoxipropiónico en acetato de etilo con Pd(C) y H_2 bajo presión de balón. Se filtró entonces a través de celita y se concentró para obtener el compuesto del título.

Etapa G

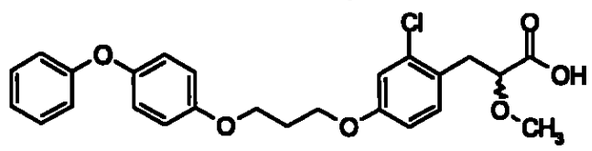
Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-clorofenil}-2-metoxipropiónico



Se dejó reaccionar a una mezcla en solución del éster etílico de ácido 3-(2-cloro-4-hidroxifenil)-2-metoxipropiónico de la Etapa F y 3-(bifenil-4-iloxi)-propan-1-ol según las condiciones de acoplamiento estándar de Mitsounobu B (DIAD/tolueno), para obtener el correspondiente producto acoplado, el cual, mediante el procedimiento estándar de hidrólisis C (NaOH) dio el compuesto del título. MS (ES) para $C_{25}H_{25}ClO_5$ $[M+NH_4]^+$: 458.

Ejemplo 192

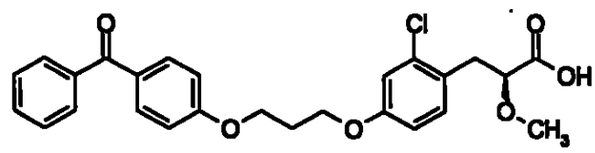
Ácido 3-{2-cloro-4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se dejó reaccionar a una mezcla en solución del éster etílico de ácido 3-(2-cloro-4-hidroxifenil)-2-metoxipropiónico del Ejemplo 191, Etapa F, y 3-(4-fenoxifenoxi)propan-1-ol según las condiciones de acoplamiento estándar de Mitsounobu B (DIAD/tolueno) para obtener el correspondiente producto acoplado, el cual, mediante el procedimiento estándar de hidrólisis C (NaOH), dio el compuesto del título. MS (ES) para $C_{25}H_{25}ClO_6$ $[M+NH_4]^+$: 474.

Ejemplo 193

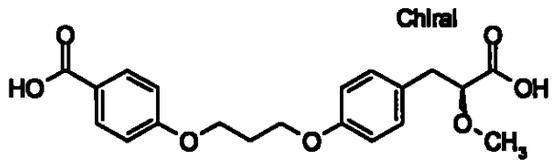
Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-2-clorofenil}-2-metoxipropiónico



Se dejó reaccionar a una mezcla en solución del éster etílico de ácido 3-(2-cloro-4-hidroxifenil)-2-metoxipropiónico del Ejemplo 132, Etapa F, y [4-(3-hidroxipropoxi)fenil]fenilmetanona según las condiciones estándar de acoplamiento de Mitsounobu B (DIAD/tolueno), para obtener el correspondiente producto acoplado, el cual, mediante el procedimiento estándar de hidrólisis C (NaOH) dio el compuesto del título. MS (ES) para $C_{26}H_{25}ClO_6$ $[M+H]^+$: 469.

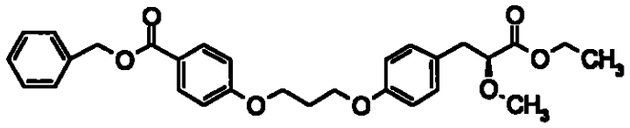
Ejemplo 194

Ácido (2S)-4-{3-[4-(2-carboxi-2-metoxietil)fenoxi]propoxi}benzoico



Etapa A

Éster bencílico del ácido (2S)-4-{3-[4-(2-etoxicarbonil-2-metoxietil)fenoxi]propoxi}benzoico



Se trataron éster etílico de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico de **0**, Etapa B, y éster bencílico de ácido 4-hidroxibenzoico según las condiciones estándar de acoplamiento de Mitsounobu B, para obtener el compuesto del título.

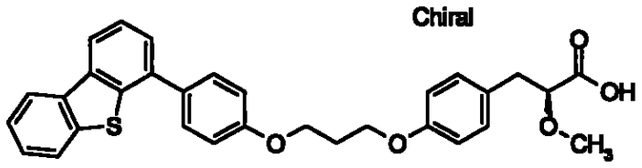
Etapa B

Ácido (2S)-4-{3-[4-(2-carboxi-2-metoxietil)fenoxi]propoxi}benzoico

Se preparó el compuesto del título a partir de éster bencílico de ácido (2S)-4-{3-[4-(2-etoxicarbonil-2-metoxietil)fenoxi]propoxi}benzoico (Etapa A) mediante el procedimiento estándar de hidrólisis C (NaOH). MS (ES) para $C_{20}H_{22}O_7$ $[M+Na]^+$: 397.

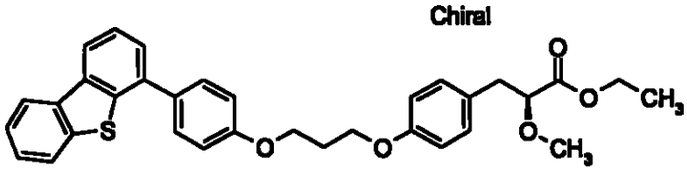
Ejemplo 195

Ácido (2S)-3-{4-[3-(4-dibenzotiofen-4-ilfenoxi)propoxi]-fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-{4-[3-(4-dibenzotiofen-4-ilfenoxi)propoxi]fenil}-2-metoxipropiónico



Se trataron éster etílico del ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico del Ejemplo 171, Etapa B, y 4-dibenzotiofen-4-ilfenol según las condiciones de acoplamiento estándar de Mitsounobu B, para obtener el compuesto del título.

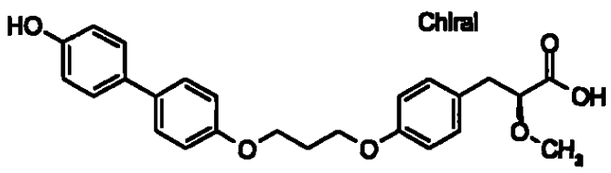
Etapa B

Ácido (2S)-3-{4-[3-(4-dibenzotiofen-4-ilfenoxi)propoxi]-fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-{4-[3-(4-dibenzotiofen-4-ilfenoxi)propoxi]fenil}-2-metoxipropiónico (Etapa A) mediante el procedimiento estándar de hidrólisis C (NaOH). MS (ES) para $C_{31}H_{28}O_5S$ $[M+NH_4]^+$: 530.

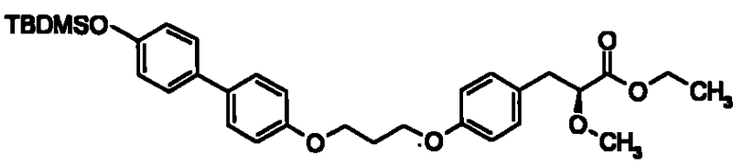
Ejemplo 196

Ácido (2S)-3-{4-[3-(4'-hidroxibifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2S)-3-(4-{3-[4'-(terc-butildimetilsilaniloxi)bifenil-4-iloxi]propoxi}fenil)-2-metoxipropiónico



Se trataron éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, y 4-(*terc*-butildimetilsilaniloxi)bifenil-4-ol con $CsCO_3$ (3 eq) en DMF y se agitó a temperatura ambiente durante la noche. Se filtró y se concentró a vacío para obtener el compuesto del título.

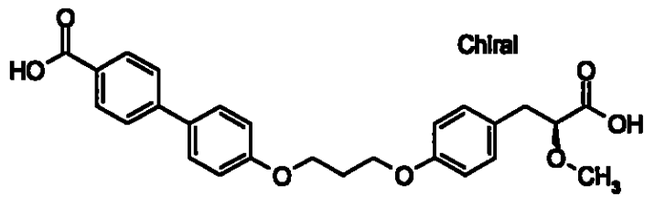
Etapa B

Ácido (2S)-3-{4-[3-(4'-hidroxibifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-(4-{3-[4'-(terc-butildimetilsilaniloxi)bifenil-4-iloxi]propoxi}fenil)-2-metoxipropiónico (Etapa A) mediante el procedimiento estándar de hidrólisis C (NaOH). MS (ES) para $C_{25}H_{26}O_6$ $[M+Na]^+$: 445.

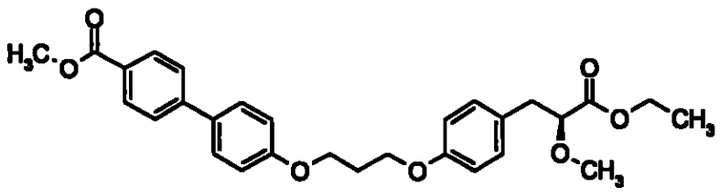
Ejemplo 197

Ácido (2S)-4'-{3-[4-(2-carboxi-2-metoxietil)fenoxi]propoxi}bifenil-4-carboxílico



Etapa A

Éster metílico del ácido (2S)-4'-{3-[4-(2-etoxicarbonil-2-metoxietil)fenoxi]propoxi}bifenil-4-carboxílico



Se trataron éster etílico de ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico del Ejemplo 171, Etapa B, y éster metílico de ácido 4'-hidroxi-bifenil-4-carboxílico según las condiciones de acoplamiento estándar de Mitsounobu B para obtener el compuesto del título.

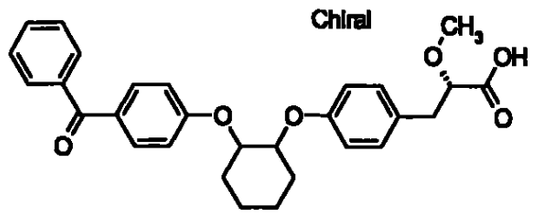
Etapa B

Ácido (2S)-4'-{3-[4-(2-carboxi-2-metoxietil)fenoxi]propoxi}bifenil-4-carboxílico

Se preparó el compuesto del título a partir de éster metílico de ácido (2S)-4'-{3-[4-(2-etoxicarbonil-2-metoxietil)fenoxi]propoxi}bifenil-4-carboxílico Etapa A) mediante el procedimiento estándar de hidrólisis C (NaOH). MS (ES) para $C_{26}H_{26}O_7$ $[M+NH_4]^+$: 468, $[M+Na]^+$: 473.

Ejemplo 198

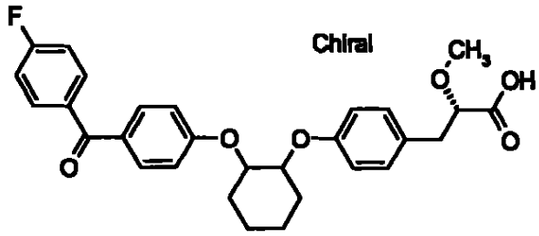
Ácido (2S)-3-{4-[2-(4-benzoilfenoxi)ciclohexiloxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa C) mediante el acoplamiento de Mitsounobu (Procedimiento estándar F), para obtener ácido 3-[4-(2-hidroxiciclohexiloxi)fenil]-2-metoxipropiónico unido a la resina. Una segunda reacción de acoplamiento de Mitsounobu con 4-hidroxibenzofenona mediante el Procedimiento estándar G nos permite obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200MHz): 7,75 (d, 4H, J= 8,6); 7,57-7,43 (m, 3H); 7,13 (d, 2H, J= 8,9); 6,89 (d, 2H, J= 9,1); 6,79 (d, 2H, J= 8,6); 4,53-4,36 (m, 2H); 4,04-3,99 (m, 1H); 3,43 (s, 3H); 3,08-2,94 (m, 2H); 1,38-1,29 (m, 8H) ppm.

Ejemplo 199

Ácido (2S)-3-(4-{2-[4-(4-fluorobenzoil)fenoxi]ciclohexiloxi}fenil)-2-metoxipropiónico

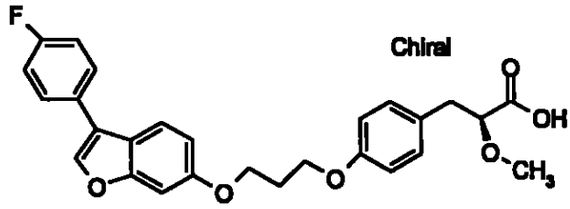


Se preparó el compuesto del título a partir de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico unido

a resina de Wang (Ejemplo 94, Etapa C) mediante el acoplamiento de Mitsounobu (Procedimiento estándar F), para obtener ácido 3-[4-(2-hidroxiciclohexiloxi)fenil]-2-metoxipropiónico unido a la resina. Una segunda reacción de acoplamiento de Mitsounobu con 4-fluoro-4'-hidroxibenzofenona mediante el Procedimiento estándar G nos permite obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200MHz): 7,83-7,69 (m, 4H); 7,19-7,11 (m, 4H); 6,89 (d, 2H, J= 8,9); 6,79 (d, 2H, J= 8,6); 4,53-4,33 (m, 2H); 4,02 (dd, 1H, J= 6,5, 4,8); 3,43 (s, 3H); 3,10 (dd, 1H, J= 14,4, 4,8), 2,98 (dd, 1H, J= 14,4, 6,5); 1,38-1,29 (m, 8H) ppm.

Ejemplo 200

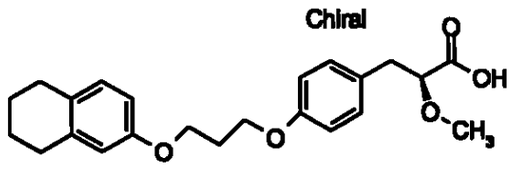
Ácido (2S)-3-{4-{3-[3-(4-fluorofenil)benzofuran-6-iloxi]-propoxi}fenil)-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 3-(4-fluorofenil)benzofuran-6-ol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{25}FO_6$ $[M+NH_4]^+$: 482, $[M+Na]^+$: 487, $[M+H]^+$: 464.

Ejemplo 201

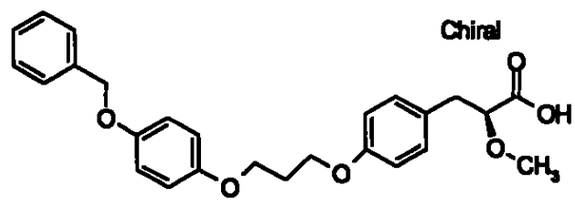
Ácido (2S)-2-metoxi-3-{4-[3-(5,6,7,8-tetrahidronaftalen-2-iloxi)propoxi]fenil}propiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 5,6,7,8-tetrahidronaftalen-2-ol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH) para obtener el compuesto del título. MS(ES) para $C_{23}H_{28}O_5$ $[M+Na]^+$: 407, $[M+H]^+$: 385.

Ejemplo 202

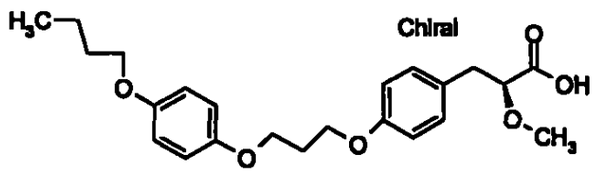
Ácido (2S)-3-{4-[3-(4-benciloxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 4-benciloxifenol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{28}O_6$ $[M-H]^-$: 435.

Ejemplo 203

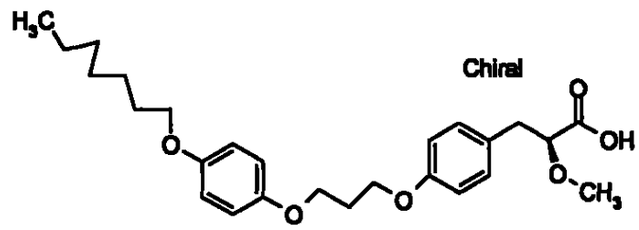
Acido (2S)-3-{4-[3-(4-butoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 4-butoxifenol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH) para obtener el compuesto del título. MS(ES) para $C_{23}H_{30}O_6$ $[M+NH_4]^+$: 420, $[M+Na]^+$: 425, $[M+H]^+$: 403.

Ejemplo 204

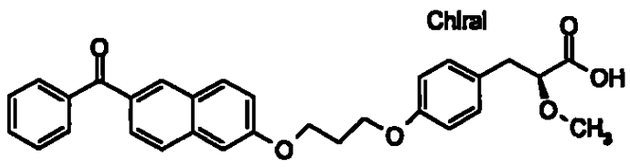
Ácido (2S)-3-{4-[3-(4-heptiloxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 4-heptiloxifenol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{36}H_{36}O_6$ $[M+Na]^+$: 467, $[M+H]^+$: 445.

Ejemplo 205

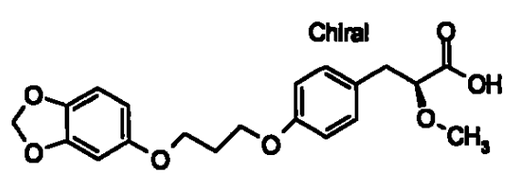
Ácido (2S)-3-{4-[3-(6-benzoilnaftalen-2-iloxi)propoxi]fenil}-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con (6-hidroxinaftalen-2-il)fenilmetanona según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{30}H_{28}O_6$ $[M+Na]^+$: 507, $[M+H]^+$: 485.

Ejemplo 206

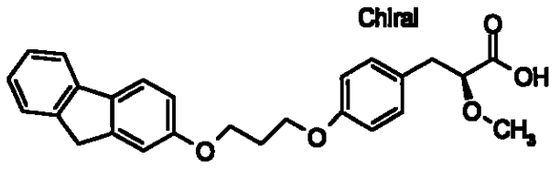
Ácido (2S)-3-{4-[3-(benzo[1,3]dioxol-5-iloxi)propoxi]fenil}-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con benzo[1,3]dioxol-5-ol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{20}H_{22}O_7$ $[M+Na]^+$: 397, $[M+H]^+$: 375.

Ejemplo 207

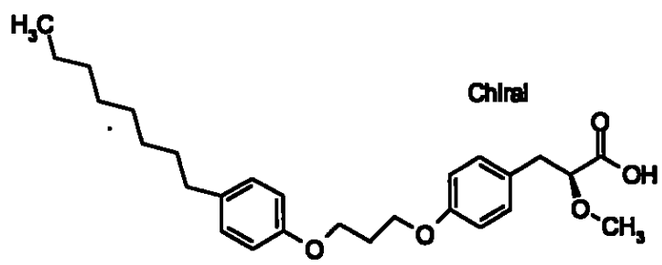
Ácido (2S)-3-{4-[3-(9H-fluoren-2-iloxi)propoxi]fenil}-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 9H-fluoren-2-ol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{26}O_5$ $[M+Na]^+$: 441.

Ejemplo 208

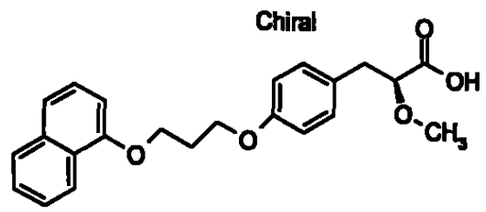
Ácido (2S)-2-metoxi-3-{4-[3-(4-octilfenoxi)propoxi]fenil}propiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 4-octilfenol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{38}O_5$ $[M+Na]^+$: 466.

Ejemplo 209

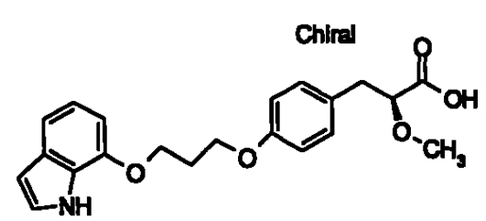
Ácido (2S)-2-metoxi-3-{4-[3-(naftalen-1-iloxi)propoxi]fenil}propiónico



Se trató el éster etílico del ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con naftalen-1-ol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{23}H_{24}O_5$ $[M+Na]^+$: 403, $[M+H]^+$: 381.

Ejemplo 210

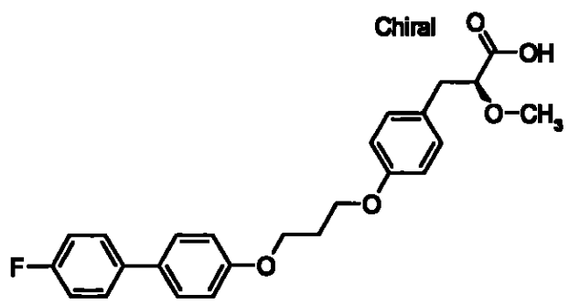
Ácido (2S)-3-{4-[3-(1H-indol-7-iloxi)propoxi]fenil}-2-metoxipropiónico



Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con 1H-indol-7-ol según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{21}H_{23}NO_5$ $[M+Na]^+$: 392, $[M+H]^+$: 370.

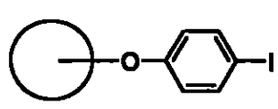
Ejemplo 211

Ácido (2S)-3-{4-[3-(4'-fluorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

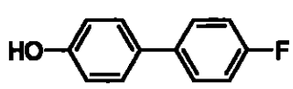
Preparación de p-yodofenol unido a la resina de Wang



Se suspendieron resina de Wang, (1 eq), *p*-yodofenol (4,5 eq) y PPh_3 (5-8 eq) en un vial y se enfrió a 0°C y se añadió luego DIAD (5 eq). Se dejó que la mezcla de reacción llegara a la temperatura ambiente y se agitó durante la noche. Se filtró y se lavó con MeOH-CH_2Cl_2-THF-HCl ac. y CH_2Cl_2, para obtener el producto.

Etapa B

4'-Fluorobifenil-4-ol



Se suspendió una mezcla del *p*-yodofenol unido a la resina de Wang de la Etapa A (1 eq), ácido 4-fluorobencenoborónico (6 eq), K_2CO_3 (12 eq) y $Pd(OAc)_2$ (0,5 eq) en una mezcla de dioxano/agua (6/1) y se calentó la mezcla a 100°C y se agitó durante 36 horas. Se lavó la resina con DMF/H_2O y MeOH/THF/HCl diluido y MeOH/CH_2Cl_2.

Después de secarla, se suspendió en diclorometano y se añadió TFA al 95%. Se agitó la mezcla a temperatura ambiente durante 30 min y luego se filtró y se lavó con MeOH y diclorometano. Se concentraron los solventes a sequedad para obtener el producto del título

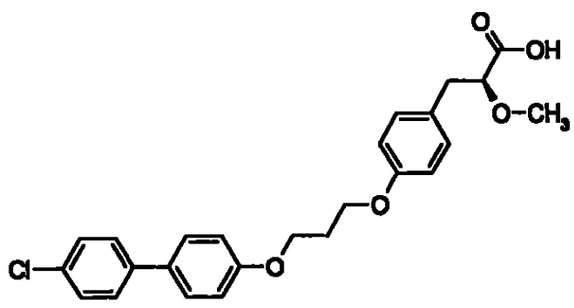
Etapa C

Ácido (2S)-3-{4-[3-(4'-fluorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 4'-fluorobifenil-4-ol de la Etapa B según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{25}H_{25}FO_5$ $[M+NH_4]^+$: 442, $[M+Na]^+$: 447.

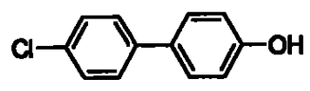
Ejemplo 212

Ácido (2S)-3-{4-[3-(4'-clorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

4-Clorobifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con

813

ácido 4-clorofenilborónico.

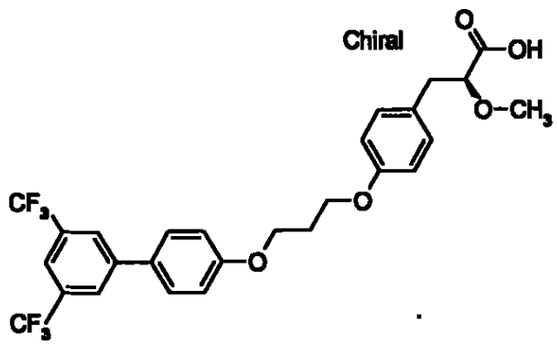
Etapa B

Ácido (2S)-3-{4-[3-(4'-clorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el clorobifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{25}H_{25}ClO_5$ $[M+Na]^+$: 463, $[M+H]^+$: 441.

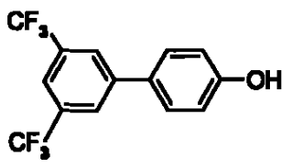
Ejemplo 213

Ácido (2S)-3-{4-[3-(3',5'-bistrifluorometilbifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

3',5'-Bistrifluorometilbifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 3,5-bis(trifluorometil)fenilborónico.

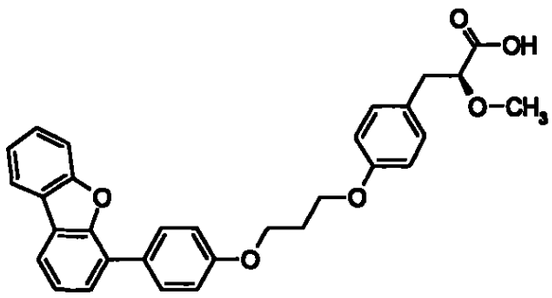
Etapa B

Ácido (2S)-3-{4-[3-(3',5'-bistrifluorometilbifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 3',5'-bistrifluorometilbifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH) para obtener el compuesto del título. MS(ES) para $C_{27}H_{24}F_6O_5$ $[M+Na]^+$: 565, $[M+H]^+$: 543.

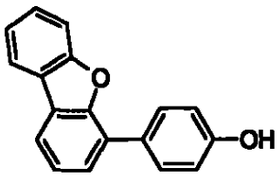
Ejemplo 214

Ácido (2S)-3-{4-[3-(4-dibenzofuran-4-ilfenoxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

4-Dibenzofuran-4-ilfenol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 4-dibenzofuranoborónico.

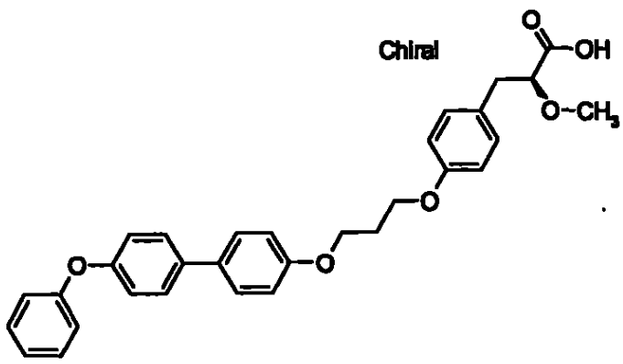
Etapa B

Ácido (2S)-3-{4-[3-(4-dibenzofuran-4-ilfenoxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico de 0, Etapa A, con el 4-dibenzofuran-4-ilfenol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{31}H_{30}O_6$ $[M+Na]^+$: 519.

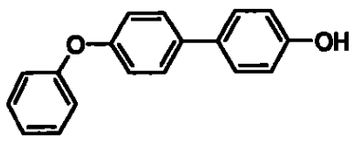
Ejemplo 215

Ácido (2S)-2-metoxi-3-{4-[3-(4'-fenoxibifenil-4-iloxi)-propoxi]fenil}propiónico



Etapa A

4'-Fenoxibifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 4-fenoxifenilborónico.

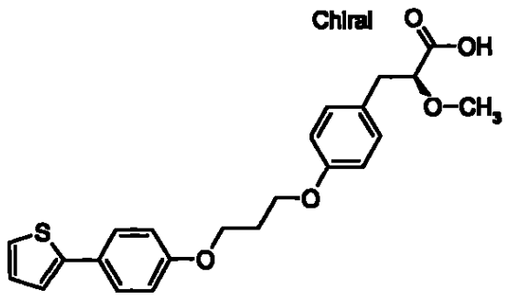
Etapa B

Ácido (2S)-2-metoxi-3-{4-[3-(4'-fenoxibifenil-4-iloxi)-propoxi]fenil}propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 4'-fenoxibifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH) para obtener el compuesto del título. MS(ES) para $C_{31}H_{30}O_6$ $[M+NH_4]^+$: 516, $[M+Na]^+$: 521.

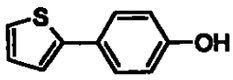
Ejemplo 216

Ácido (2S)-2-metoxi-3-{4-[3-(4-tiofen-2-ilfenoxi)propoxi]fenil}propiónico



Etapa A

4-Tiofen-2-ilfenol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B con ácido tiofeno-2-borónico.

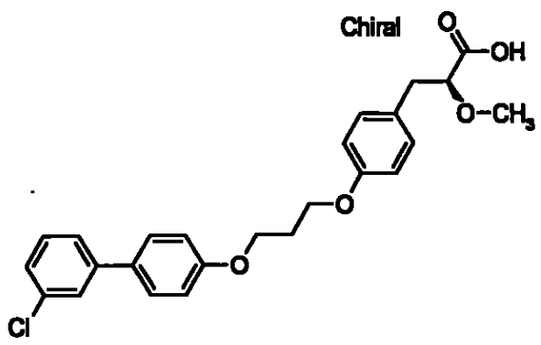
Etapa B

Ácido (2S)-2-metoxi-3-{4-[3-(4-tiofen-2-ilfenoxi)propoxi]fenil}propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 4-tiofen-2-ilfenol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{23}H_{24}O_5S$ $[M+NH_4]^+$: 430, $[M+Na]^+$: 435.

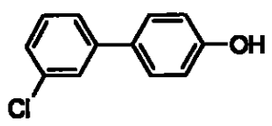
Ejemplo 217

Ácido (2S)-3-{4-[3-(3'-clorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

3'-Clorobifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 3-clorofenilborónico.

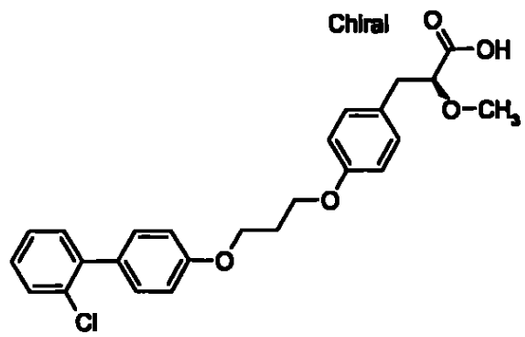
Etapa B

Ácido (2S)-3-{4-[3-(3'-clorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se ácido trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico de 0, Etapa A, con el 3'-clorobifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{25}H_{25}ClO_5$ $[M+NH_4]^+$: 458, $[M+Na]^+$: 463.

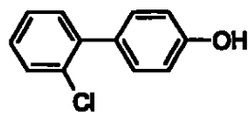
Ejemplo 218

Ácido (2S)-3-{4-[3-(2'-clorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

2'-Clorobifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 2-clorofenilborónico.

Etapa B

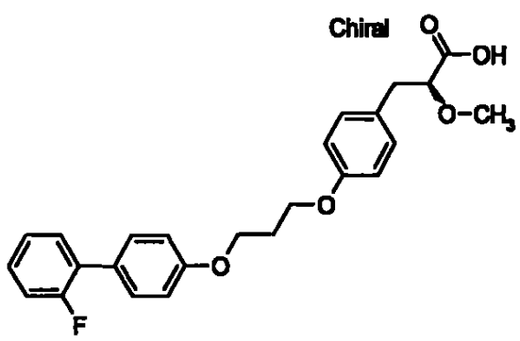
Ácido (2S)-3-{4-[3-(2'-clorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 2-clorobifenil-4-ol de la Etapa A

según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{25}H_{25}ClO_5$ $[M+NH_4]^+$: 458, $[M+Na]^+$: 463.

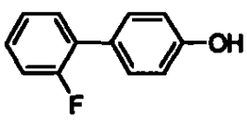
Ejemplo 219

Ácido (2S)-3-{4-[3-(2'-fluorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

2'-Fluorobifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 2-fluorofenilborónico.

Etapa B

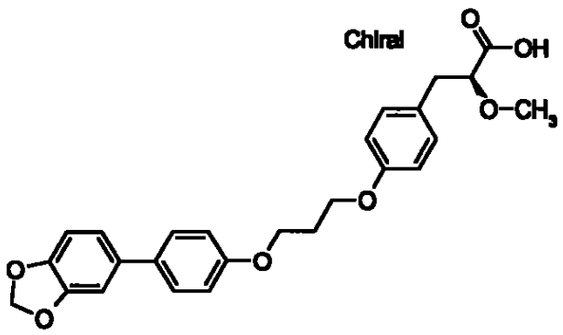
Ácido (2S)-3-{4-[3-(2'-fluorobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico del ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 2-fluorobifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento

estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{25}H_{25}FO_5$ $[M+NH_4]^+$: 442, $[M+Na]^+$: 447.

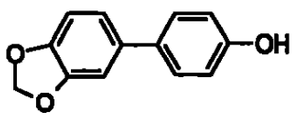
Ejemplo 220

Ácido (2S)-3-{4-[3-(4-benzo[1,3]dioxol-5-ilfenoxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

4-Benzo[1,3]dioxol-5-ilfenol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 3,4-metilendioxofenilborónico.

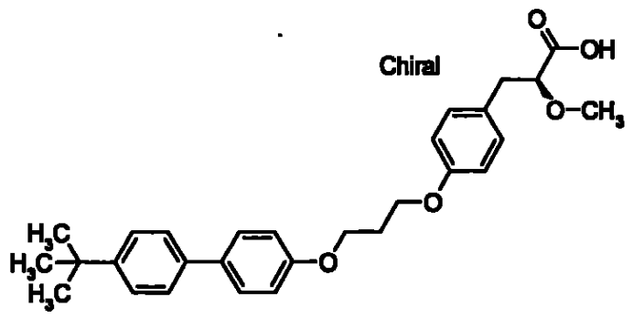
Etapa B

Ácido (2S)-3-{4-[3-(4-benzo[1,3]dioxol-5-ilfenoxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 4-benzo[1,3]dioxol-5-ilfenol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{26}O_7$ $[M+NH_4]^+$: 468, $[M+Na]^+$: 473.

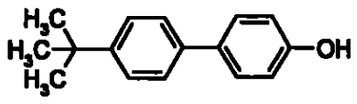
Ejemplo 221

Ácido (2S)-3-{4-[3-(4'-terc-butilbifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

4'-terc-Butilbifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 4-*terc*-butilfenilborónico.

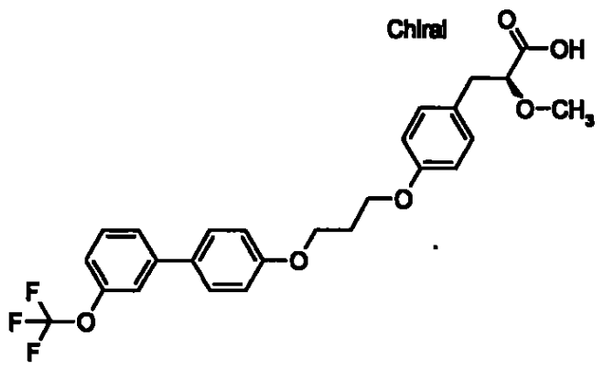
Etapa B

Ácido (2S)-3-{4-[3-(4'-terc-butilbifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 4'-*terc*-butilbifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{29}H_{34}O_5$ $[M+NH_4]^+$: 480, $[M+Na]^+$: 485.

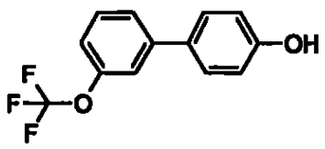
Ejemplo 222

Acido (2S)-2-metoxi-3-{4-[3-(3'-trifluorometoxibifenil-4-iloxi)propoxi]fenil}propiónico



Etapa A

3'-Trifluorometoxibifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 3-trifluorometoxibencenoborónico.

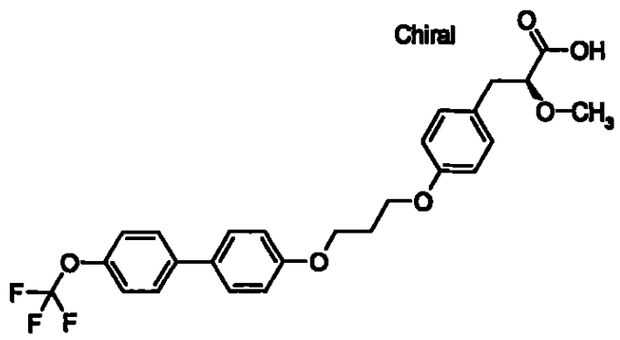
Etapa B

Ácido (2S)-2-metoxi-3-{4-[3-(3'-trifluorometoxibifenil-4-iloxi)propoxi]fenil}propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 3'-trifluorometoxibifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{25}F_3O_6$ $[M+Na]^+$: 513, $[M+H]^+$: 491.

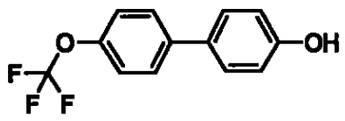
Ejemplo 223

Ácido (2S)-2-metoxi-3-{4-[3-(4'-trifluorometoxibifenil-4-iloxi)propoxi]fenil}propiónico



Etapa A

4'-Trifluorometoxibifenil-4-ol



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 211, Etapa B, con ácido 4-trifluorometoxibencenoborónico.

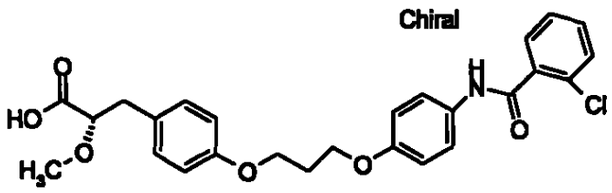
Etapa B

Ácido (2S)-2-metoxi-3-{4-[3-(4'-trifluorometoxibifenil-4-iloxi)propoxi]fenil}propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con el 4'-trifluorometoxibifenil-4-ol de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{25}F_3O_6$ $[M+NH_4]^+$: 508, $[M+Na]^+$: 513.

Ejemplo 224

Ácido (2S)-3-(4-{3-[4-(2-clorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico



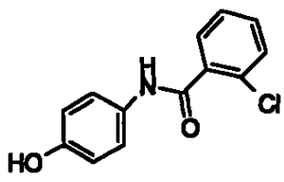
Etapa A

p-Aminofenol unido a resina de Wang

Se trató una suspensión de resina de Wang en THF/CH_2Cl_2 con DIAD (5 eq), Ph_3P (5 eq) y p-nitrofenol (5 eq). Se agitó la mezcla durante la noche y luego se filtró la resina y se lavó con MeOH/CH_2Cl_2 varias veces. Después de secarla, se suspendió la resina en DMF y se trató con $SnCl_2$ (10 eq) y se agitó de nuevo durante la noche. Se filtró y se lavó con MeOH/CH_2Cl_2 varias veces y se secó para obtener el producto.

Etapa B

2-Cloro-N-(4-hidroxifenil)benzamida



Se trató una suspensión de p-aminofenol unido a la resina de Wang de la Etapa A (1 eq) en diclorometano con trietilamina (2 ml/mmol) y cloruro de 2-clorobenzoílo (10 eq). Se agitó la mezcla de reacción durante 1 hora y luego se filtró la resina, se lavó con MeOH/CH_2Cl_2 varias veces y se secó. Se trató después la resina con TFA 95%/H_2O 5% y se agitó a temperatura ambiente durante 30 minutos. Se filtró y se lavó con diclorometano/metanol y

se concentró a sequedad, para dar lugar al compuesto del título.

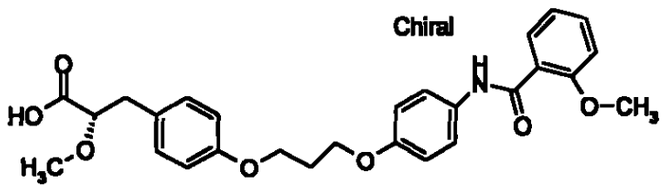
Etapa C

Ácido (2S)-3-(4-{3-[4-(2-clorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 2-cloro-N-(4-hidroxifenil)benzamida de la Etapa B según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{26}ClNO_6$ $[M+H]^+$: 484.

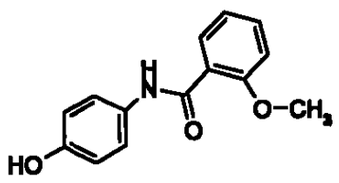
Ejemplo 225

Ácido (2S)-2-metoxi-3-(4-{3-[4-(2-metoxibenzoilamino)fenoxi]propoxi}fenil)propiónico



Etapa A

N-(4-Hidroxifenil)-2-metoxibenzamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en 0, Etapa B, con cloruro de 2-metoxibenzoílo.

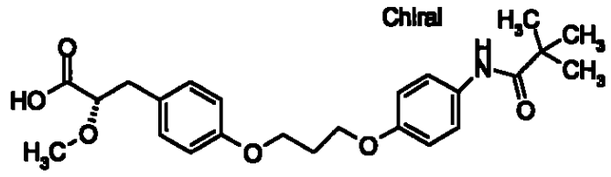
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(2-metoxibenzoilamino)fenoxi]propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la N-(4-hidroxifenil)-2-metoxibenzamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{29}NO_7$ $[M+H]^+$: 480.

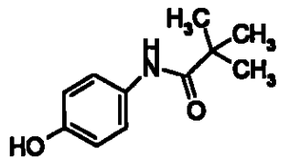
Ejemplo 226

Ácido (2S)-3-(4-{3-[4-(2,2-dimetilpropionilamino)fenoxi]-propoxi}fenil)-2-metoxipropiónico



Etapa A

N-(4-Hidroxifenil)-2,2-dimetilpropionamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B, con cloruro de 2,2-dimetilpropionilo.

Etapa B

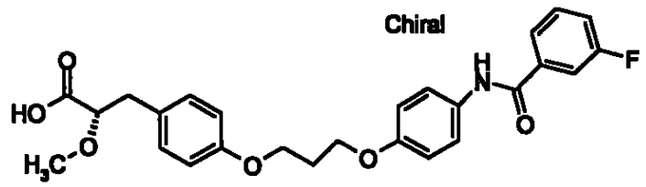
Ácido (2S)-3-(4-{3-[4-(2,2-dimetilpropionilamino)fenoxi]-propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la N-(4-hidroxifenil)-2,2-dimetilpropionamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), pa-

ra obtener el compuesto del título. MS(ES) para $C_{24}H_{31}NO_6$ $[M+H]^+$: 430.

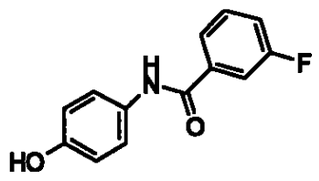
Ejemplo 227

Ácido (2S)-3-(4-{3-[4-(3-fluorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

3-Fluoro-N-(4-hidroxifenil)benzamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B, con cloruro de 3-fluorobenzoílo.

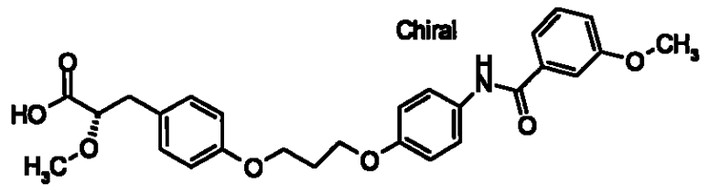
Etapa B

Ácido (2S)-3-(4-{3-[4-(3-fluorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 3-fluoro-N-(4-hidroxifenil)benzamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{26}FNO_6$ $[M+H]^+$: 468.

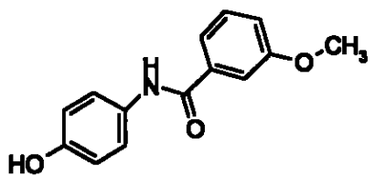
Ejemplo 228

Ácido (2S)-2-metoxi-3-(4-{3-[4-(3-metoxibenzoilamino)fenoxi]propoxi}fenil)propiónico



Etapa A

N-(4-Hidroxifenil)-3-metoxibenzamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B, con cloruro de 3-metoxibenzoílo.

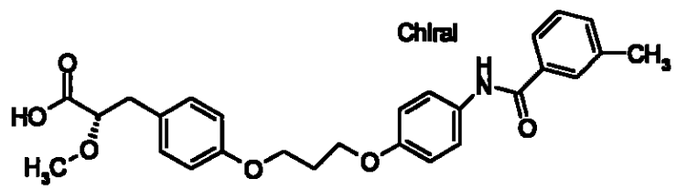
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(3-metoxibenzoilamino)fenoxi]propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la N-(4-hidroxifenil)-3-metoxibenzamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{29}NO_7$ $[M+H]^+$: 480.

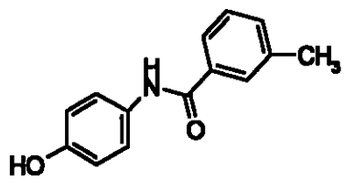
Ejemplo 229

Ácido (2S)-2-metoxi-3-(4-{3-[4-(3-metilbenzoilamino)fenoxi]propoxi}fenil)propiónico



Etapa A

N-(4-Hidroxifenil)-3-metilbenzamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B, con cloruro de 3-metil-benzoílo.

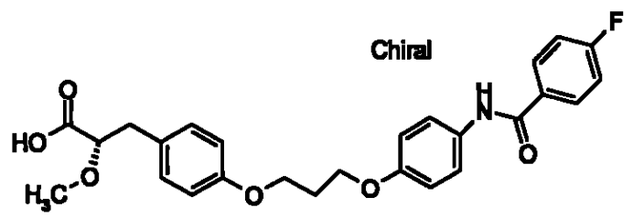
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(3-metilbenzoilamino)fenoxi]propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la N-(4-hidroxifenil)-3-metilbenzamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{29}NO_6$ $[M+H]^+$: 464.

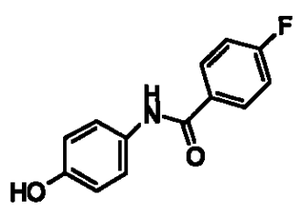
Ejemplo 230

Ácido (2S)-3-(4-{3-[4-(4-fluorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

4-Fluoro-N-(4-hidroxifenil)benzamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B con cloruro de 4-fluorobenzoílo.

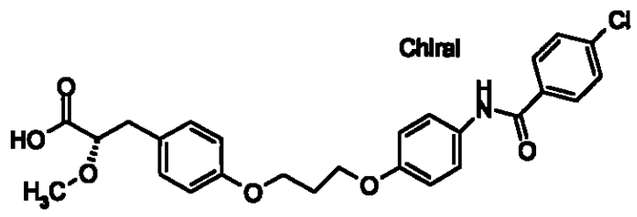
Etapa B

Acido (2S)-3-(4-{3-[4-(4-fluorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 4-fluoro-N-(4-hidroxifenil)benzamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{26}FNO_6$ $[M+H]^+$: 468.

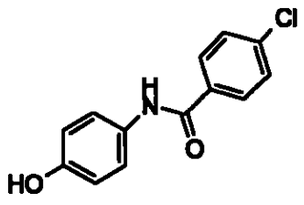
Ejemplo 231

Ácido (2S)-3-(4-{3-[4-(4-clorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

4-Cloro-N-(4-hidroxifenil)benzamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B, con cloruro de 4-clorobenzoílo.

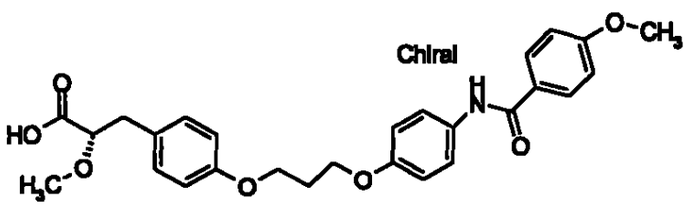
Etapa B

Ácido (2S)-3-(4-{3-[4-(4-clorobenzoilamino)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 4-cloro-N-(4-hidroxifenil)benzamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{26}ClNO_6$ $[M+H]^+$: 484.

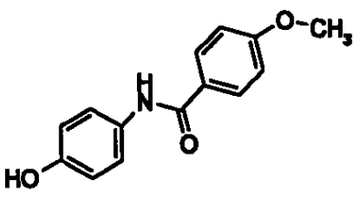
Ejemplo 232

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-metoxibenzoilamino)fenoxi]propoxi}fenil)propiónico



Etapa A

N-(4-Hidroxifenil)-4-metoxibenzamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B, con cloruro de 4-metoxibenzoílo.

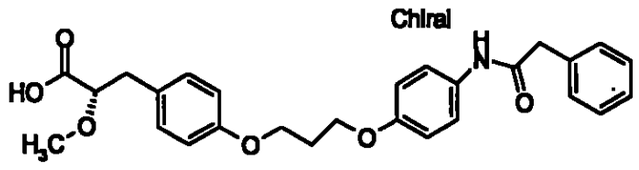
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-metoxibenzoilamino)fenoxi]propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 4-metoxi-N-(4-hidroxifenil)benzamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{29}NO_7$ $[M+H]^+$: 480.

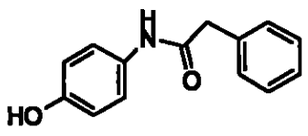
Ejemplo 233

Ácido (2S)-2-metoxi-3-{4-[3-(4-fenilacetilaminofenoxi)-propoxi]fenil}propiónico



Etapa A

N-(4-Hidroxifenil)-2-fenilacetamida



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 224, Etapa B, con cloruro de fenilacetilo.

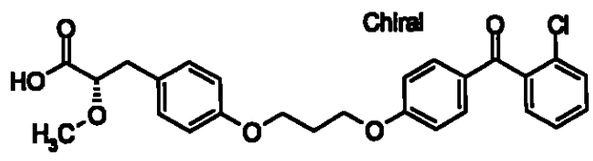
Etapa B

Ácido (2S)-2-metoxi-3-{4-[3-(4-fenilacetilaminofenoxi)-propoxi]fenil}propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la N-(4-hidroxifenil)-2-fenilacetamida de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{29}NO_6$ $[M+H]^+$: 484.

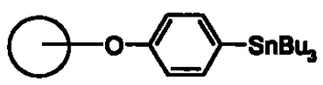
Ejemplo 234

Ácido (2S)-3-(4-{3-[4-(2-clorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

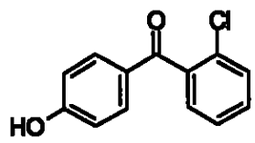
4-Tributilestanilfenol unido a resina de Wang



Se suspendió el p-yodofenol unido a resina de Wang del Ejemplo 211, Etapa A, en tolueno y se añadió bistributilestaño (5 eq). Se agitó la mezcla de reacción a 100°C durante la noche. Se filtró entonces y se lavó la resina con CH_2Cl_2/MeOH/hexano/MeOH/CH_2Cl_2, para obtener el compuesto.

Etapa B

(2-Clorofenil)-(4-hidroxifenil)metanona



Se suspendieron el 4-tributilestanilfenol unido a resina de Wang de la Etapa A (1 eq), $Pd_2(dba)_3$ (0,3 eq) y K_2CO_3 (70 mg) en THF/diisopropilmetilamina. A esta mezcla se añadió cloruro de 2-clorobenzoílo y se agitó durante 2 horas. Se filtró la suspensión y se lavó la resina con MeOH/CH_2Cl_2/DMF y luego con HCl diluido/dioxano y Na_2CO_3 al 5%(dioxano) y DMF/MeOH/CH_2Cl_2. Una vez se hubo secado la resina, se añadieron TFA al 95% y CH_2Cl_2 se agitó la mezcla a temperatura ambiente durante 30 min. Se filtró la resina y se lavó con MeOH/CH_2Cl_2. Se recogieron los solventes y se concentraron a sequedad para obtener el producto del título.

Etapa C

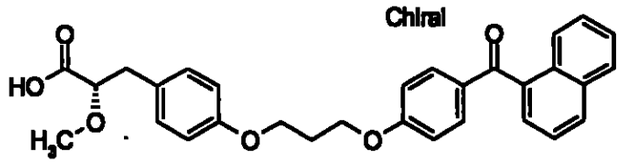
Acido (2S)-3-(4-{3-[4-(2-clorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-

(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la (2-clorofenil)-(4-hidroxifenil)metanona de la Etapa B según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{25}ClO_6$ $[M+NH_4]^+$: 491, $[M+H]^+$: 469.

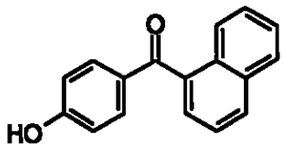
Ejemplo 235

Ácido (2S)-2-metoxi-3-(4-{3-[4-(naftalen-1-carbonil)fenoxi]propoxi}fenil)propiónico



Etapa A

(4-Hidroxifenil)naftalen-1-ilmetanona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de naftalen-1-carbonilo.

Etapa B

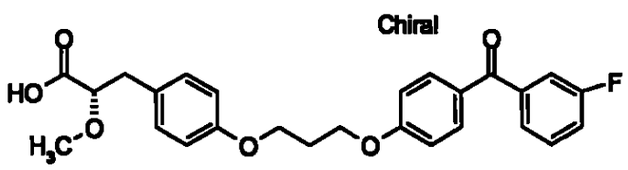
Ácido (2S)-2-metoxi-3-(4-{3-[4-(naftalen-1-carbonil)fenoxi]propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la (4-hidroxifenil)naftalen-1-ilmetanona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{30}H_{28}O_6$ $[M+NH_4]^+$:

507, $[M+H]^+$: 485.

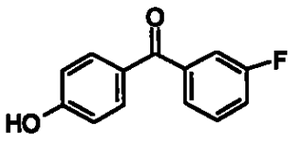
Ejemplo 236

Ácido (2S)-3-(4-{3-[4-(3-fluorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

(3-Fluorofenil)-(4-hidroxifenil)metanona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de 3-fluorobenzoílo.

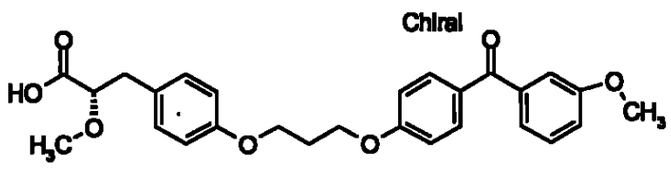
Etapa B

Ácido (2S)-3-(4-{3-[4-(3-fluorobenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la (3-fluorofenil)-(4-hidroxifenil)metanona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{26}H_{25}FO_6$ $[M+H]^+$: 453,5.

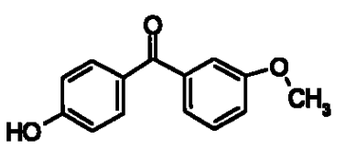
Ejemplo 237

Ácido (2S)-2-metoxi-3-(4-{3-[4-(3-metoxibenzoil)fenoxi]-propoxi}fenil)propiónico



Etapa A

(4-Hidroxifenil)-(3-metoxifenil)metanona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de 3-metoxibenzoílo.

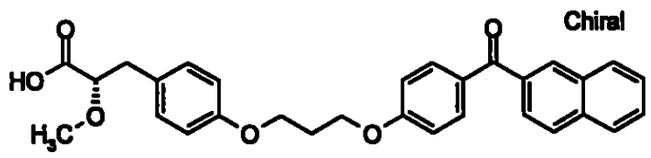
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(3-metoxibenzoil)fenoxi]-propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la (4-hidroxifenil)-(3-metoxifenil)metanona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{28}O_7$ $[M+H]^+$: 465.

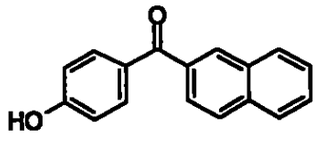
Ejemplo 238

Ácido (2S)-2-metoxi-3-(4-{3-[4-(naftalen-2-carbonil)fenoxi]propoxi}fenil)propiónico



Etapa A

(4-Hidroxifenil)naftalen-2-ilmetanona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de naftalen-2-carbonilo.

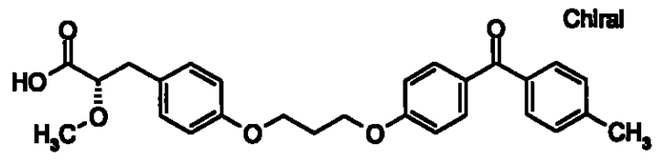
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(naftalen-2-carbonil)fenoxi]propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la (4-hidroxifenil)naftalen-2-ilmetanona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{30}H_{28}O_6$ $[M+H]^+$: 485.

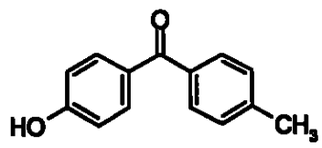
Ejemplo 239

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-metilbenzoil)fenoxi]-propoxi}fenil)propiónico



Etapa A

(4-Hidroxifenil)-p-tolilmetanona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de 4-metilbenzoílo.

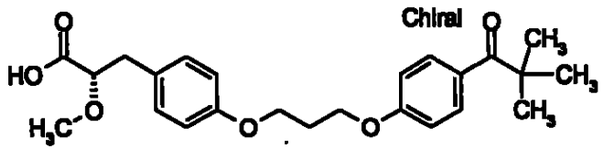
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(4-metilbenzoil)fenoxi]-propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la (4-hidroxifenil)-p-tolilmetanona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{27}H_{28}O_6$ $[M+NH_4]^+$: 471 $[M+H]^+$: 449.

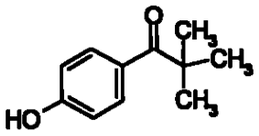
Ejemplo 240

Ácido (2S)-3-(4-{3-[4-(2,2-dimetilpropionil)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

1-(4-Hidroxifenil)-2,2-dimetilpropan-1-ona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de 2,2-dimetilpropionilo.

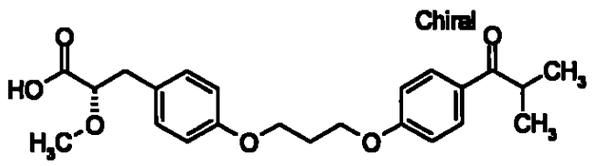
Etapa B

Ácido (2S)-3-(4-{3-[4-(2,2-dimetilpropionil)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 1-(4-hidroxifenil)-2,2-dimetilpropan-1-ona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{24}H_{30}O_6$ $[M+NH_4]^+$: 437 $[M+H]^+$: 415.

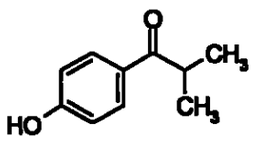
Ejemplo 241

Ácido (2S)-3-{4-[3-(4-isobutirilfenoxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

1-(4-Hidroxifenil)-2-metilpropan-1-ona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de isobutirilo.

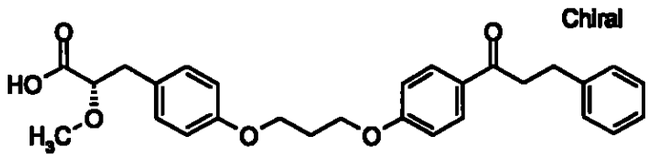
Etapa B

Ácido (2S)-3-{4-[3-(4-isobutirilfenoxi)propoxi]fenil}-2-metoxipropiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 1-(4-hidroxifenil)-2-metilpropan-1-ona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{23}H_{28}O_6$ $[M+NH_4]^+$: 423 $[M+H]^+$: 401.

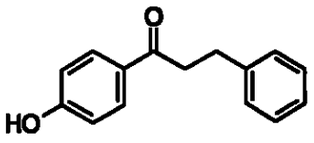
Ejemplo 242

Acido (2S)-2-metoxi-3-(4-{3-[4-(3-fenilpropionil)fenoxi]-propoxi}fenil)propiónico



Etapa A

1-(4-Hidroxifenil)-3-fenilpropan-1-ona



Se preparó el compuesto del título siguiendo el procedimiento descrito en el Ejemplo 234, Etapa B, con cloruro de 3-fenilpropionilo.

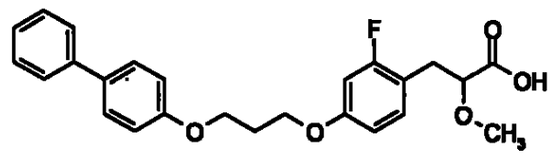
Etapa B

Ácido (2S)-2-metoxi-3-(4-{3-[4-(3-fenilpropionil)fenoxi]-propoxi}fenil)propiónico

Se trató el éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico del Ejemplo 173, Etapa A, con la 1-(4-hidroxifenil)-3-fenilpropan-1-ona de la Etapa A según el Procedimiento estándar J. Se dejó que el compuesto así obtenido reaccionara según el procedimiento estándar de hidrólisis C (NaOH), para obtener el compuesto del título. MS(ES) para $C_{28}H_{30}O_6$ $[M+NH_4]^+$: 485 $[M+H]^+$: 463.

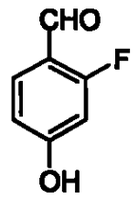
Ejemplo 243

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-2-metoxipropiónico



Etapa A

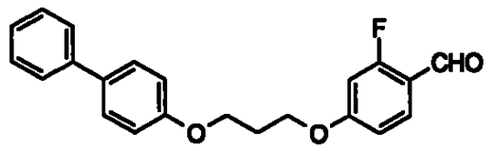
2-Fluoro-4-hidroxibenzaldehído



Se añadió 2-fluoro-4-metoxibenzaldehído (1 g, 6,49 mmol) a una suspensión de yoduro de potasio anhidro (2,15 g, 13 mmol) y tricloruro de aluminio (1,04 g, 7,8 mmol) en tolueno anhidro (10 ml) y se agitó la mezcla a 40°C durante 3 horas. Se añadieron tricloruro de aluminio (2,15 g, 13 mmol) y yoduro de potasio anhidro (0,86 g, 6,49 mmol) y se agitó la mezcla durante 3 horas. Se diluyó la mezcla con agua (10 ml) y se extrajo con acetato de etilo (5 X 20 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío. Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 4:1), para obtener 2-fluoro-4-hidroxibenzaldehído como un sólido blanco (260 mg, 29%). ^1H RMN (200 MHz, acetona-d_6): δ 10,08 (s, 1H), 9,77 (a, 1H), 7,69 (t, 1H, J=8,4), 6,78 (dd, 1H, J=8,8, 2,6), 6,65 (dd, 1H, J=12,5, 2,2)ppm.

Etapa B

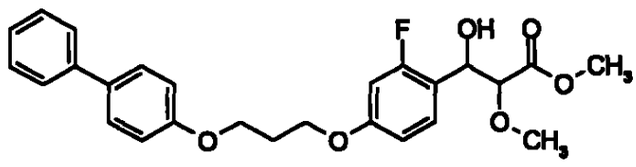
4-[3-(Bifenil-4-iloxi)propoxi]-2-fluorobenzaldehído



Se añadió *terc*-butóxido de potasio (0,217 g, 1,93 mmol) a una solución de 2-fluoro-4-hidroxibenzaldehído (0,246 g, 1,76 mmol) en DMF anhidra (5 ml) a 0°C y se agitó la mezcla durante 30 min. Se añadió 4-(3-bromopropoxi)bifenilo (0,564 g, 1,93 mmol, Ejemplo 132, Etapa D) y se agitó la mezcla a temperatura ambiente durante 24 horas. Se diluyó la mezcla de reacción con agua y se extrajo con EtOAc (5 X 15 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío. Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 4:1), para obtener 4-[3-(bifenil-4-iloxi)propoxi]-2-fluorobenzaldehído como un sólido blanco (540 mg, 88%). ^1H RMN (200 MHz, $CDCl_3$): δ 10,19 (s, 1H), 7,80 (t, 1H, J=8,4); 7,55-7,48 (m, 4H); 7,42-7,27 (m, 3H); 6,99-6,93 (m, 2H); 6,78 (dd, 1H, J=8,8, 2,6); 6,64 (dd, 1H, J=12,4, 2,2); 4,27-4,15 (m, 4H); 2,30 (q, 2H, J=5,9)ppm.

Etapa C

Éster metílico del ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-3-hidroxi-2-metoxipropiónico

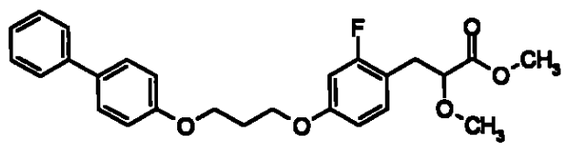


Se añadió por goteo una solución de 4-[3-(bifenil-4-iloxi)propoxi]-2-fluorobenzaldehído (0,320 g, 0,91 mmol) y metoxiacetato de metilo (0,099 ml, 1 mmol)

en THF (10 ml) a -78°C a bis(trimetilsilil)amiduro de sodio (1 ml, 1 mmol, 1N en THF) a -78°C. Se agitó la mezcla de reacción durante 3 horas, se apagó con HCl 1N (1 ml) y se dejó calentar hasta la temperatura ambiente. Se diluyó la mezcla con agua (10 ml) y se extrajo con acetato de etilo (3 X 30 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron a vacío. Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 2:1), para obtener una mezcla diastereomérica 1:1 de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluoro-fenil}-3-hidroxi-2-metoxipropiónico como un sólido blanco (250 mg, 60%). ^1H RMN (200 MHz, $CDCl_3$): 7,55-7,47 (m, 4H), 7,42-7,23 (m, 4H), 6,95 (d, 2H, J=8,4), 6,73-6,66 (m, 1H), 6,59 (dd, 1H, J=12,4, 2,6), 5,19 (dd, 1H, J=15,4, 4,8), 4,18-4,04 (m, 4H), 3,93 (d, 1H, J=5,1), 3,68 y 3,63 (2 s, 3H), 3,39 y 3,37 (2 s, 3H), 3,12 (a, 1H), 2,24 (q, 2H, J=6,2)ppm.

Etapa D

Éster metílico del ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-2-metoxipropiónico



Se añadieron anhídrido trifluoroacético (0,043 ml, 0,37 mmol) y piridina (0,074 ml, 0,93 mmol) a una solución éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-3-hidroxi-2-metoxipropiónico (0,142 g, 0,31 mmol) en cloruro de metileno (1 ml) a 0°C. Se agitó la mezcla resultante durante 4 horas a temperatura ambiente y se concentró a vacío. Se disolvió el residuo en acetato de etilo (50 ml) y se añadió paladio al 10% sobre carbono (0,064 g) a la solución. Se agitó la

mezcla bajo presión de hidrógeno (5 atm) durante 16 horas. Se filtró la mezcla a través de celita y se concentró a vacío. Se purificó el residuo por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 4:1), para obtener éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-2-metoxipropiónico como un sólido blanco (30 mg, 22 %). ^{1}H RMN (200 MHz, $CDCl_3$): 7,60-7,50 (m, 4H); 7,46-7,27 (m, 3H); 7,18-7,09 (m, 1H); 7,03-6,96 (m, 2H); 6,70-6,61 (m, 2H); 4,17 (dt, 4H, *J*=9,1, 6,2); 4,00 (dd, 1H, *J*=7,3, 5,9); 3,74 (s, 3H); 3,37 (s, 3H); 3,13-2,93 (m, 2H); 2,28 (q, 2H, *J*=6,2).

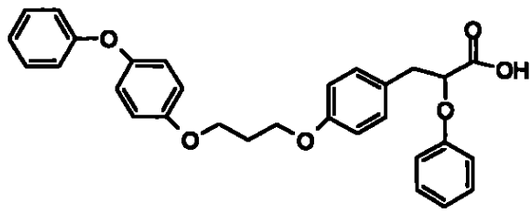
Etapa E

Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-2-metoxipropiónico

Se añadió una solución acuosa 1N de hidróxido de litio (1,37 ml) a una solución de éster metílico de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-2-metoxipropiónico (0,075 g, 0,17 mmol) en THF (2 ml) a temperatura ambiente. Se agitó la mezcla de reacción durante la noche, se diluyó con agua (10 ml) y se extrajo con éter dietílico (3 X 20 ml). Se acidificó la capa acuosa con HCl 1N a pH 1 y se extrajo con acetato de etilo (3 X 25 ml). Se secaron las capas orgánicas combinadas ($MgSO_4$), se filtraron y se concentraron para obtener ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-fluorofenil}-2-metoxipropiónico como un sólido blanco (60 mg, 83%). ^{1}H RMN (200 MHz, $CDCl_3$): 7,56-7,29 (m, 7H), 7,18-7,09 (m, 1H), 6,98 (d, 2H, *J*=8,6), 6,66-6,60 (m, 2H), 4,17 (dt, 4H, *J*=8,9, 5,9), 4,03 (dd, 1H, *J*=6,7, 4,8), 3,40 (s, 3H), 3,23-3,14 (m, 1H), 2,97 (dd, 1H, *J*=14,0, 6,7), 2,26 (c, 2H, *J*=5,9)ppm.

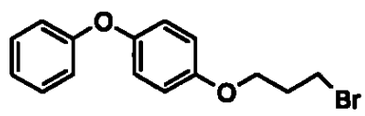
Ejemplo 244

Ácido 2-fenoxi-3-[4-(4-fenoxifenoxi)propoxifenil]propanoico



Etapa A

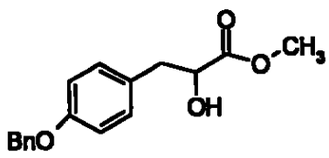
1-(3-Bromopropoxi)-4-fenoxibenceno



Se preparó el compuesto del título a partir de 4-fenoxifenol siguiendo el mismo procedimiento que en el Ejemplo 132, Etapa D. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,35-7,25 (m, 2H), 7,09-6,87 (m, 7H), 4,10 (t, 2H, J=5,9), 3,62 (t, 2H, J=6,1), 2,55-2,21 (m, 2H)ppm.

Etapa B

Éster metílico del ácido 4-benciloxifenil-2-hidroxipropanoico

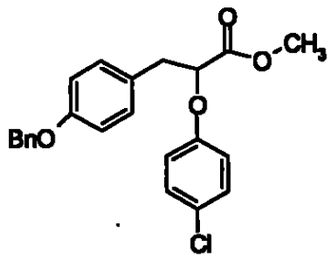


Se agitó una solución de ácido DL-4-hidroxifenil-láctico (0,5 g, 2,74 mmol) durante la noche en una solución saturada de MeOH/HCl. Se concentró la reacción a sequedad y se trató el producto bruto (0,545 g, 2,7 mmol) con K_2CO_3 (3 eq.) y bromuro de bencilo (0,507 g, 2,97 mmol) en acetonitrilo (20 ml) y se sometió a reflujo du-

rante la noche. Se filtró la reacción bruta y se concentró para producir un producto bruto. Se purificó el residuo por cromatografía (gel de sílice, hexanos/acetato de etilo (3:1), para obtener un aceite blanco (97%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,43-7,35 (m, 5H), 7,14 (d, 2H, J=8,59), 6,92 (d, 2H, J=8,59), 5,04 (s, 2H), 4,42 (dd, 1H, J=10,7, 6,1), 2,97 (ddd, 2H, J=4,5, 13,9, 31,1)2,73 (d, 1H, J=6,1).

Etapa C

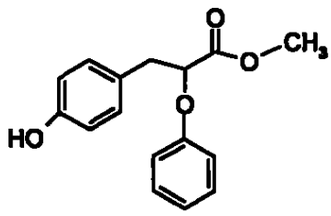
Éster metílico del ácido 4-benciloxifenil-2-(4-clorofenoxi)propanoico



Se trató una solución de trifenilfosfina (0,1 g, 0,38 mmol) en 5 ml de THF seco a 0°C con DEAD (0,066 g, 0,38 mmol) y se agitó a lo largo de 30 min. Se añadieron entonces una solución de éster metílico de ácido 4-benciloxifenil-2-hidroxipropanoico (0,1 g, 0,35 mmol) y p-clorofenol (0,048 g, 0,38 mmol) en 2 ml de THF a la solución y se agitó la mezcla de reacción a temperatura ambiente durante la noche. Se concentró la mezcla a sequedad y se cromatografió en gel de sílice (hexanos/acetato de etilo 3:1), para obtener 0,082 g de producto (60%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,46-7,31 (m, 5H), 7,28-7,13 (m, 4H), 6,93 (d, 2H, J=8,8), 6,75 (d, 2H, J=8,8), 5,04 (s, 2H), 4,73(t, 1H, J=6,1), 3,71 (s, 3H), 3,18 (d, 2H, J=6,4).

Etapa D

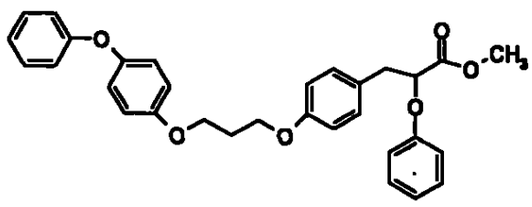
Éster metílico de ácido 4-hidroxifenil-2-fenoxipropanoico



Se agitó una solución de éster metílico de ácido 4-benciloxifenil-2-(4-clorofenoxi)propanoico en etanol con Pd 10%/C (5% p) bajo una atmósfera de hidrógeno (1 atm) a lo largo de 2 horas. Se eliminó el catalizador mediante filtración a través de una almohadilla de celita y se concentró el filtrado a vacío para producir el compuesto del título (90%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,25-7,14 (m, 4H), 7,94-7,73 (m, 4H), 4,81-4,69 (m, 1H), 3,70 (s, 3H), 3,16 (d, 2H, J=4,1).

Etapa E

Éster metílico del ácido 2-fenoxi-3-[4-(4-fenoxifenoxi)-propoxifenil]propanoico



Se agitó una mezcla de éster metílico de ácido 3-(4-hidroxifenil)-2-fenoxipropanoico (0,055 g, 0,18 mmol) con 1-(3-bromopropoxi)-4-fenoxibenceno (Etapa A) (0,055 g, 0,18 mmol) y terc-butóxido de potasio (0,020 g, 0,18 mmol) en DMF (5 ml) durante la noche. Se concentró la mezcla de reacción a vacío con tolueno (2 veces), se reconstituyó en acetato de etilo y se lavó con agua (3 veces) y salmuera, se secó (Na_2SO_4) y se concentró, para

obtener un producto bruto, que fue purificado por cromatografía en gel de sílice (hexanos/acetato de etilo, 3:1) para obtener 0,022 g del compuesto del título (23%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,34-7,15 (m, 6H), 7,07-6,71 (m, 12H), 4,80-4,68 (m, 1H), 4,13 (t, 4H, J=15,1), 3,71 (s, 3H), 3,20-3,15 (m, 2H), 2,30-2,18 (c, 2H).

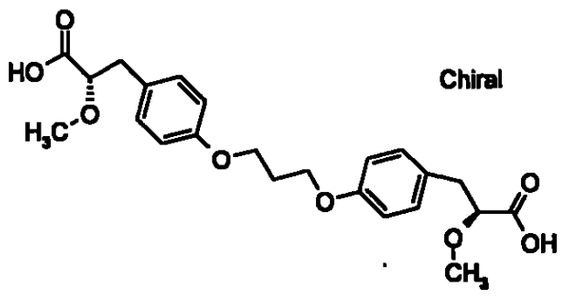
Etapa F

Ácido 2-fenoxi-3-[4-(4-fenoxifenoxi)propoxifenil]propanoico

Se preparó el compuesto del título a partir de éster metílico de ácido 2-fenoxi-3-[4-(4-fenoxifenoxi)propoxifenil]propanoico (0,022 g, 0,04 mmol) el cual fue agitado con un exceso de LiOH 3N (5 eq.) en THF (3 ml) durante la noche. Se aciduló la solución con HCl 1N (a pH 1-2) y se extrajo con acetato de etilo. Se secó la capa orgánica (Na_2SO_4) y se concentró a vacío, para producir un sólido oleoso (80%). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,33-7,16 (m, 6H), 7,03-6,70 (m, 12H), 4,84-4,71 (m, 1H), 4,13 (t, 4H, J= 6,1), 3,24-3,19 (m, 2H)ppm.

Ejemplo 245

Ácido (2S,2'S)-3-(4-{3-[4-(2'-carboxi-2'-metoxietil)fenoxi]propoxi}fenil)-2-metoxipropiónico



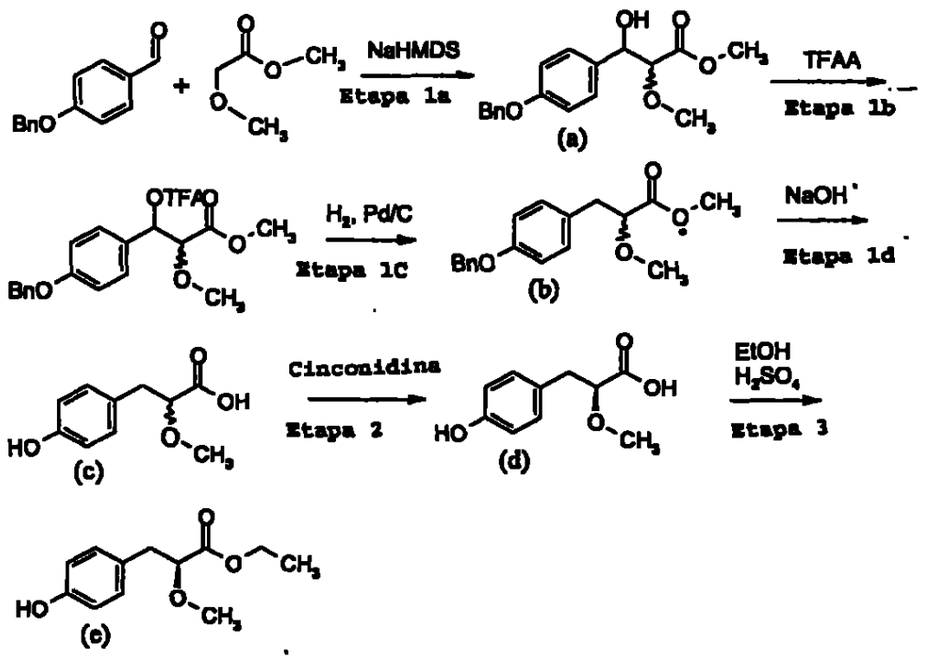
Se dejó reaccionar a una mezcla éster etílico de ácido (2S)-3-[4-(3-hidroxifenil]-2-metoxipropiónico (2 eq) y propilenglicol (1,3 eq) según las condiciones estándar de acoplamiento de Mitsounobu B (DIAD/tolueno) y se trató el producto resultante de esta reacción siguien-

do las condiciones estándar de hidrólisis C, para obtener el compuesto del título. MS(ES) para $C_{23}H_{28}O_8$ $[M+NH_4]^+$: 450, $[M+H]^+$: 433.

Ejemplo 246

Síntesis del intermediario α-metoxicinamato, 2*S*-2-metoxi-3-(4-hidroxifenil)propanoato de etilo (e)

Esquema



Etapa 1a: 3-hidroxi-2-metoxi-3-[4-(fenilmetoxi)fenil]propanoato de metilo (a)

Se enfrió bis(trimetilsilil)amiduro de sodio (440 ml, 0,44 mol, 1,0 M en THF) a -70°C bajo una atmósfera de nitrógeno. Se añadió una solución de 4-benciloxibenzaldehído (85 g, 0,4 mol) y metoxiacetato de metilo (52 g, 0,5 mol) en THF (0,5 L) por goteo a -70°C a lo largo de 2 horas y se agitó la mezcla durante una hora. Se añadió una solución de HCl concentrado (85 ml) y agua (85 ml) a -70°C. Se dejó que la solución resultante se calentara hasta la temperatura ambiente y se extrajo

con MTBE (2 x 0,5 L). Se lavaron los extractos combinados con salmuera (0,5 L), se secaron ($MgSO_4$), se filtraron y se concentraron, para obtener 133 g de un aceite rojo.

Etapa 1b y Etapa 1c: 3-(4-hidroxifenil)-2-metoxipropanoato de metilo (b)

Se disolvió 3-hidroxi-2-metoxi-3-[4-(fenilmetoxi)fenil]propanoato de metilo (133 g, bruto de antes) en CH_2Cl_2 (700 ml) y se añadió piridina (129 ml, 1,6 mol). Se enfrió la solución resultante en un baño de agua y se añadió anhídrido trifluoroacético (85 ml, 0,6 mol) por goteo bajo nitrógeno. Se retiró el baño y se agitó la mezcla a temperatura ambiente durante 16 horas. Se enfrió la solución a 0°C y se añadió HCl concentrado (150 ml) en agua (1 L) por goteo. Se separó la capa orgánica y se concentró y se añadió acetato de etilo (0,5 L). Se trató la solución resultante con hidrógeno gaseoso bajo 50 psi en presencia de Pd 5%-C (80 g, 50% humedecido con agua) a temperatura ambiente durante 16 horas. Se filtró el catalizador y se concentró el filtrado a vacío para obtener 122 g de aceite. ^{1}H-RMN ($CDCl_3$): 7,1 (2H, d); 6,7 (d, 2H); 5,4 (s, 1H); 4,0 (m, 1H); 3,7 (s, 3H); 3,4 (s, 3H); 3,0 (m, 1H). MS (ES)=209,2 (M-1).

Etapa 1d: Ácido 3-(4-hidroxifenil)-2-metoxipropanoico (c)

Se disolvió 3-(4-hidroxifenil)-2-metoxipropanoato de metilo (132 g, 0,631 mol) en metanol (700 ml) y se añadió hidróxido de sodio 5N (631 ml, 3,16 mol) por goteo a temperatura ambiente. Se agitó la solución durante 16 horas a temperatura ambiente. Se eliminó el metanol a vacío y se añadió agua (500 ml). Se extrajo la mezcla con MTBE (2 x 500 ml). Se llevó la solución acuosa a pH=1 con HCl concentrado y luego se extrajo con MTBE (2 x 500 ml). Se secaron los extractos orgánicos ($MgSO_4$), se filtraron y se concentraron a vacío, para obtener el ácido racémico como un aceite (110 g), el cual cristalizó con el reposo. ^{1}H-RMN (DMSO): 7,0 (d, 2H); 6,6 (d, 2H); 4,0

(m, 1H); 2,8 (m, 2H). MS (ES)= 195,1 (M-1).

Etapa 2: ácido (2S)-3-(4-hidroxifenil)-2-metoxipropanoico (d)

Sal de cinconidina de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropanoico.

Se calentó una suspensión consistente en ácido 3-(4-hidroxifenil)-2-metoxipropanoico (21,21 g, 0,1081 mol), (-)-cinconidina (31,83 g, 0,1081 mol) y THF (424 ml) brevemente a reflujo para obtener una solución de color rojo-marrón. Se enfrió la mezcla hasta la temperatura ambiente y se agitó durante 3 días. Se enfrió la suspensión resultante a 0°C durante 4 horas y se filtró, para obtener aproximadamente 17,06 g de la sal de cinconidina (71,2% ee por HPLC quiral). Se suspendió la sal de cinconidina en THF, se calentó a reflujo durante 1 hora y se enfrió a temperatura ambiente durante la noche. Se enfrió la mezcla a 0°C durante 2 horas y se filtró para obtener aproximadamente 14,87 g de la sal de cinconidina (83,0% ee por HPLC quiral). Se suspendió la sal de cinconidina de nuevo en THF y se calentó a reflujo durante 1 hora y se enfrió a la temperatura ambiente. Se enfrió la mezcla a o 0 °C durante 2 horas y se filtró para obtener aproximadamente 12,87 g (24%) de la sal de cinconidina del ácido (2S)-3-(4-hidroxifenil)-2-metoxipropanoico (91,4% ee por HPLC quiral).

Ácido (2S)-3-(4-hidroxifenil)-2-metoxipropanoico

Se suspendió la sal de cinconidina del ácido (2S)-3-(4-hidroxifenil)-2-metoxipropanoico (73,59 g, 0,15 mol) (98,1% ee por HPLC quiral) en una solución 1N de HCl (750 ml) y se extrajo con metil terc-butil éter (3 x 200 ml). Se secaron los extractos combinados (Na_2SO_4) y se concentraron para obtener aproximadamente 24,12 g (82%) de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropanoico (96,7% ee por HPLC quiral). ^1H RMN (DMSO-d_6): δ 2,72-2,89 (m, 2H), 3,21 (s, 3H), 3,8-3,87 (m, 1H), 6,64-6,67 (d,

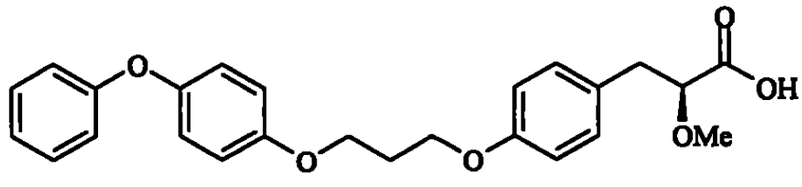
2H), 6,97-7,02 (d, 2H), 9,15 (s, amplio, 1H), 12,62 (s, amplio, 1H). MS (ES^+) m/z 219,0 ($[M+Na]^+$). MS (ES^-) m/z 195,1 ($[M-H]^-$). $[\alpha]_D$ = -2,2° (c = 1, MeOH).

Etapa 3: 2*S*-2-metoxi-3-(4-hidroxifenil)propanoato de etilo (e)

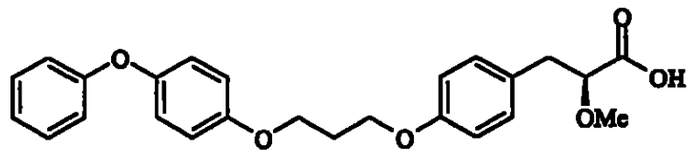
Se mezcló una solución de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropanoico (35 g) en 140 ml de etanol con 5,66 ml de ácido sulfúrico concentrado y se agitó a temperatura ambiente hasta completarse, según indicó la HPLC. Se eliminó el etanol mediante destilación a vacío (55°C/28" Hg) y se añadieron 110 ml de agua. Se ajustó el pH a aproximadamente 7 a 8 con bicarbonato de sodio y se extrajo la mezcla con 50 ml de acetato de etilo (3 x 50 ml). Se combinaron las capas orgánicas, se lavaron con 50 ml de una solución al 20% NaCl, se secaron con 15 g de sulfato de magnesio y se concentró el producto para obtener 2*S*-2-metoxi-3-(4-hidroxifenil)propanoato de etilo como un aceite. ^{1}H-RMN ($CDCl_3$): 7,1(d, 2H); 6,7(d, 2H); 4,2(m, 2H); 3,9(m, 1H); 3,6(s, 3H); 2,95(m, 2H); 1,25(t, 3H). MS (ES): 223,2 (M-1).

Ejemplo 247

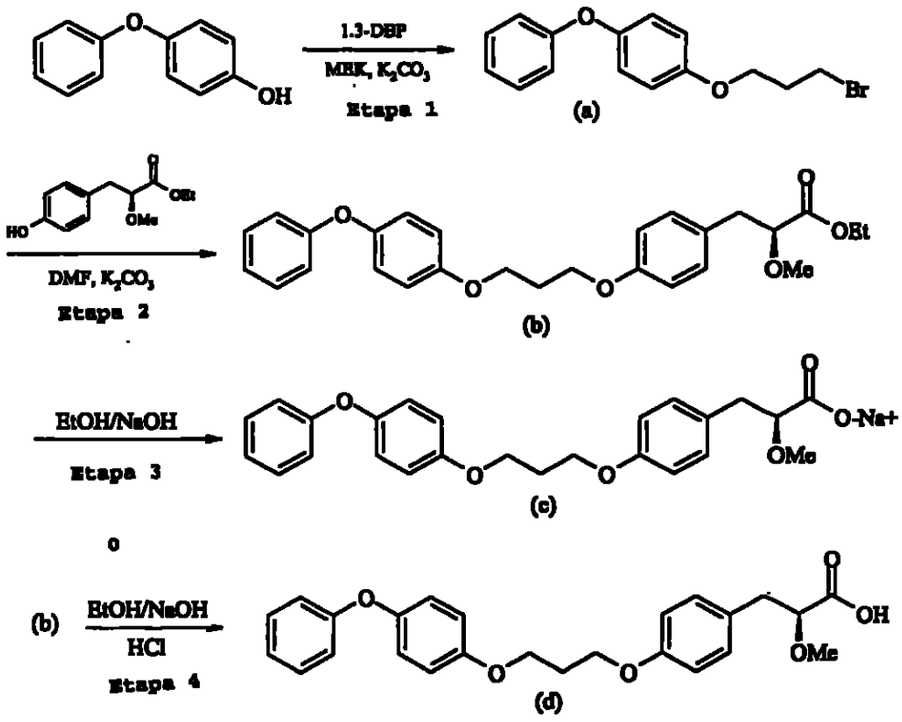
Síntesis de ácido 2*S*-2-metoxi-3-{4-[3-(4-fenoxifenoxi)-propoxi]fenil}propanoico



Esquema



Scheme



Etapa 1: 1-bromo-3-(4-fenoxifenil)propano (a)

A un matraz de 22 L se añadieron 4-fenoxifenol (900 g), 1,3-dibromopropano (5.858 g), carbonato de potasio en polvo (1.335 g) y metiletilcetona (9 L). Se agitó la mezcla durante 30 minutos a 22°C. Se calentó la suspensión de color blanco sucio hasta un reflujo suave (~83°C) y se mantuvo a esa temperatura durante 16 horas. Se enfrió la suspensión de color blanco sucio a 25°C y se filtró a vacío, lavando la torta de sales inorgánicas con

metiletilcetona (4 L). Se concentró el filtrado en un evaporador rotatorio mientras se aumentaba la temperatura a 90°C bajo un vacío casero. Después de cesar la condensación, se mantuvo el aceite a 90°C a vacío durante dos horas más para asegurarse de que el resto del 1,3-dibromopropano estaba por debajo del 8% por análisis de GC (cromatografía gaseosa). Se disolvió el residuo en 3L de alcohol metílico y se enfrió la suspensión blanca lentamente hasta aproximadamente 0-5°C y se mantuvo a esa temperatura durante la noche. Se filtró el producto, se lavó con alcohol metílico frío (6 L) y se secó a 30°C durante aproximadamente 20 horas, para obtener aproximadamente 1.234 g de compuesto (a) en un rendimiento del 84% (99,4% puro por GC). ^{1}H-RMN ($CDCl_3$): 7,3(2H, m), 7,1(2H, m), 7,0(2H, m), 6,9(2H, m), 4,1(2H, m); 3,6(2H, m); 2,3(2H, m).

Etapa 2: 2*S*-2-metoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propanoato de etilo (b)

Se cargaron 1-bromo-3-(4-fenoxifenil)propano (1.337 g), 2*S*-2-metoxi-3-(4-hidroxifenil)propanoato de etilo (957 g) y dimetilformamida (5 L) en un matraz de 22 L. Después de obtener una solución, se añadió carbonato de potásio en polvo (1.770 g). Se agitó la mezcla durante 16 horas a temperatura ambiente y luego se apagó por adición de agua (6,5 L), manteniendo al mismo tiempo la temperatura a 20 a 30°C. Se extrajo la capa acuosa tres veces con acetato de etilo (5 L cada una). Se lavaron las capas orgánicas combinadas con agua (3 x 4 L) y salmuera (4 L). Se secó luego la capa orgánica con sulfato de sodio (1.000 g), se filtró y se lavó con acetato de etilo. Se concentró el filtrado, para obtener aproximadamente 1.974 g de (b) bruto. ^{1}H-RMN ($CDCl_3$): 7,3(m, 2H); 7,2(d, 2H); 7,0(m, 1H); 6,95(m, 4H); 6,9(d, 2H); 6,85(d, 2H); 4,2(m, 2H); 4,15(m, 4H); 3,9(t, 1H); 3,39(s, 3H); 2,99(m, 2H); 2,25(m, 2H); 1,25(m, 3H). MS (ES)= 468,2 ($M+NH_4$).

Etapa 3: ácido 2*S*-2-metoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propanoico, sal sódica (c)

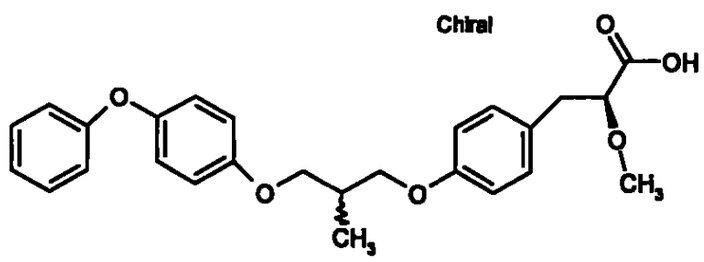
A un matraz de 22L, se añadió una solución de compuesto (b) (987 g) en etanol (10 L) y se agitó, seguido de adición de NaOH 5N (4,4 L) a lo largo de 60 minutos a una temperatura de 20 a 30°C. Se agitó la suspensión durante aproximadamente una hora a temperatura ambiente y se enfrió después a 10-15°C, manteniéndose a esa temperatura durante 1 hora, y se filtró. Se lavó el sólido con alcohol (8 L) y MTBE (50 L), para obtener el compuesto (c), que puede ser además purificado por recristalización a partir de acetato de etilo: ^{1}H-RMN (DMSO): 7,35(m, 2H); 7,1(m, 3H); 7,0(m, 4H); 6,9(d, 2H); 6,8(d, 2H); 4,1(m, 4H); 3,4(t, 1H); 3,1(s, 3H); 2,8(dd, 1H); 2,6(m, 1H); 2,15(m, 2H). MS (ES): 421,2 (M-1).

Etapa 4: ácido 2*S*-2-metoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propanoico (d)

Se disolvió éster etílico de ácido. 2-metoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propiónico (b) (12,15 g, 27 mmol) en etanol (250 ml) a temperatura ambiente y se añadió por goteo NaOH 5N (54 ml, 270 mmol). Se agitó la suspensión a temperatura ambiente durante 2 horas. Se diluyó la mezcla con agua (250 ml) y se añadió por goteo HCl conc. (33 ml). Se agitó la suspensión resultante a temperatura ambiente durante aproximadamente 2 horas. Se filtró el sólido blanco y se secó a vacío a 70°C durante 16 horas, para obtener aproximadamente 10,5 g del compuesto (d). ^{1}H-RMN ($CDCl_3$): 7,3 (m, 2H), 7,18 (d, 2H), 7,07 (t, 1H), 6,9 (m, 8H), 4,19 (m, 4H), 4,0 (m, 1H), 3,4 (s, 3H), 3,0 (m, 2H), 2,25 (m 2H). MS (ES): 421,2 (M-1).

Ejemplo 248

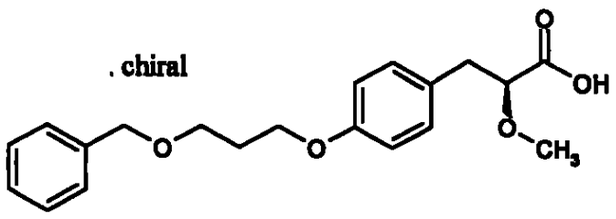
Ácido (2*S*)-(2'*RS*)-2-metoxi-{4-[2'-metil-3-(4-fenoxifenoxi)propoxi]fenil}propiónico



Se trató una solución de ácido (2*S*)-2-metoxi-3-{4-[2-(4-fenoxifenoxi)propoxi]fenil}propiónico y ácido {4-[2-metilen-3-(4-fenoxifenoxi)propoxil]fenil}propiónico del Ejemplo 74 en etanol con Pd/C y H_2 a lo largo de 2 horas a 1 atm. Se filtró la mezcla a través de celita y se concentró a sequedad, para obtener el compuesto del título como una mezcla de isómeros. MS (ES) para $C_{26}H_{28}O_6$ $[M+NH_4]^+$: 454,2, $[M-H]^-$: 435,2.

Ejemplo 249

Ácido 2(S)-3-[4-(3-benciloxipropoxi)fenil]-2-metoxipropiónico

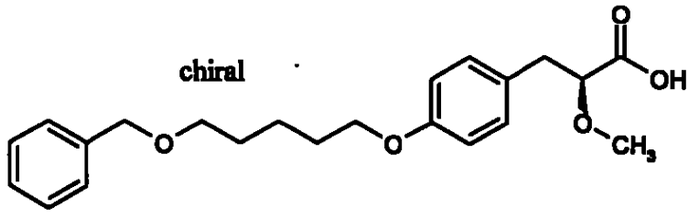


Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxifenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa C) mediante la reacción-escisión de Mitsunobu (Procedimiento estándar G). ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,4-7,2 (m, 5H), 7,14 (d, 2H, *J*=8,6), 6,82 (d, 2H, *J*=8,6), 4,52 (s, 2H), 4,06 (t, 2H, *J*=6,2), 3,97 (dd, 1H, *J*=7,2, 4,6), 3,65 (t, 2H,

J=6,2), 3,39 (s, 3H), 3,09 (dd, 1H, J=14,4, 4,4), 2,95 (dd, 1H, J=14,4, 7,2), 2,07 (q, 2H, J=6,2).

Ejemplo 250

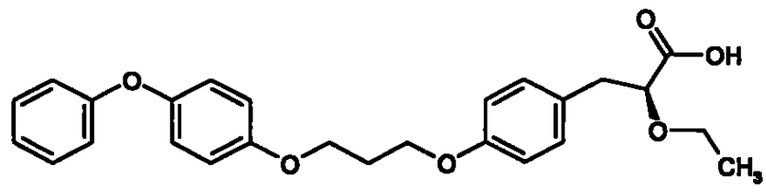
Ácido (2S)-3-[4-(5-benciloxipentiloxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-[4-(3-hidroxifenil]-2-metoxipropiónico unido a resina de Wang (Ejemplo 94, Etapa C) mediante la reacción-escisión de Mitsunobu (Procedimiento estándar G) con 5-benziloxipentan-1-ol. ^{1}H-RMN (200,15 MHz, $CDCl_3$): 7,4-7,3 (m, 5H), 7,14 (d, 2H, J=8,6), 6,81 (d, 2H, J=8,6), 4,51 (s, 2H), 4,0-3,9 (m, 3H), 3,50 (t, 2H, J=6,2), 3,39 (s, 3H), 3,08 (dd, 1H, J=14,2, 4,3), 2,95 (dd, 1H, J=14,2, 7,5), 1,9-1,5 (m, 6H).

Ejemplo 251

Ácido (2S)-2-etoxi-{4-[3-(4-fenoxifenoxi)propoxil]fenil}-propiónico



Etapa A

Éster etílico del ácido (2S)-2-hidroxi-3-(4-hidroxifenil)propiónico

Se agitó una solución de ácido (2S)-2-hidroxi-3-(4-hidroxifenil)propiónico en etanol y H_2SO_4 (catalítico) durante la noche. Se concentró la mezcla a seque-

dad y se reconstituyó en acetato de etilo. Se lavó la capa orgánica con $NaHCO_3$, se secó sobre $MgSO_4$ y se concentró a sequedad, para obtener el producto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,03 (d, 2H, *J* = 8,6), 7,00 (d, 2H, *J* = 8,7), 6,72-6,77 (m, 1H), 4,44-4,30 (m, 1H), 4,22 (c, 2H, *J* = 7,9), 3,13-2-77 (m, 2H), 1,24 (t, 3H, *J* = 7,9).

Etapa B

Éster etílico del ácido (2S)-2-hidroxi-3-{4-[3-(4-fenoxi-fenoxi)propoxi]fenil}propiónico

A una solución del compuesto (Etapa A) en DMF, se añadieron $CsCO_3$ (1,0 eq) y 4-(3-bromopropoxi)-1-fenoxibenceno (1,1 eq) (Ejemplo 244, Etapa A). Se agitó la mezcla a temperatura ambiente durante la noche. Se concentró el solvente a vacío y se añadió acetato de etilo. Se lavó la capa orgánica con agua y se concentró para obtener, tras cromatografía en gel de sílice, el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,28 (dd, 2H, *J* = 8,3, 0,8), 7,17-6,84 (m, 11H), 4,44-4,36 (m, 1H), 4,28-4,12 (m, 6H), 3,13-2,87 (m, 2H), 2,79-2,76 (m, 1H), 2,32-2,19 (m, 2H), 1,29 (t, 3H, *J* = 7,9).

Etapa C

Éster etílico del ácido 2-etoxi-3-{4-[3-(4-fenoxifenoxi)-propoxi]fenil}propiónico

Se agitó una solución de éster etílico de ácido (2S)-2-hidroxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propiónico, AgO_2 (1,5 eq) y yoduro de etilo (exceso) en diclorometano a lo largo de 10 días. Se filtró la mezcla bruta a través de celita y se concentró a sequedad. Se purificó el compuesto por cromatografía, para obtener el producto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,34-7,26 (m, 2H), 7,18-6,82 (m, 11H), 4,18-4,17 (m, 6H), 4,01-3,94 (m, 1H), 3,68-3,53 (m, 1H), 3,43-3,28 (m, 1H), 2,96 (d, 2H, *J* = 6,5), 2,25 (q, 2H, *J* = 6,2), 1,20 (dt, 6H, *J* = 12,6, 7,3).

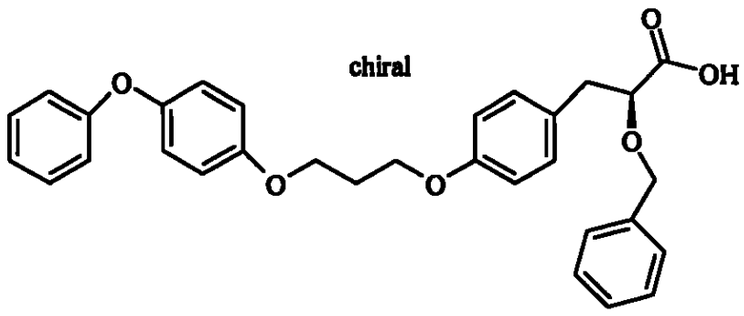
Etapa D

Ácido (2S)-2-etoxi-{4-[3-(4-fenoxifenoxi)propoxil]fenil}-propiónico

Se preparó el compuesto del título a partir de éster etílico de ácido 2-etoxi-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}propiónico (Etapa C) por el procedimiento de hidrólisis estándar C (LiOH). MS (ES) para $C_{26}H_{28}O_6$ $[M+NH_4]^+$: 454,2, $[M-H]^-$:435,2.

Ejemplo 252

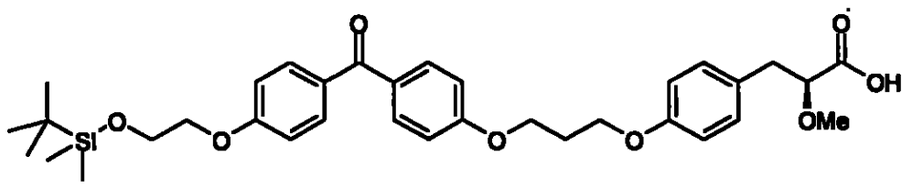
Ácido (2S)-2-benciloxi-3-{4-[3-(4-fenoxifenoxi)propoxi]-fenil}propiónico



Se preparó el compuesto del título como en el Ejemplo 251 utilizando bromuro de bencilo como agente alquilante. La hidrólisis según el Procedimiento estándar C del correspondiente derivado de éster etílico dio el compuesto del título. MS (ES) para $C_{31}H_{30}O_6$ $[M+NH_4]^+$: 516,2, $[M-H]^-$: 497,2.

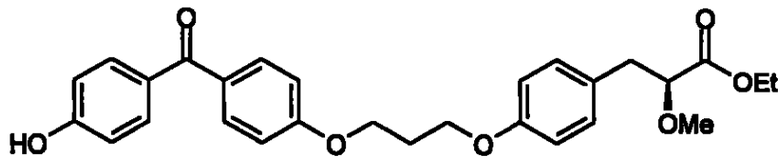
Ejemplo 253

Ácido (2S)-3-{4-[3-(4-{4-[2-(terc-butildimetilsilanil-oxi)etoxi]benzoil}fenoxi)propoxi]fenil}-2-metoxipropióni-co



Etapa A

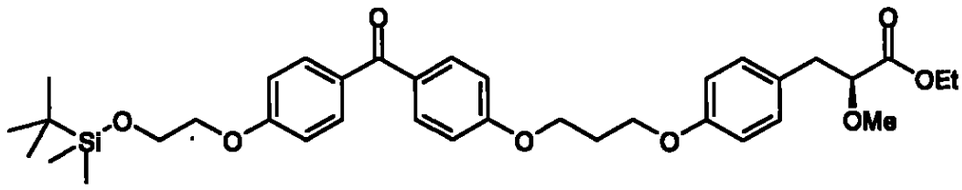
Éster etílico del ácido (2S)-3-{4-{3-[4-(4-hidroxibenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico



Se añadió ácido sulfúrico concentrado (0,05 mL) a una solución de ácido (2S)-3-(4-{3-[4-(4-hidroxibenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico (0,18 mmol, 80 mg) (Ejemplo 170) en etanol (20 mL) a temperatura ambiente. Se agitó la mezcla a temperatura ambiente durante tres días y se concentró el solvente a vacío. Después de añadir agua, se neutralizó la mezcla con $NaHCO_3$ sólido y se extrajo con acetato de etilo (3 x 15 mL). Se secaron las capas orgánicas combinadas sobre $MgSO_4$, se filtraron y se concentraron a vacío, para obtener el compuesto del título. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,76 (d, 2H, J=8,6), 7,71 (d, 2H, J=8,8), 7,13 (d, 2H, J=8,6), 6,97-6,80 (m, 6H), 6,37 (s a, 1H), 4,25-4,10 (m, 6H), 3,93 (dd, 1H, J=7,0, 5,6), 3,35 (s, 3H), 2,95 (m, 2H), 2,27 (q, 2H, J=5,9), 1,23 (t, 3H, J=7,1).

Etapa B

Éster etílico del ácido (2S)-3-{4-[3-(4-{4-[2-(terc-butildimetilsilaniloxi)etoxi]benzoil}fenoxi)propoxi]fenil}-2-metoxipropiónico



Se añadió azodicarboxilato de diisopropilo (0,2 mmol, 0,04 mL) por goteo a una solución de 2-(terc-

butildimetilsilaniloxi)etanol (0,26 mmol, 46 mg) (Ejemplo 122, Etapa A), éster etílico de ácido (2S)-3-{4-{3-[4-(4-hidroxibenzoil)fenoxi]propoxi}fenil)-2-metoxipropiónico (0,13 mmol, 65 mg) y trifenilfosfina (0,2 mmol, 38 mg) en tolueno anhidro (2 mL) a 0°C bajo nitrógeno. Se agitó la mezcla durante la noche a temperatura ambiente, se apagó con agua y se extrajo con acetato de etilo (3 x 15 mL). Se secaron las capas orgánicas combinadas sobre $MgSO_4$, se filtraron y se concentraron a vacío. Se cromatografió la mezcla bruta en gel de sílice usando una mezcla 4/1 de hexano/EtOAc como eluyente, para obtener el producto del título. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,76 (d, 4H, *J*=8,9), 7,13 (d, 2H, *J*=8,6), 6,96 (d, 4H, *J*=8,6), 6,83 (d, 2H, *J*=8,6), 4,26-4,09 (m, 8H), 4,02-3,87 (m, 3H), 3,35 (s, 3H), 2,97 (m, 2H), 2,28 (q, 2H, *J*=5,9), 1,23 (t, 3H, *J*=7,1), 0,91 (s, 9H), 0,11 (s, 6H).

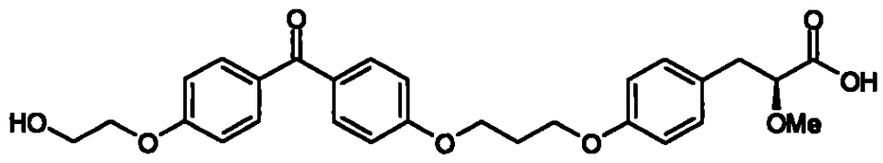
Etapa C

Ácido (2S)-3-{4-[3-(4-{4-[2-(terc-butildimetil-silanil-oxi)etoxi]benzoil}fenoxi)propoxi]fenil}-2-metoxi-propiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-{4-[3-(4-{4-[2-(terc-butildimetilsilaniloxi)etoxi]benzoil}fenoxi)propoxi]fenil}-2-metoxipropiónico por el procedimiento estándar de hidrólisis C (LiOH). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,76 (dd, 4H, *J*=8,6, 1,6), 7,15 (d, 2H, *J*=8,6), 6,95 (dd, 4H, *J*=8,8, 1,6), 6,83 (d, 2H, *J*=8,6), 4,24 (t, 2H, *J*=6,0), 4,17-4,09 (m, 5H), 4,02-3,94 (m, 3H), 3,39 (s, 3H), 3,12-2,90 (m, 2H), 2,27 (q, 2H, *J*=6,0), 0,91 (s, 9H), 0,11 (s, 6H).

Ejemplo 254

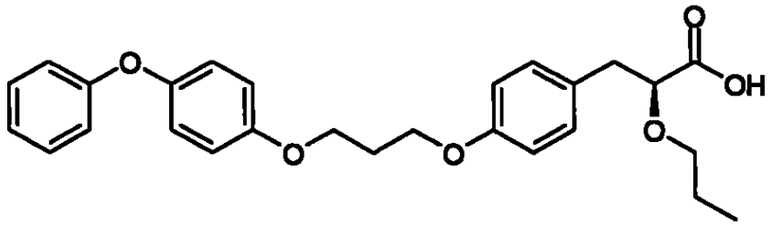
Ácido (2S)-3-[4-(3-{4-[4-(2-hidroxietoxi)benzoil]fenoxi}-propoxi)fenil]-2-metoxipropiónico



Se disolvió el compuesto ácido (2S)-3-{4-[3-(4-{4-[2-(terc-butildimetilsilaniloxi)etoxi]benzoil}fenoxi)propoxi]fenil}-2-metoxipropiónico (Ejemplo 253, Etapa C) (0,05 mmol, 30 mg) en 5 mL de una mezcla de ácido acético, THF y H_2O (3:1:1) y se agitó a temperatura ambiente durante 2 horas. Se diluyó la mezcla con H_2O y se extrajo con acetato de etilo (4 x 20 mL). Se secaron las capas orgánicas combinadas sobre $MgSO_4$, se filtraron y se concentraron a vacío, para obtener el compuesto del título. MS (ES) para $C_{28}H_{30}O_8$ $[M+H]^+$: 495,1

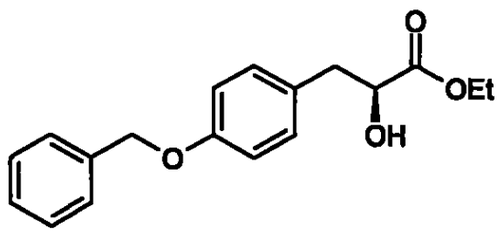
Ejemplo 255

Ácido (2S)-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-propoxipropiónico



Etapa A

Éster etílico del ácido 3-(4-benciloxifenil)-2-hidroxi-propiónico

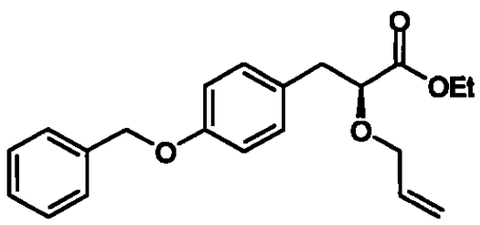


Se sometió a reflujo durante la noche una mezcla de éster etílico de ácido 2-hidroxi-3-(4-hidroxife-nil)propiónico (Ejemplo 251, Etapa A) (5,2 mmol, 1,1 g), bromuro de bencilo (5,2 mmol, 0,62 mL) y carbonato de potasio (15,7 mmol, 2,2 g) en acetonitrilo (20 mL). Se enfrió la mezcla hasta la temperatura ambiente y se concentró a sequedad, para obtener un producto bruto, que fue purificado por cromatografía en gel de sílice para obtener el producto del título.

MS (ES) para $C_{18}H_{20}O_4$ $[M+NH_4]^+$: 318,3

Etapa B

Éster etílico del ácido (2S)-2-aliloxi-3-(4-benciloxife-nil)propiónico

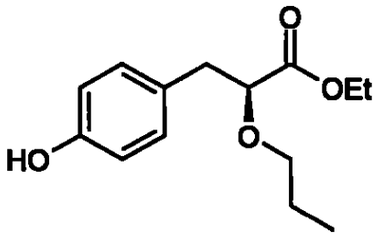


Se añadió óxido de plata (I) (5,7 mmol, 1,3 g) a una mezcla de éster etílico de ácido (S)-3-(4-benciloxifenil)-2-hidroxipropiónico (3,8 mmol, 1,2 g) y bromuro de alilo (19 mmol, 1,6 mL) en DMF (10 mL) a temperatura ambiente y se calentó la mezcla de reacción a 50°C durante 20 horas. Después de enfriar a temperatura am-

biente, se diluyó la mezcla con H_2O y se extrajo con acetato de etilo (5 x 25 mL). Se lavaron las capas orgánicas combinadas con agua (4 x 20 mL) y salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. Se cromatografió la mezcla bruta en gel de sílice usando una mezcla 4/1 de hexano/acetato de etilo como eluyente, para obtener el producto del título. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,46-7,32 (m, 5H), 7,18 (d, 2H, J=8,9), 6,91 (d, 2H, J=8,9), 5,91-5,72 (m, 1H), 5,25-5,12 (m, 2H), 5,05 (s, 2H), 4,11-4,03 (4H, m), 3,94-3,84 (m, 1H), 2,99 (d, 2H, J=7,0), 1,23 (t, 3H, J=7,0).

Etapa C

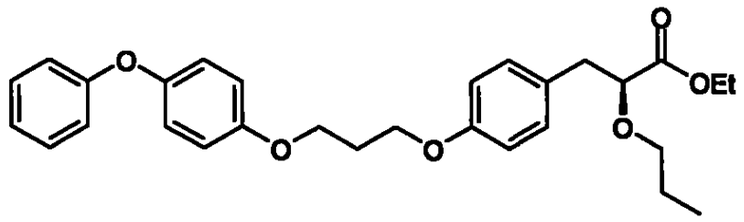
Éster etílico del ácido (2S)-3-(4-hidroxifenil)-2-propoxipropiónico



Se agitó una mezcla de éster etílico de ácido (S)-2-aliloxi-3-(4-benciloxifenil)propiónico (1,33 mmol, 450 mg) y Pd 10%/C (45 mg) en EtOH (15 mL) bajo una atmósfera de hidrógeno (1 atm) durante 18 horas. Se filtró la mezcla a través de celita y se concentró a vacío, para obtener el producto del título. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,10 (d, 4H, J=8,6), 6,73 (d, 2H, J=8,4), 5,90 (s a, 1H), 4,16 (c, 2H, J=7,3), 3,94 (t, 1H, J=6,7), 3,53-3,45 (m, 1H), 3,27-3,16 (m, 1H), 2,93 (d, 2H, J=6,5), 1,54 (m, 2H), 1,22 (t, 3H, J=7,3), 0,84 (t, 3H, J=7,5).

Etapa D

Éster etílico del ácido (2S)-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-propoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (S)-3-(4-hidroxifenil)-2-propoxipropiónico y bromuro de 3-(4-fenoxifenoxi)propilo (Ejemplo 244) usando el Procedimiento estándar I. Se purificó el producto por cromatografía en gel de sílice utilizando una mezcla 9/1 de hexano/acetato de etilo como eluyente, para obtener el producto del título. MS (ES) para $C_{29}H_{34}O_6$ $[M+NH_4]^+$: 496,3.

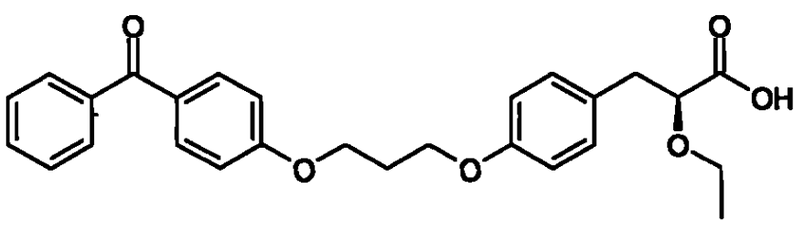
Etapa E

Ácido (2S)-3-{4-[3-(4-fenoxifenoxi)propoxi]fenil}-2-propoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (S)-3-{4-[3-(4-fenoxifenoxi)-propoxi]fenil}-2-propoxipropiónico mediante el procedimiento estándar de hidrólisis C (LiOH). MS (ES) para $C_{27}H_{30}O_6$ $[M-H]^-$: 449,2.

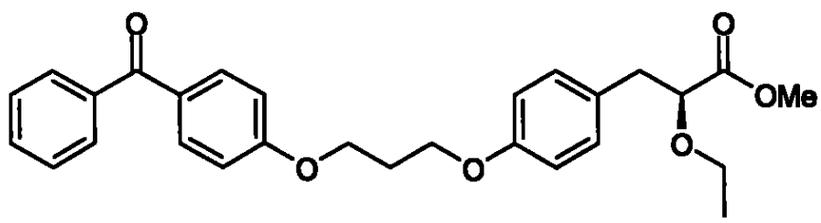
Ejemplo 256

Ácido (2S)-3-{4-[3-(4-benzoilfenoxi)propoxi]fenil}-2-etoxipropiónico



Etapa A

Éster metílico del ácido (2S)-3-{4-[3-(4-benzoilfenoxi)-propoxi]fenil}-2-etoxipropiónico



Se preparó el compuesto del título a partir de éster metílico de ácido 2-etoxi-3-(4-hidroxifenil)-propiónico y [4-(3-bromopropoxi)fenil]fenilmetanona (preparada a partir de 4-hidroxibenzofenona siguiendo el mismo procedimiento que en el Ejemplo 132, Etapas B to D, utilizando el Procedimiento estándar I. Se purificó el producto por cromatografía en gel de sílice usando una mezcla de hexano/acetato de etilo (4/1) como eluyente, para obtener el producto racémico. Se sometió esta mezcla racémica a separación por HPLC quiral, para obtener el enantiómero puro. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,83-7,72 (m, 4H), 7,57-7,42 (m, 3H), 7,14 (d, 2H, *J*=8,8), 6,96 (d, 2H, *J*=8,8), 6,83 (d, 2H, *J*=8,6), 4,25 (t, 2H, *J*=6,1), 4,15 (t, 2H, *J*=6,2), 3,98 (dd, 1H, *J*=7,1, 6,0), 3,70 (s, 3H), 3,58 (dd, 1H, *J*=9,1, 7,0), 3,33 (dd, 1H, *J*=9,1, 7,0), 2,94 (m, 2H), 2,28 (q, 2H, *J*=6,2), 1,25 (t, 3H, *J*=7,3).

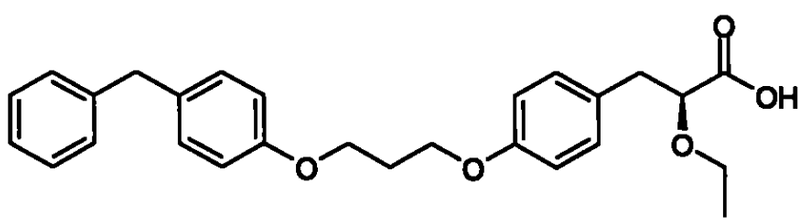
Etapa B

Ácido (2S)-3-{4-[3-(4-benzoilfenoxi)propoxi]fenil}-2-etoxipropiónico

Se preparó el compuesto del título a partir de éste metílico de ácido (S)-3-{4-[3-(4-benzoilfenoxi)-propoxi]fenil}-2-etoxipropiónico mediante el procedimiento estándar de hidrólisis C (LiOH). MS (ES) para $C_{27}H_{28}O_6$ $[M-H]^-$: 447,1.

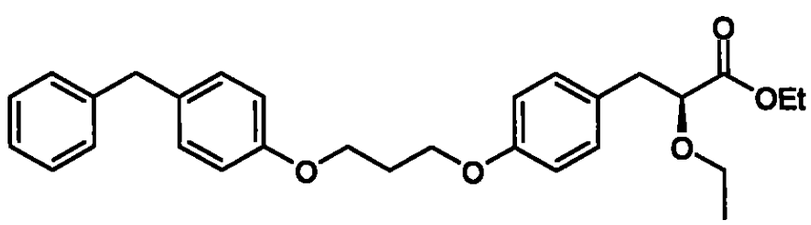
Ejemplo 257

Ácido (2S)-3-{4-[3-(4-bencilfenoxi)propoxi]fenil}-2-etoxipropiónico



Etapa A

Éster etílico de ácido (2S)-3-{4-[3-(4-bencilfenoxi)propoxi]fenil}-2-etoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (S)-2-etoxi-3-(4-hidroxifenil)-propiónico y bromuro de 3-(4-bencilfenoxi)propilo (preparado a partir de 4-bencilfenol siguiendo el mismo procedimiento que en el Ejemplo 132, Etapas B a D, utilizando el Procedimiento estándar I. Se purificó el producto por cromatografía en gel de sílice empleando una mezcla de hexano/acetato de etilo (4/1) como eluyente, para obtener el producto del título. MS (ES) para $C_{29}H_{34}O_5$ $[M+NH_4]^+$: 480,2.

Etapa B

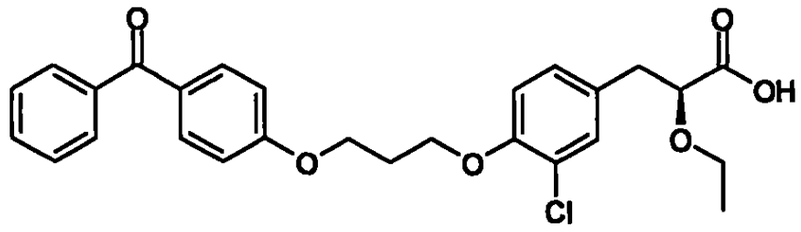
Ácido (2S)-3-{4-[3-(4-bencilfenoxi)propoxi]fenil}-2-etoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (S)-3-{4-[3-(4-bencilfenoxi)-propoxi]fenil}-2-etoxipropiónico mediante el procedimien-

to estándar de hidrólisis C (LiOH). MS (ES) para $C_{27}H_{30}O_5$ $[M-H]^-$: 433,1.

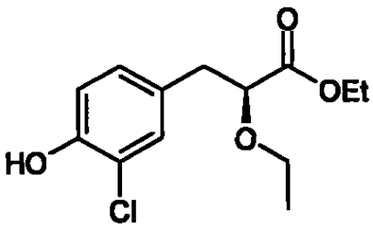
Ejemplo 258

Ácido (2S)-3-{4-[3-(4-benzoilfenoxi)propoxi]-3-clorofenil}-2-etoxipropiónico



Etapa A

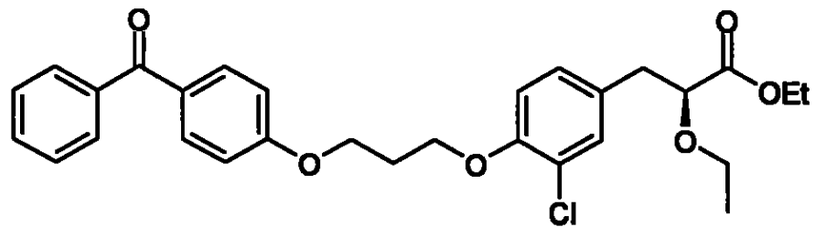
Éster etílico de ácido (2S)-3-(3-cloro-4-hidroxifenil)-2-etoxipropiónico



Se añadió *N*-clorosuccinimida (2,1 mmol) a una solución de éster etílico de ácido (S)-2-etoxi-3-(4-hidroxifenil)propiónico (2,1 mmol) en acetonitrilo (12 mL) a temperatura ambiente y se agitó la mezcla a la misma temperatura durante 5 días. Se evaporó el solvente a vacío y se lavó el residuo con CCl_4. Se filtró la suspensión resultante y se concentró el filtrado a vacío y se cromatografió en gel de sílice usando una mezcla 9/1 de hexano/EtOAc como eluyente para obtener el producto del título. MS (ES) para $C_{13}H_{17}ClO_4$ $[M-H]^-$: 271,0

Etapa B

Éster etílico de ácido (2S)-3-{4-[3-(4-benzoilfenoxi)propoxi]-3-clorofenil}-2-etoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (S)-2-etoxi-3-(3-cloro-4-hidroxifenil)propiónico y [4-(3-bromopropoxi)fenil]fenilmetanona (Ejemplo 256) usando el Procedimiento estándar I. Se purificó el producto por cromatografía en gel de sílice usando una mezcla 4/1 de hexano/acetato de etilo como eluyente, para obtener el producto del título. MS (ES) para $C_{29}H_{31}ClO_6$ $[M+H]^+$: 511,1.

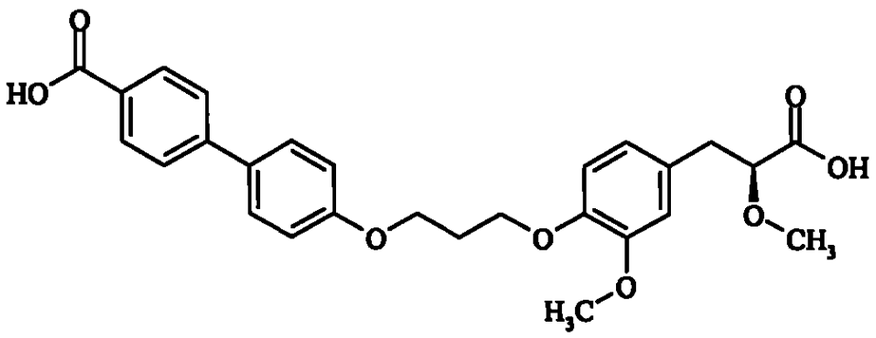
Etapa C

Ácido (2S)-3-{4-[3-(4-benzoilfenoxi)propoxi]-3-clorofenil}-2-etoxipropiónico

Se preparó el compuesto del título a partir de éster metílico de ácido (S)-3-{4-[3-(4-benzoilfenoxi)-propoxi]-3-clorofenil}-2-etoxipropiónico mediante el procedimiento estándar de hidrólisis C (LiOH). ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,82-7,72 (m, 4H), 7,56-7,43 (m, 3H), 7,07 (dd, 1H, J=8,8, 2,0), 6,97 (d, 2H, J=8,9), 6,86 (d, 2H, J=8,3), 4,31 (t, 2H, J=6,0), 4,21 (t, 2H, J=6,0), 4,10-4,02 (m, 1H), 3,66-3,44 (m, 2H), 3,10-2,87 (m, 2H), 2,33 (q, 2H, J=6,2), 1,20 (t, 3H, J=7,0).

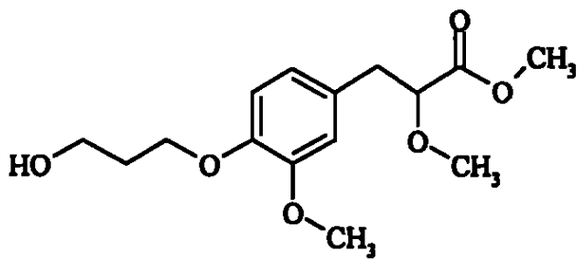
Ejemplo 259

Ácido (2*S*)-4'-{3-[4-(2-carboxi-2-metoxietil)-2-metoxifenoxi]propoxi}bifenil-4-carboxílico



Etapa A

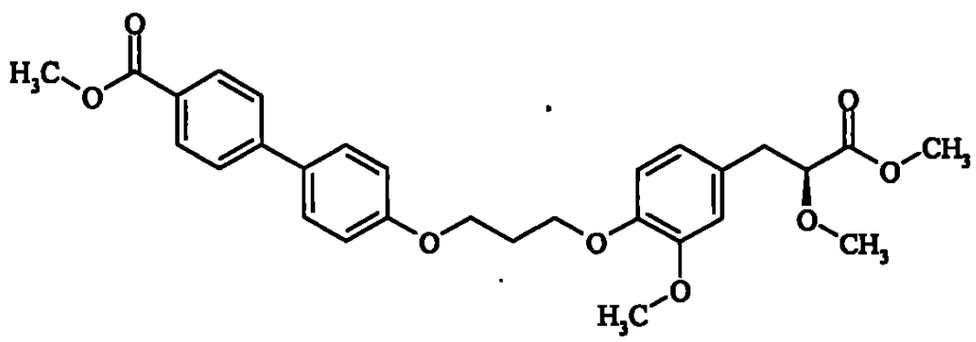
Éster metílico del ácido 3-[4-(3-hidroxipropoxi)-3-metoxifenil]-2-metoxipropiónico



Se trató una mezcla de éster metílico de ácido 3-(4-hidroxi-3-metoxifenil)-2-metoxipropiónico (Ejemplo 130, Etapa B) y 3-(*terc*-butildimetilsilaniloxi)-propan-1-ol según las condiciones estándar de Mitsunobu B usando DIAD y tolueno. Se trató el producto obtenido según el Procedimiento estándar E para la escisión de alcoholes protegidos, para obtener el producto del título. Se separó el isómero 2*S* del isómero 2*R* por quiral. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 6,84-6,72 (m, 3H), 4,17 (t, 2H, *J*= 5,9), 3,94 (dd, 2H, *J*= 7,0, 5,4), 3,87 (t, 2H, *J*= 5,4), 3,84 (s, 3H), 3,73 (s, 3H), 3,35 (s, 3H), 2,97-2,93 (m, 2H), 2,11-2,00 (m, 2H).

Etapa B

Éster metílico de ácido (2*S*)-4'-{3-[2-metoxi-4-(2-metoxi-2-metoxicarboniletil)fenoxi]propoxi}bifenil-4-carboxílico



Se trató éster metílico de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxipropiónico (Etapa A) y éster metílico de ácido 4'-hidroxibifenil-4-carboxílico (Ejemplo 197, Etapa A) según las condiciones estándar de Mitsunobu B. Se purificó el producto bruto por cromatografía en gel de sílice (hexanos/acetato de etilo 7:3), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,07 (d, 2H, *J*= 8,6), 7,58 (dd, 4H, *J*= 10,8, 8,9), 7,14 (d, 2H, *J*= 8,9), 6,99 (d, 2H, *J*= 8,9), 6,84 (d, 2H, *J*= 8,6), 4,24-4,12 (m, 6H), 3,94-3,90 (m, 4H), 3,35 (s, 3H), 2,97-2,94 (m, 2H), 2,27 (q, 2H, *J*= 5,9), 1,23 (t, 3H, *J*= 7,0).

Etapa C

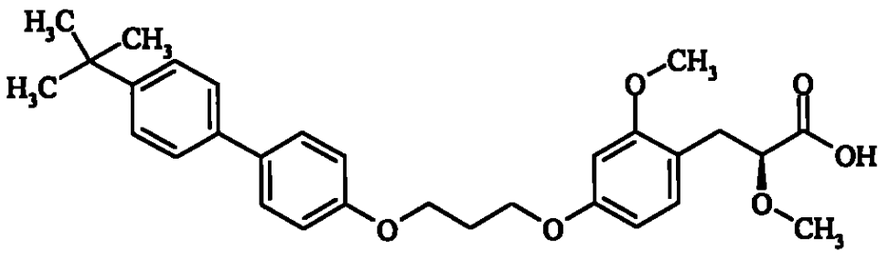
Ácido (2*S*)-4'-{3-[4-(2-carboxi-2-metoxietil)-2-metoxifenoxi]propoxi}bifenil-4-carboxílico

Se preparó el compuesto del título a partir de éster metílico de ácido 4'-{3-[2-metoxi-4-(2-metoxi-2-metoxicarboniletil)fenoxi]propoxi}bifenil-4-carboxílico (Etapa B) por el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN (MeOD, 300,15 MHz): δ 8,07 (d, 2H, *J*=8,5), 7,69 (d, 2H, *J*=8,5), 7,63 (d, 2H, *J*=8,7), 7,06 (d, 2H, *J*=8,7), 6,91-6,88 (m, 2H), 6,78 (dd, 1H, *J*=8,1, 1,6), 4,25 (t, 2H, *J*=6,3), 4,18 (t, 2H, *J*=6,0), 3,94 (dd, 1H,

J=7,9, 4,4), 3,82 (s, 3H), 3,33 (s, 3H), 3,01 (dd, 1H, J=14,1, 4,4), 2,88 (dd, 1H, J=13,9, 7,7), 2,26 (q, 2H, J=6,0).

Ejemplo 260

Ácido (2*S*)-3-{4-[3-(4'-*terc*-butilbifenil-4-iloxi)propoxi]-2-metoxipropiónico



Etapa A

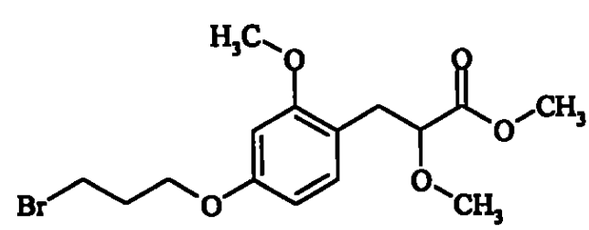
3-Bromopropan-1-ol



A una solución de 1,3-propanodiol (5 g, 66 mmol) y benceno (132 mL), se añadió ácido bromhídrico al 48% (8 mL). Se calentó la mezcla resultante a reflujo durante 20 horas, al tiempo que se atrapaba el agua formada usando un separador de agua Dean-Stark. Se lavó la mezcla con una solución 2N de NaOH, HCl al 5%, agua y salmuera. Se secó la capa orgánica (Na_2SO_4) y se evaporó a presión reducida. ^{1}H-RMN ($CDCl_3$, 300,15 MHz): δ 3,78 (2H, t, J= 6,0), 3,52 (2H, t, J= 6,0), 2,07 (2H, m).

Etapa B

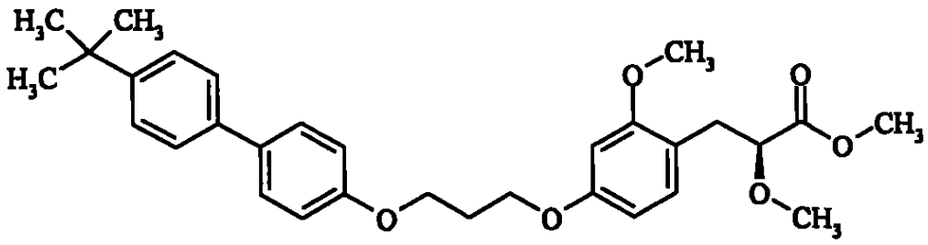
Éster metílico del ácido 3-[4-(3-bromopropoxi)-2-metoxifenil]-2-metoxipropiónico



Se trataron éster metílico de ácido 3-(4-hidroxi-2-metoxifenil)-2-metoxipropiónico (Ejemplo 188, Etapa C) y 3-bromopropan-1-ol (Etapa A) en las condiciones estándar de Mitsunobu B (DIAD/tolueno), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,01 (d, 1H, *J*= 8,3), 6,39 (m, 2H), 4,06 (t, 2H, *J*= 5,9), 4,00-3,96 (m, 1H), 3,78 (s, 3H), 3,67 (s, 3H), 3,57 (t, 2H, *J*= 6,4), 3,31 (s, 3H), 2,99 (dd, 1H, *J*= 13,7, 6,2), 2,91 (dd, 1H, *J*= 13,7, 7,5), 2,34-2,22 (m, 2H).

Etapa C

Éster metílico del ácido (2*S*)-3-{4-[3-(4'-*terc*-butilbifenil-4-iloxi)propoxi]-2-metoxifenil}-2-metoxipropiónico



Se trataron éster metílico de ácido 3-[4-(3-bromopropoxi)-2-metoxifenil]-2-metoxipropiónico (Etapa B) y 4'-*terc*-butilbifenil-4-ol (Ejemplo 221, Etapa A) según el Procedimiento estándar K. Se separaron los enantiómeros por HPLC quiral. Se separó el isómero 2*S* del isómero 2*R* por HPLC quiral (Chiralpack AD, hexano 0,05% TFA/IPA, 75/25, modo isocrático, 1 mL/min; TR = 7,70 min). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,53-7,41 (m, 6H), 7,05-6,95 (m, 3H), 6,45-6,40 (m, 2H), 4,21 (d, 2H, *J*= 6,2), 4,14 (d, 2H, *J*= 6,2), 4,05-3,98 (m, 1H), 3,80 (s, 3H), 3,69 (s, 3H), 3,33 (s, 3H), 3,01 (dd,1H,*J*= 13,4, 6,2), 2,92 (dd, 1H, *J*= 13,4, 7,5), 2,27 (q, 2H, *J*= 6,2).

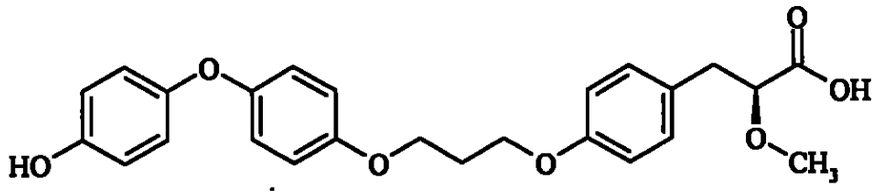
Etapa D

Ácido (2*S*)-3-{4-[3-(4'-*terc*-butilbifenil-4-iloxi)propoxi]-2-metoxifenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster metílico de ácido (2*S*)-3-{4-[3-(4'-*terc*-butilbifenil-4-iloxi)propoxi]-2-metoxifenil}-2-metoxipropiónico (Etapa C) por el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN (acetona-d_6, 300,15 MHz): δ 7,57 (d, 2H, *J*=8,7), 7,53 (d, 2H, *J*=8,7), 7,45 (d, 2H, *J*=8,5), 7,06-7,02 (m, 3H), 6,55 (d, 1H, *J*=2,0), 6,46 (dd, 1H, *J*=8,3, 2,2), 4,26-4,17 (m, 4H), 3,96 (dd, 1H, *J*=7,9, 5,7), 3,81 (s, 3H), 3,26 (s, 3H), 2,25 (q, 2H, *J*=6,3), 1,33 (s, 9H).

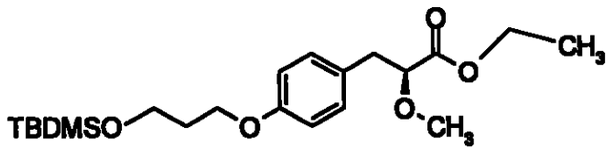
Ejemplo 261

Ácido (2*S*)-3-(4-{3-[4-(4-hidroxifenoxi)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

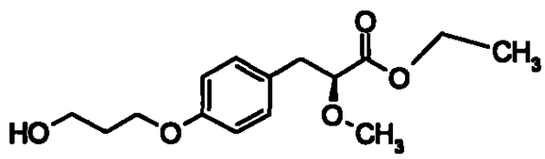
Éster etílico del ácido (2*S*)-3-{4-[3-(terc-butildimetilsilaniloxi)propoxi]fenil}-2-metoxipropiónico



Se trató una mezcla de éster etílico de ácido (2*S*)-3-(4-hidroxifenil)-2-metoxipropiónico y 3-(terc-butildimetilsilaniloxi)propan-1-ol según las condiciones estándar de acoplamiento de Mitsounobu B usando DIAD y tolueno.

Etapa B

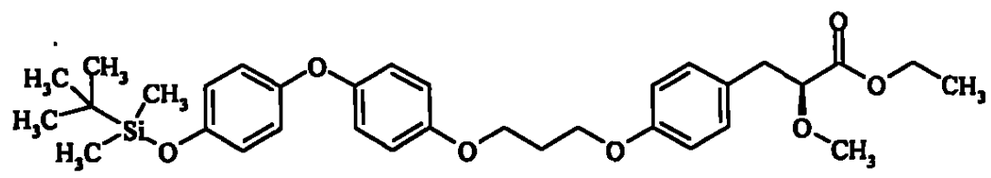
Éster etílico del ácido (2S)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico



Se trató una solución de éster etílico de ácido (2S)-3-{4-[3-(terc-butildimetilsilaniloxi)propoxi]-fenil}-2-metoxipropiónico según el Procedimiento estándar E para la escisión de alcoholes protegidos, para obtener el producto del título.

Etapa C

Éster etílico del ácido 3-(4-{3-[4'-(terc-butildimetil-silaniloxi)bifenil-4-iloxi]propoxi}fenil)-2-metoxipropió-nico



Se trataron éster etílico de ácido (2*S*)-3-[4-(3-hidroxipropoxi)fenil]-2-metoxipropiónico y 4'-(*terc*-butildimetilsilaniloxi)bifenil-4-ol (Ejemplo 196, Etapa A) según el procedimiento de Mitsunobu B (DIAD, tolueno), para obtener el compuesto del título.

Etapa D

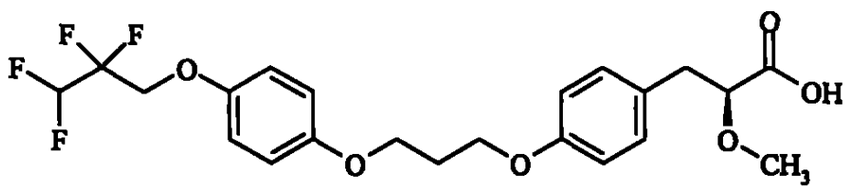
Ácido (2*S*)-3-(4-{3-[4-(4-hidroxifenoxi)fenoxi]propoxi}fe-nil)-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido 3-(4-{3-[4'-(terc-butil-dime-tilsilaniloxi)bifenil-4-iloxi]propoxi}fenil)-2-metoxipro-piónico (Etapa A) por el procedimiento estándar de hidró-lisis C (NaOH). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,15 (d,

2H, J=8,6), 6,92-6,74 (m, 10H), 4,15-4,09 (m, 4H), 3,98 (dd, 1H, J=7,3, 4,6), 3,39 (s, 3H), 3,09 (dd, 1H, J=14,2, 4,6), 2,95 (dd, 1H, J=14,2, 7,3), 2,23 (q, 2H, J=5,9).

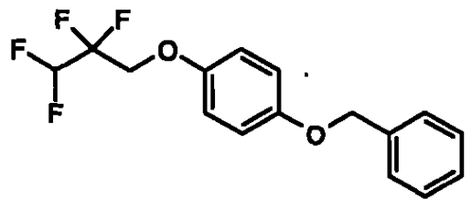
Ejemplo 262

Ácido (2*S*)-2-metoxi-3-(4-{3-[4-(2,2,3,3-tetrafluoropropoxi)fenoxi]propoxi}fenil)propiónico



Etapa A

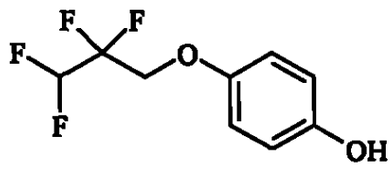
4-(2,2,3,3-Tetrafluoropropoxi)-1-benciloxifenol



A una solución de éster 2,2,3,3-tetrafluoropropílico del ácido metanosulfónico (obtenido de 2,2,3,3-tetrafluoropropanol y cloruro de metanosulfonilo como se ha descrito en el Ejemplo 268, Etapa A) (0,35 mmol, 74 mg) y 4-benciloxifenol (0,175 mmol, 35 mg) en DMF (1 mL), se añadió K_2CO_3 y se agitó la mezcla resultante a 100°C durante 20 horas. Se añadió agua y se extrajo la capa acuosa dos veces con hexano y una vez con acetato de etilo. Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se evaporaron. Se purificó el producto bruto por cromatografía en gel de sílice (hexano/acetato de etilo 4:1), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,42-7,32 (m, 5H), 6,96-6,84 (m, 4H), 6,06 (tt, 1H, J= 53,0, 5,1), 5,03 (s, 2H), 4,29 (dt, J= 12,0, 1,6).

Etapa B

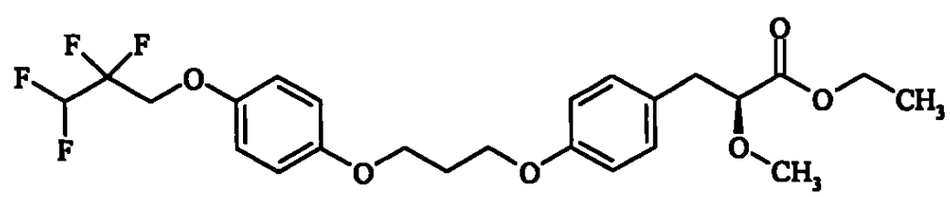
4-(2,2,3,3-Tetrafluoropropoxi)fenol



Se disolvió 4-(2,2,3,3-tetrafluoropropoxi)-benciloxifenol (0,09 mmol, 28 mg) (Etapa A) en MeOH (2 mL) y se añadió Pd(C) (40% peso, 10 mg). Se agitó la mezcla durante 90 minutos bajo una atmósfera de H_2 (1 atm) y se filtró a través de una almohadilla de celita (EtOH). Se concentró el filtrado, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 6,85-6,75 (m, 4H), 6,05 (dt, *J*= 53,2, 4,8), 4,28 (dt, 2H, *J*= 12,1, 1,6).

Etapa C

Éster etílico del ácido (2*S*)-2-metoxi-3-(4-{3-[4-(2,2,3,3-tetrafluoropropoxi)fenoxi]propoxi}fenil)propiónico



Se trataron éster etílico de ácido 3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 173, Etapa A) y 4-(2,2,3,3-tetrafluoropropoxi)fenol (Etapa B) bajo el éster K, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,13 (d, 2H, *J*= 8,6), 6,85-6,80 (m, 6H), 6,05 (dt, 1H, *J*= 53,2, 5,1), 4,22-4,08 (m, 8H), 3,90 (dd, 1H, *J*= 7,0, 5,6), 3,35 (s, 3H), 3,04-2,86 (m, 2H), 2,22 (q, 2H, *J*= 6,2).

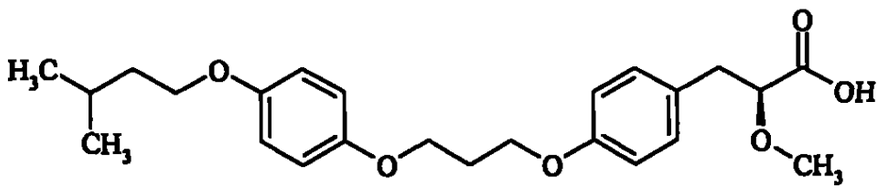
Etapa D

Ácido (2*S*)-2-metoxi-3-(4-{3-[4-(2,2,3,3-tetrafluoropropoxi)fenoxi]propoxi}fenil)propiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-2-metoxi-3-(4-{3-[4-(2,2,3,3-tetrafluoropropoxi)fenoxi]propoxi}fenil)propiónico (Etapa C) por el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,14 (d, 2H, *J*= 8,6), 6,84-6,79 (m, 6H), 6,04 (tt, 1H, *J*= 53,0, 4,8), 4,27 (t, 2H, *J*= 12,0), 4,09 (t, 4H, *J*= 5,9), 3,97-3,91 (m, 1H), 3,34 (s, 3H), 3,11-2,87 (m, 2H), 2,20 (q, 2H, *J*= 5,9).

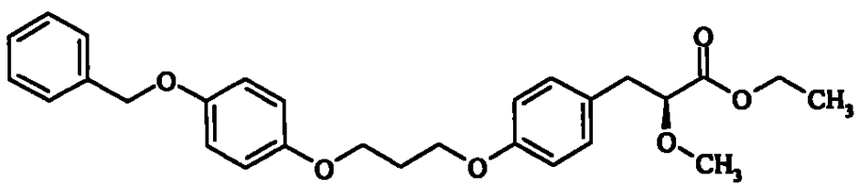
Ejemplo 263

Ácido (2*S*)-2-metoxi-3-(4-{3-[4-(3-metilbutoxi)fenoxi]propoxi}fenil)propiónico



Etapa A

Éster etílico del ácido (2*S*)-3-{4-[3-(4-benciloxifenoxi]-propoxi}fenil)-2-metoxipropiónico

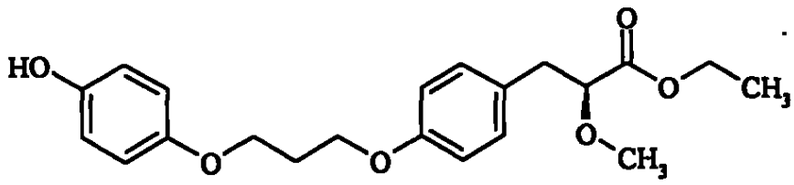


Se trataron éster metílico de ácido 3-[4-(3-bromopropoxi)-3-metoxifenil]-2-metoxipropiónico (Ejemplo 175, Etapa B) y 4-benciloxifenol según las condiciones estándar de Mitsunobu B, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,44-7,30 (m, 5H),

7,13 (d, 2H, J= 8,6), 6,93-6,73 (m, 6H), 5,01 (s, 2H), 4,20-4,06 (m, 6H), 3,90 (dd, 1H, J= 7,0, 5,6), 3,35 (s, 3H), 3,00-2,93 (m, 2H), 2,22 (q, 2H, J= 6,2), 1,23 (t, 3H, J= 7,2).

Etapa B

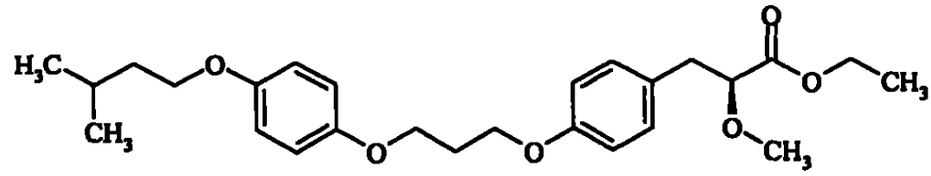
Éster etílico del ácido (2*S*)-3-{4-[3-(4-hidroxifenoxi)-propoxi]fenil}-2-metoxipropiónico



Se obtuvo el compuesto del título siguiendo el procedimiento de hidrogenación (Ejemplo 261, Etapa B), partiendo de éster etílico de ácido (2*S*)-3-{4-[3-(4-benciloxifenoxi]propoxi}fenil)-2-metoxipropiónico. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,13 (d, 2H, J= 8,9), 6,84-6,71 (m, 6H), 4,23-4,06 (m, 6H), 3,91 (dd, 1H, J= 7,3, 5,9), 3,35 (s, 3H), 2,97-2,93 (m, 2H), 2,21 (q, 2H, J= 6,2), 1,23 (t, 3H, J= 7,3).

Etapa C

Éster etílico del ácido (2*S*)-2-metoxi-3-(4-{3-[4-(3-metilbutoxi)fenoxi]propoxi}fenil)propiónico



Se hizo reaccionar al éster etílico del ácido (2*S*)-3-{4-[3-(4-hidroxifenoxi)propoxi]fenil}-2-metoxipropiónico (Etapa A) según el procedimiento de Mitsunobu B (DIAD, tolueno) con 3-metilbutanol, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,13 (d, 2H, J= 8,6), 6,85-6,81 (m, 6H), 4,18 (c, 4H, J= 7,0),

4,08 (d, 2H, J= 5,9), 3,96-3,87 (m, 3H), 3,35 (s, 3H), 2,97-2,93 (m, 2H), 2,22 (q, 2H, J= 6,2), 1,86-1,60 (m, 3H), 1,23 (t, 5H, J= 7,0), 0,95 (d, 6H, J= 6,4).

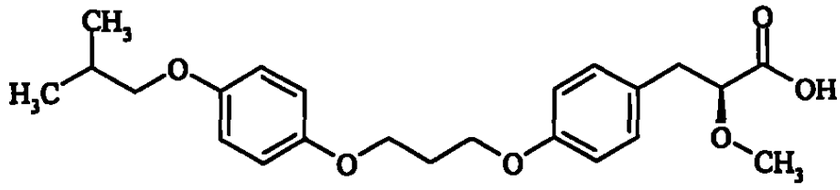
Etapa D

Ácido (2*S*)-2-metoxi-3-(4-{3-[4-(3-metilbutoxi)fenoxi]propoxi}fenil)propiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-2-metoxi-3-(4-{3-[4-(3-metilbutoxi)fenoxi]propoxi}fenil)propiónico (Etapa B) por el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,12 (d, 2H, J=8,4), 6,84-6,80 (m, 6H), 4,09 (c, 4H, J= 6,2), 3,99-3,88 (m, 3H), 3,37 (s, 3H), 3,07 (dd, 1H, J= 14,3, 4,4), 2,93 (dd, 1H, J= 14,3, 7,0), 2,19 (q, 2H, J= 6,2), 1,90-1,71 (m, 1H), 1,62 (c, 2H, J= 6,9), 0,93 (d, 6H, J= 6,6).

Ejemplo 264

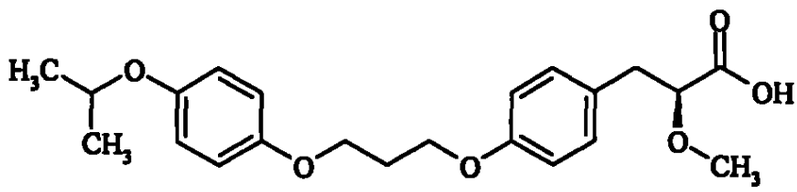
Ácido (2*S*)-3-{4-[3-(4-isobutoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se acopló éster etílico de ácido (2*S*)-(3-{4-[3-(4-hidroxifenoxi)propoxi]fenil}-2-metoxipropiónico (Ejemplo 263, Etapa B) bajo el éster J con 1-bromo-2-metilpropano, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,14 (d, 2H, J= 8,6), 6,86-6,82 (m, 6H), 4,11 (c, 4H, J =6,2), 3,98 (dd, 1H, J= 7,3, 4,6), 3,66 (d, 2H, J= 6,5), 3,40 (s, 3H), 3,10 (dd, 1H, J= 14,5, 4,6), 2,95 (dd, 1H, J= 14,5, 7,3), 2,21 (q, 2H, J= 6,2), 2,11-1,98 (m, 1H), 1,01 (d, 6H, J= 6,7).

Ejemplo 265

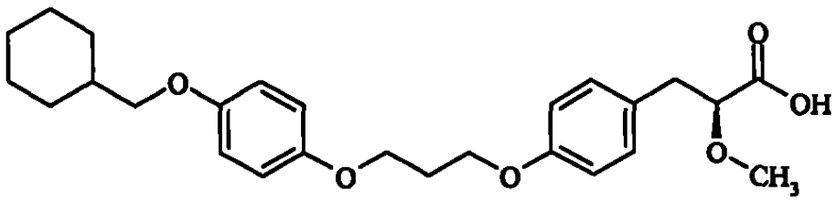
Ácido (2*S*)-3-{4-[3-(4-isopropoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-hidroxifenoxi)-propoxi]fenil}-2-metoxipropiónico (Ejemplo 263, Etapa B) y 2-bromopropeno, siguiendo el procedimiento descrito para el Ejemplo 264. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,14 (d, 2H, *J*= 8,3), 6,86-6,82 (m, 6H), 4,40 (q, 1H, *J*= 5,9), 4,11 (c, 4H, *J*= 5,9), 3,98 (dd, 1H, *J*= 7,3, 4,6), 3,40 (s, 3H), 3,10 (dd, 1H, *J*= 14,2, 4,3), 3,01-2,90 (dd, 1H, *J*= 14,2, 7,2), 2,22 (q, 2H, *J*= 5,9), 1,30 (d, 6H, *J*= 6,2).

Ejemplo 266

Ácido (2*S*)-3-{4-[3-(4-ciclohexilmetoxifenoxi)propoxi]fenil}-2-metoxipropiónico

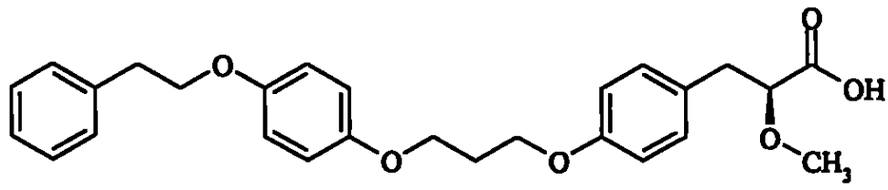


Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-hidroxifenoxi)-propoxi]fenil}-2-metoxipropiónico (Ejemplo 263, Etapa B) y (bromometil)ciclohexano siguiendo el procedimiento descrito para el Ejemplo 264. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,14 (d, 2H, *J*= 8,6), 6,86-6,81 (m, 6H), 4,11 (c, 4H, *J*= 6,2), 3,99 (dd, 1H, *J*= 7,3, 4,6), 3,70 (d, 2H, *J*= 6,2),

3,40 (s, 3H), 3,10 (dd, 1H, *J*= 14,5, 4,6), 2,96 (dd, 1H, *J*= 14,2, 7,3), 2,23 (q, 2H, *J*= 6,2), 1,88-1,67 (m, 6H), 1,39-0,94 (m, 5H).

Ejemplo 267

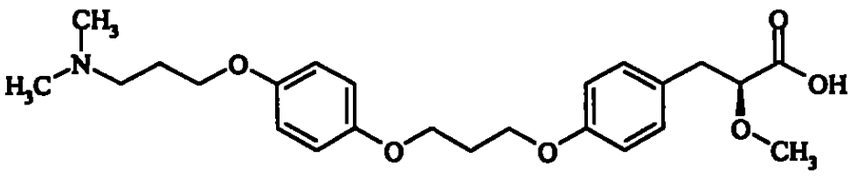
Ácido (2*S*)-2-metoxi-3-{4-[3-(4-feneti1oxifenoxi)propoxi]-fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-hidroxifenoxi)-propoxi]fenil}-2-metoxipropiónico (Ejemplo 263, Etapa B) y (1-bromoetil)benceno siguiendo el procedimiento descrito para Ejemplo 264. ^{1}H-RMN ($CDCl_3$, 300,15 MHz): δ 7,32-7,26 (m, 5H), 7,14 (d, 2H, *J*= 8,5), 6,86-6,82 (m, 6H), 4,15-4,08 (m, 6H), 4,00 (dd, 1H, *J*= 6,9, 4,4), 3,41 (s, 3H), 3,14-3,05 (m, 3H), 2,97 (dd, 1H, *J*= 14,5, 6,9), 2,22 (q, 2H, *J*= 6,1).

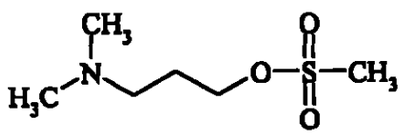
Ejemplo 268

Ácido (2*S*)-3-(4-{3-[4-(3-dimetilaminopropoxi)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

Éster 3-dimetilaminopropílico del ácido metanosulfónico



Se disolvió 3-dimetilamino-1-propanol (0,98 mmol, 0,12 mL) en THF (2 mL). Se añadió trietilamina (1,47 mmol, 0,20 mL) y se enfrió la mezcla a 0°C. Se añadió cloruro de metanosulfonilo (1,08 mmol, 0,08 mL) y se retiró el baño. Se calentó la mezcla hasta la temperatura ambiente y se agitó durante 2 horas. Se añadieron hexanos y se eliminaron los precipitados por filtración a través de celita (hexanos). Se concentró el filtrado para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 4,29 (t, 2H, *J*= 6,4), 3,00 (s, 3H), 2,39 (t, 2H, *J*= 7,0), 2,22 (s, 6H), 1,90 (q, 2H, *J*= 6,7).

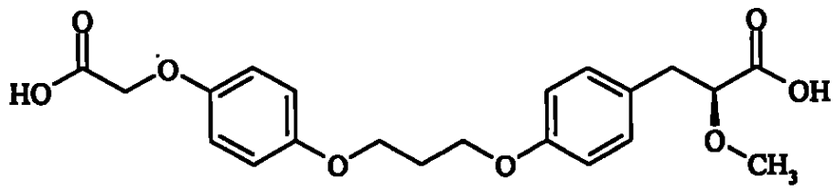
Etapa B

Ácido (2*S*)-3-{4-[3-[4-(3-dimetilaminopropoxi)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-hidroxifenoxi)-propoxi]fenil}-2-metoxipropiónico (Ejemplo 263, Etapa B) y éster 3-dimetilaminopropílico de ácido metanosulfónico (Etapa A) siguiendo el procedimiento descrito para Ejemplo 264. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,14 (d, 2H, *J*= 7,8), 6,83-6,77 (m, 6H), 4,10-4,04 (m, 5H), 3,95-3,89 (m, 4H), 3,37 (s, 3H), 3,16-3,13 (m, 2H), 3,06-2,99 (m, 2H), 2,77 (s, 6H), 2,21-2,15 (m, 4H).

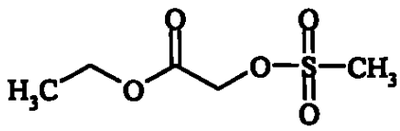
Ejemplo 269

Ácido (2*S*)-3-{4-[3-(4-carboximetoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

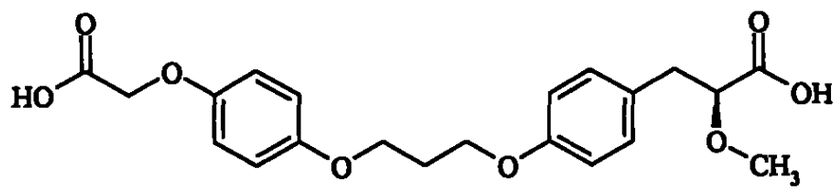
Éster etílico del ácido metanosulfoniloxiacético



Se preparó el compuesto del título siguiendo el procedimiento descrito para el éster 3-dimetilaminopropílico del ácido metanosulfónico (Ejemplo 268, Etapa A) partiendo de glicolato de etilo. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 4,75 (s, 2H), 4,27 (c, 2H, *J*= 7,3), 3,20 (s, 3H), 1,31 (t, 3H, *J*= 7,3).

Etapa B

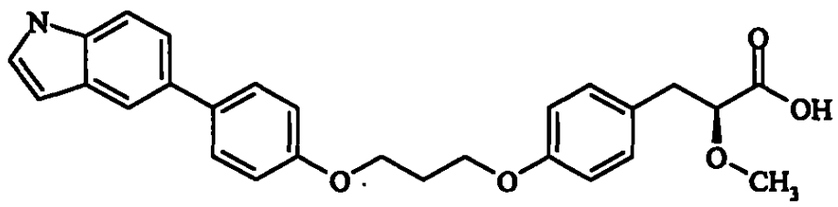
Ácido (2*S*)-3-{4-[3-(4-carboximetoxifenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-hidroxifenoxi)-propoxi]fenil}-2-metoxipropiónico (Ejemplo 263, Etapa B) y éster etílico de ácido metanosulfoniloxiacético (Etapa A) siguiendo el procedimiento descrito para Ejemplo 264. ^{1}H-RMN (MeOD, 200,15 MHz): δ 7,13 (d, 2H, *J*= 8,6), 6,86-6,81 (m, 6H), 4,57 (s, 2H), 4,15-4,06 (m, 4H), 3,91 (dd, 1H, *J*= 7,8, 4,8), 3,31 (s, 3H), 2,99 (dd, 1H, *J*= 14,2, 4,6), 2,85 (dd, 1H, *J*= 14,2, 7,5), 2,17 (q, 2H, *J*= 6,2).

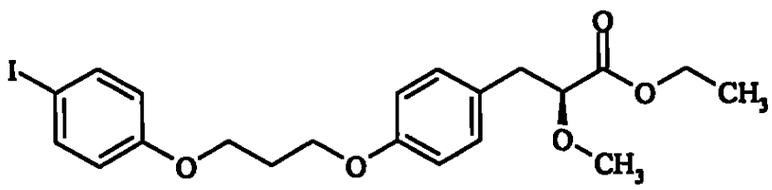
Ejemplo 270

Ácido (2*S*)-3-{4-{3-[4-(1H-indol-5-il)fenoxi]propoxi}fenil)-2-metoxipropiónico



Etapa A

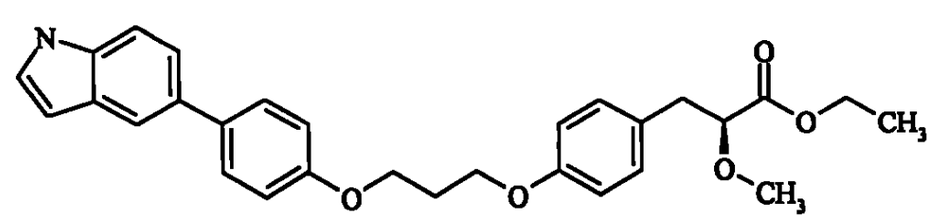
Éster etílico del ácido (2*S*)-3-{4-[3-(4-yodofenoxi)propoxi]fenil}-2-metoxipropiónico



Se trataron éster etílico de ácido (2*S*)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 173, Etapa A) y 4-yodofenol bajo el éster K (Cs_2CO_3), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,54 (d, 2H, *J*= 8,9), 7,13 (d, 2H, *J*= 8,6), 6,82 (d, 2H, *J*= 8,9), 6,68 (d, 2H, *J*= 9,1), 4,23-4,08 (m, 6H), 3,90 (dd, 1H, *J*= 7,3, 5,9), 3,35 (s, 3H), 2,97-2,93 (m, 2H), 2,23 (q, 2H, *J*= 6,2), 1,23 (t, 3H, *J*= 7,0).

Etapa B

Éster etílico del ácido (2*S*)-3-(4-{3-[4-(1H-indol-5-il)-fenoxi]propoxi}fenil)-2-metoxipropiónico



A una mezcla agitada de éster etílico de ácido (2*S*)-3-{4-[3-(4-yodofenoxi)propoxi]fenil}-2-metoxipropiónico (0,10 mmol, 50 mg) (Etapa A), ácido 5-indolilborónico (0,114 mmol, 18 mg) y carbonato de cesio en polvo (0,23 mmol, 35 mg) en DME (0,5 mL), se añadió $Pd(PPh_3)_4$ (0,003 mmol, 4 mg). Se lavó la mezcla con nitrógeno y se mantuvo bajo nitrógeno mientras se calentaba a reflujo en un baño de aceite a 100°C. Se agitó la mezcla durante 6 horas y se enfrió después a la temperatura ambiente y se diluyó con acetato de etilo y agua. Se secó la capa orgánica (Na_2SO_4) y se concentró. Se purificó el producto bruto por cromatografía en gel de sílice (CH_2Cl_2/EtOAc 96:4), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,20 (amplio s, 1H), 7,80 (d, 1H, *J*= 0,8), 7,56 (d, 3H, *J*= 8,9), 7,41 (d, 2H, *J*= 1,6), 7,23 (dd, 1H, *J*= 3,2, 2,4), 7,15 (d, 3H, *J*= 8,6), 6,99 (d, 2H, *J*= 8,9), 6,85 (d, 3H, *J*= 8,6), 6,60-6,58 (m, 1H), 4,24-4,11 (m, 8H), 3,92 (dd, 1H, *J*= 7,3, 5,9), 3,35 (s, 4H), 2,98-2,94 (m, 3H), 2,28 (q, 2H, *J*= 5,9), 1,24 (t, 4H, *J*= 7,3).

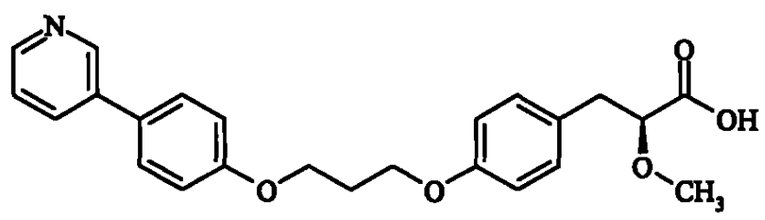
Etapa C

Ácido (2*S*)-3-(4-{3-[4-(1H-indol-5-il)fenoxi]propoxi}fenil)-2-metoxipropiónico

Se obtuvo el compuesto del título a partir de éster etílico de ácido (2*S*)-3-(4-{3-[4-(1H-indol-5-il)fenoxi]propoxi}fenil)-2-metoxipropiónico (Etapa B) siguiendo el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,17 (amplio s, 1H), 7,80 (s, 1H), 7,56 (d, 2H, *J*= 8,6), 7,42 (s, 2H), 7,24-7,21 (m, 1H), 7,15 (d, 2H, *J*= 8,6), 6,98 (d, 2H, *J*= 8,6), 6,86 (d, 2H, *J*= 8,6), 6,59-6,59 (m, 1H), 4,23-4,13 (m, 4H), 3,98 (dd, 1H, *J*= 7,3, 4,3), 3,39 (s, 3H), 3,10 (dd, 1H, *J*= 14,5, 4,0), 2,95 (dd, 1H, *J*= 14,5,7,3), 2,27 (q, 2H, *J*= 6,2).

Ejemplo 271

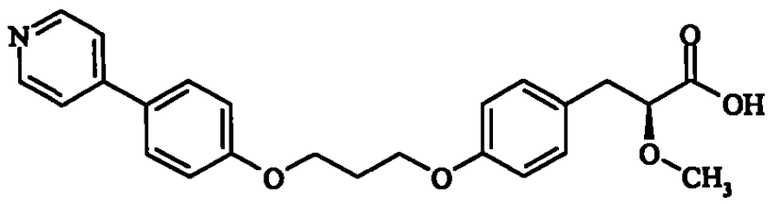
Ácido (2*S*)-2-metoxi-3-{4-[3-(4-piridin-3-ilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-yodofenoxi)propoxi]fenil}-2-metoxipropiónico (Ejemplo 270, Etapa A) y ácido 3-piridilborónico siguiendo el procedimiento descrito para Ejemplo 270 (Etapas B y C). ^{1}H-RMN (MeOD, 300,15 MHz): δ 8,76 (s, 1H), 8,46 (s, 1H), 8,05 (d, 1H, *J*= 8,1), 7,60 (d, 2H, *J*= 8,7), 7,49 (dd, 1H, *J*= 7,7,4,8), 7,19 (d, 2H, *J*= 8,5), 7,09 (d, 2H, *J*= 8,7), 6,85 (d, 2H, *J*= 8,5), 4,24 (t, 2H, *J*= 6,1), 4,17 (t, 2H, *J*= 6,3), 3,74 (dd, 1H, *J*= 8,7, 3,8), 3,27 (s, 3H), 2,97 (dd, 1H, *J*= 14,3, 3,8), 2,81 (dd, 1H, *J*= 14,1, 8,5), 2,26 (q, 2H, *J*= 6,0).

Ejemplo 272

Ácido (2*S*)-2-metoxi-3-{4-[3-(4-piridin-4-ilfenoxi)propoxi]fenil}propiónico

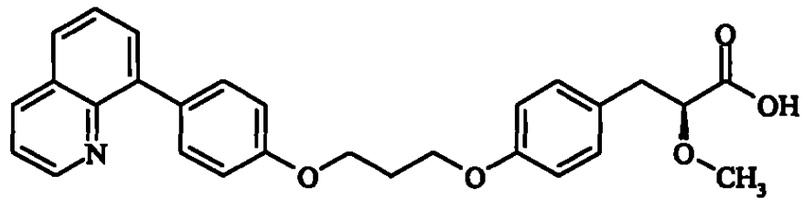


Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-yodofenoxi)propoxi]fenil}-2-metoxipropiónico (Ejemplo 270, Etapa A) y ácido 4-piridilborónico siguiendo el procedimiento des-

crito para Ejemplo 270 (Etapas B y C). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,67-8,65 (m, 2H), 8,16 (d, 2H, J= 6,6), 7,90 (d, 2H, J= 8,8), 7,16-7,09 (m, 4H), 6,82 (d, 2H, J= 8,8), 4,26 (t, 2H, J= 6,2), 4,13 (t, 2H, J= 6,2), 3,90 (dd, 1H, J= 7,7, 4,8), 2,97 (dd, 1H, J= 14,3, 5,1), 2,83 (dd, 1H, J= 14,3, 7,7), 2,24 (q, 2H, J= 5,9).

Ejemplo 273

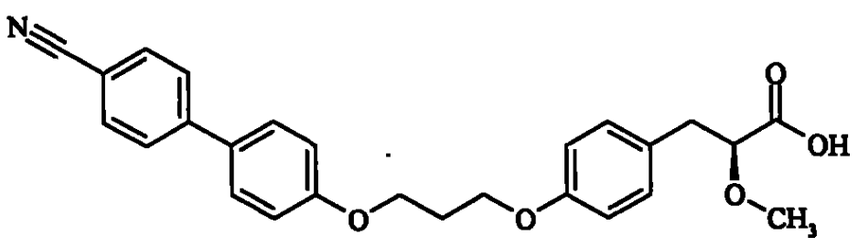
Ácido (2*S*)-2-metoxi-3-{4-[3-(4-quinolin-8-ilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4-yodofenoxi)propoxi]fenil}-2-metoxipropiónico (Ejemplo 270, Etapa A) y ácido 8-quinolinaborónico siguiendo el procedimiento descrito para el Ejemplo 270 (Etapas B y C). ^{1}H-RMN (MeOD, 300,15 MHz): δ 8,82 (d, 1H, J= 2,6), 8,39 (d, 1H, J= 8,1), 7,92 (d, 1H, J= 7,9), 7,74-7,63 (m, 2H), 7,58-7,51 (m, 3H), 7,18 (d, 2H, J= 8,5), 7,08 (d, 2H, J= 8,7), 6,88 (d, 2H, J= 8,7), 4,28 (t, 2H, J= 6,0), 4,20 (t, 2H, J= 6,3), 3,90-3,80 (m, 1H), 3,30 (s, 3H), 3,04-2,84 (m, 2H), 2,29 (q, 2H, J= 6,3).

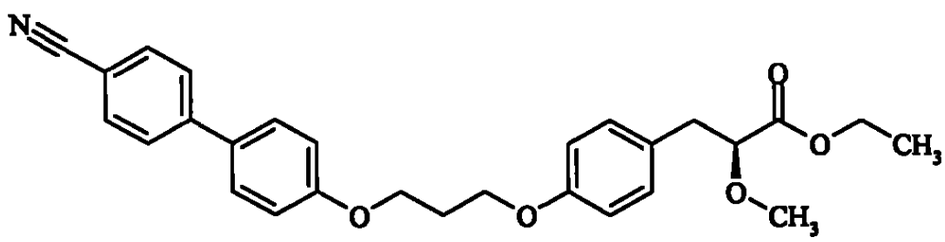
Ejemplo 274

Ácido (2*S*)-3-{4-[3-(4'-cianobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Etapa A

Éster etílico del ácido (2*S*)-3-{4-[3-(4'-cianobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



Se trataron éster etílico de ácido (2*S*)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 173, Etapa A) y 4'-hidroxi-4-bifenilcarbonitrilo según las condiciones estándar de Mitsunobu B (DIAD, tolueno), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,71-7,60 (m, 4H), 7,52 (d, 2H, *J*= 8,9), 7,14 (d, 2H, *J*= 8,9), 7,00 (d, 2H, *J*= 8,9), 6,83 (d, 2H, *J*= 8,6), 4,24-4,12 (m, 6H), 3,90 (dd, 1H, *J*= 7,3, 5,9), 3,34 (s, 3H), 2,97-2,93 (m, 2H), 2,27 (q, 2H, *J*= 6,2), 1,23 (t, 3H, *J*= 7,3).

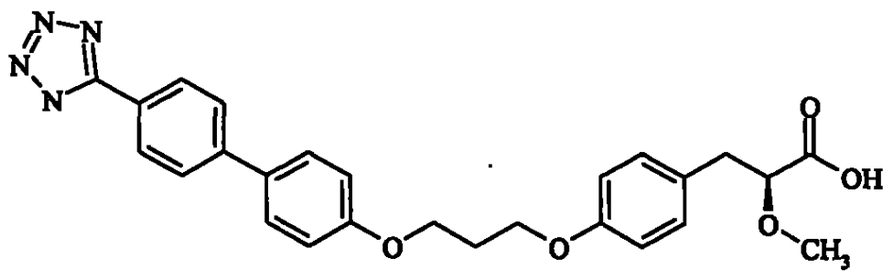
Etapa B

Ácido (2*S*)-3-{4-[3-(4'-cianobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-3-{4-[3-(4'-cianobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico (Etapa A) mediante el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN (MeOD, 300,15 MHz): δ 7,77 (s, 4H), 7,64 (d, 2H, *J*= 8,7), 7,18 (d, 2H, *J*= 8,5), 7,07 (d, 2H, *J*= 8,7), 6,86 (d, 2H, *J*= 8,3), 4,24 (t, 2H, *J*= 6,3), 4,17 (t, 2H, *J*= 6,3), 3,84-3,74 (m, 1H), 3,03-2,81 (m, 2H), 2,26 (q, 2H, *J*= 6,0).

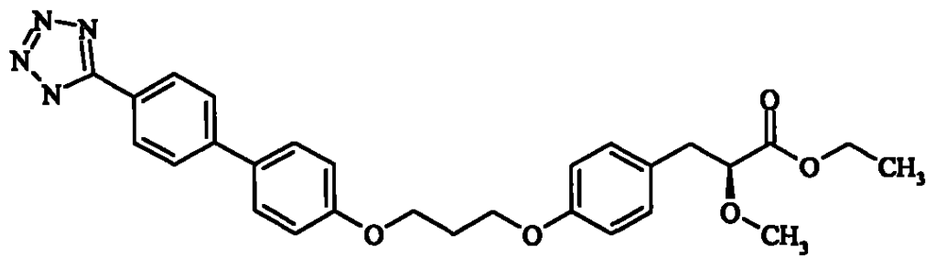
Ejemplo 275

Ácido (2*S*)-2-metoxi-3-(4-{3-[4'-(1*H*-tetrazol-5-il)bifenil-4-iloxi]propoxi}fenil)propiónico



Etapa A

Éster etílico del ácido (2*S*)-2-metoxi-3-(4-{3-[4'-(1*H*-tetrazol-5-il)bifenil-4-iloxi]propoxi}fenil)propiónico



Se añadió azidotributilestaño (0,72 mmol, 0,2 mL) a una solución de éster etílico de ácido (2*S*)-3-{4-[3-(4'-cianobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico (0,36 mmol, 0,17 g) (Ejemplo 274, Etapa A) en tolueno (1 mL). Se calentó la mezcla a 60°C durante 48 horas. Se dejó que la mezcla alcanzara la temperatura ambiente y se añadió HCl 1N. Se calentó la mezcla a reflujo durante 24 horas más. Al enfriarse, se añadió agua y se extrajo la fase acuosa con acetato de etilo. Se secó la capa orgánica (Na_2SO_4), se filtró y se evaporó. Se purificó el producto bruto por cromatografía en gel de sílice (hexanos/acetato de etilo/ácido acético 3:2:10%), para obtener el producto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,12 (d, 2H, *J*= 8,3), 7,65 (d, 2H, *J*= 8,6), 7,51

(d, 2H, *J*= 8,9), 7,11 (d, 2H, *J*= 8,6), 6,95 (d, 2H, *J*= 8,6), 6,79 (d, 2H, *J*= 8,6), 4,25-4,06 (m, 7H), 3,97 (dd, 1H, *J*= 7,0, 5,4), 3,37 (s, 3H), 2,99-2,96 (m, 2H), 2,22 (q, 2H, *J*= 5,9), 1,25 (t, 3H, *J*= 7,2).

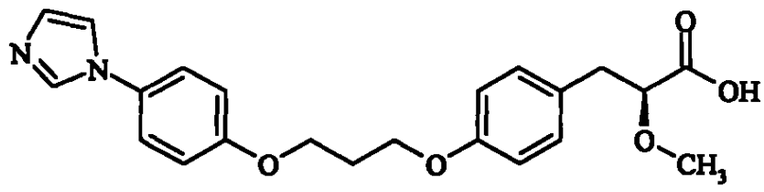
Etapa B

Ácido (2*S*)-2-metoxi-3-(4-{3-[4'-(1*H*-tetrazol-5-il)bifenil-4-iloxi]propoxi}fenil)propiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-2-metoxi-3-(4-{3-[4'-(1*H*-tetrazol-5-il)bifenil-4-iloxi]propoxi}fenil)propiónico (Etapa A) mediante el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN (MeOD, 300,15 MHz): δ 8,09 (d, 2H, *J*= 8,3), 7,70 (d, 2H, *J*= 8,3), 7,62 (d, 2H, *J*= 8,7), 7,18 (d, 2H, *J*= 8,5), 7,05 (d, 2H, *J*= 8,7), 6,86 (d, 2H, *J*= 8,7), 4,23 (t, 2H, *J*= 6,0), 4,17 (t, 2H, *J*= 6,1), 3,83 (dd, 1H, *J*= 8,3, 4,2), 3,36 (s, 3H), 2,99 (dd, 1H, *J*= 14,1, 4,0), 2,84 (dd, 1H, *J*= 13,9, 8,1), 2,26 (q, 2H, *J*= 6,3).

Ejemplo 276

Ácido (2*S*)-3-{4-[3-(4-imidazol-1-ilfenoxi)propoxi]fenil}-2-metoxipropiónico

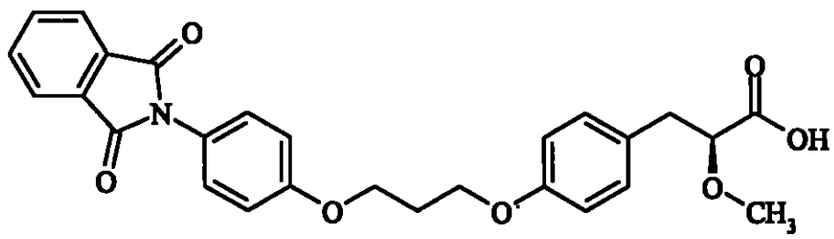


Se trataron éster etílico de ácido 3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 173, Etapa A) y 4-(imidazol-1-il)fenol bajo el éster J, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,11 (s, 1H), 7,31-7,16 (m, 7H), 6,99 (d, 2H, *J*= 8,9), 6,82 (d, 2H, *J*= 8,6), 4,19 (t, 2H, *J*= 6,2), 4,12 (t, 2H, *J*= 5,9), 3,95 (dd, 1H, *J*= 7,3, 4,8), 3,39 (s,

3H), 3,08 (dd, 1H, J= 14,4, 4,8), 2,96 (dd, 1H, J= 14,2, 7,6), 2,26 (q, 2H, J= 5,9).

Ejemplo 277

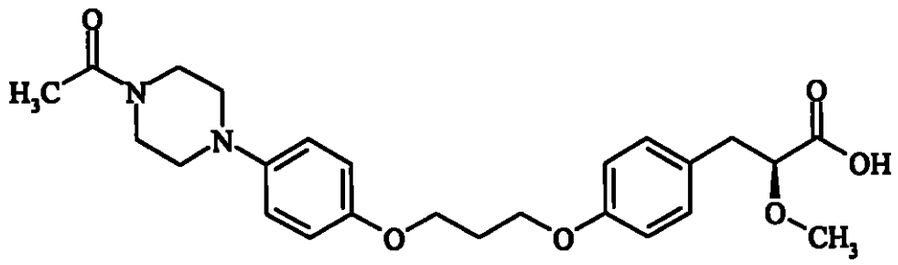
Ácido (2*S*)-3-(4-{3-[4-(1,3-dioxo-1,3-dihidroisoindol-2-il)fenoxi]propoxi}fenil)-2-metoxipropiónico



Se obtuvo el compuesto del título a partir de éster etílico de ácido (2*S*)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 173, Etapa A) y N-(4-hidroxifenil)ftalimida siguiendo el procedimiento descrito para el Ejemplo 276. ^{1}H-RMN ($CDCl_3$, 300,15 MHz): δ 7,97-7,92 (m, 2H), 7,81-7,77 (m, 2H), 7,32 (d, 2H, J= 8,9), 7,15 (d, 2H, J= 8,5), 7,02 (d, 2H, J= 8,9), 6,85 (d, 2H, J= 8,5), 4,20 (t, 2H, J= 6,0), 4,16 (t, 2H, J= 6,0), 3,99 (dd, 1H, J= 7,3, 4,4), 3,41 (s, 3H), 3,11 (dd, 1H, J= 14,3, 4,4), 2,97 (dd, 1H, J= 14,3, 7,1), 2,27 (q, 2H, J= 6,0).

Ejemplo 278

Ácido (2*S*)-3-(4-{3-[4-(4-acetilpiperazin-1-il)fenoxi]propoxi}fenil)-2-metoxipropiónico

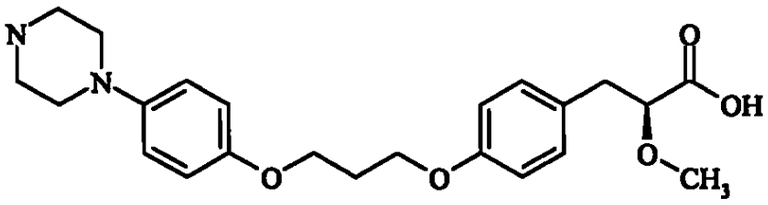


Se obtuvo el compuesto del título a partir de éster etílico de ácido (2*S*)-3-[4-(3-bromopropoxi)fenil]-

2-metoxipropiónico (Ejemplo 173, Etapa A) y 1-acetil-4-(4-hidroxifenil)piperazina siguiendo el procedimiento descrito para el Ejemplo 276. ^{1}H-RMN ($CDCl_3$, 300,15 MHz): δ 7,14 (d, 2H, *J*= 8,5), 6,90-6,80 (m, 5H), 4,15-4,09 (m, 3H), 3,98 (dd, 1H, *J*= 6,7, 4,9), 3,79-3,76 (m, 2H), 3,63-3,60 (m, 2H), 3,40 (s, 3H), 3,11-2,93 (m, 6H), 2,14 (s, 3H).

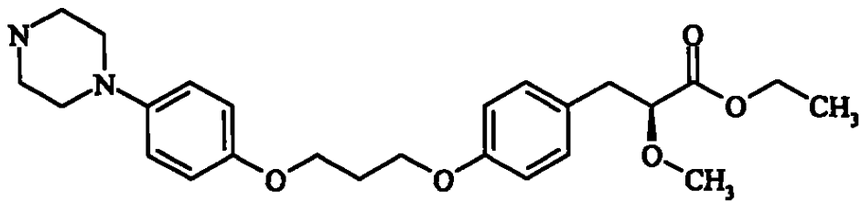
Ejemplo 279

Ácido (2*S*)-2-metoxi-3-{4-[3-(4-piperazin-1-ilfenoxi)propoxi]fenil}propiónico



Etapa A

Éster etílico del ácido (2*S*)-2-metoxi-3-{4-[3-(4-piperazin-1-ilfenoxi)propoxi]fenil}propiónico



Se trataron éster etílico de ácido 3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 173, Etapa A) y 1-(4-hidroxifenil)piperazina bajo el éster K, para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 8,01 (s, 1H), 7,13 (d, 2H, *J*= 8,6), 6,88-6,75 (m, 6H), 4,30 (t, 2H, *J*= 6,4), 4,17 (c, 2H, *J*= 7,0), 4,02 (t, 2H, *J*= 5,9), 3,94-3,87 (m, 1H), 3,64-3,60 (m, 4H), 3,34 (s, 3H), 2,98-2,96 (m, 4H), 2,18-2,04 (m, 2H), 1,23 (t, 3H, *J*= 7,3).

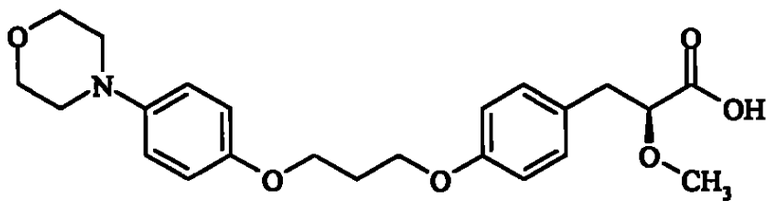
Etapa B

Ácido (2*S*)-2-metoxi-3-{4-[3-(4-piperazin-1-ilfenoxi)propoxi]fenil}propiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-2-metoxi-3-{4-[3-(4-piperazin-1-ilfenoxi)propoxi]fenil}propiónico (Etapa A) por el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN (MeOD, 300,15 MHz): δ 7,18 (d, 2H, *J*= 8,5), 6,89-6,83 (m, 4H), 6,72 (d, 2H, *J*= 9,1), 4,30 (t, 2H, *J*= 6,3), 4,07 (t, 2H, *J*= 6,1), 3,86-3,82 (m, 1H), 3,62-3,59 (m, 4H), 3,36 (s, 3H), 3,07-2,83 (m, 6H), 2,12 (q, 2H, *J*= 6,3).

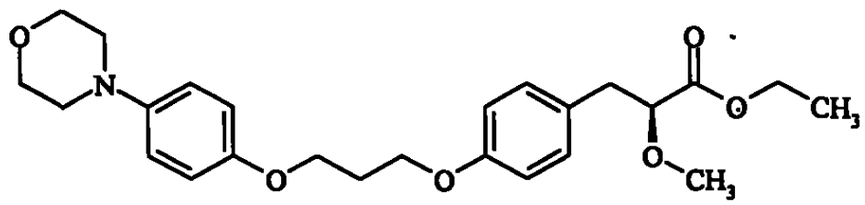
Ejemplo 280

Ácido (2*S*)-2-metoxi-3-{4-[3-(4-morfolin-4-ilfenoxi)propoxi]fenil}propiónico



Etapa A

Éster etílico del ácido (2*S*)-2-metoxi-3-{4-[3-(4-morfolin-4-ilfenoxi)propoxi]fenil}propiónico



Se calentó una mezcla de éster etílico de ácido (2*S*)-3-{4-[3-(4-yodofenoxi)propoxi]fenil}-2-metoxipropiónico (1,03 mmol, 0,5 g), morfolina (1,24 mmol, 0,11 mL), $Pd(OAc)_2$ (0,05 mmol, 12 mg), 2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,08 mmol, 48 mg) y carbonato de ce-

sio (1,45 mmol, 471 mg) en DMF (2 mL) a 110°C durante 14 horas. Se purificó la mezcla a través de una columna de gel de sílice (hexanos/acetato de etilo 7:3), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,11 (d, 2H, *J*= 8,8), 6,85 (amplio s, 2H), 6,80 (d, 4H, *J*= 8,8), 4,21-4,04 (m, 6H), 3,91-3,80 (m, 5H), 3,32 (s, 3H), 3,10-2,95 (m, 4H), 2,94-2,91 (m, 2H), 2,20 (q, 2H, *J*= 5,9), 1,23 (t, 3H, *J*= 7,2).

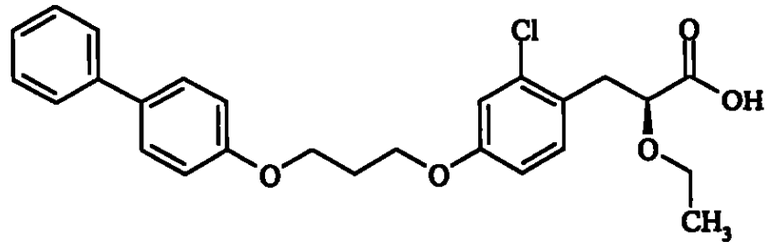
Etapa B

Ácido (2*S*)-2-metoxi-3-{4-[3-(4-morfolin-4-ilfenoxi)propoxi]fenil}propiónico

Se preparó el compuesto del título a partir de éster etílico de ácido (2*S*)-2-metoxi-3-{4-[3-(4-morfolin-4-ilfenoxi)propoxi]fenil}propiónico (Etapa A) por el procedimiento estándar de hidrólisis C (NaOH). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 9,90 (s, 1H), 7,30 (d, 2H, *J*= 9,1), 7,10 (d, 2H, *J*= 8,4), 6,91 (d, 2H, *J*= 9,1), 6,75 (d, 2H, *J*= 8,8), 4,18-3,90 (m, 9H), 3,43-3,33 (m, 7H), 3,02 (dd, 1H, *J*= 14,3, 4,8), 2,90 (dd, 1H, *J*= 14,3, 7,0), 2,18 (q, 2H, *J*= 5,9).

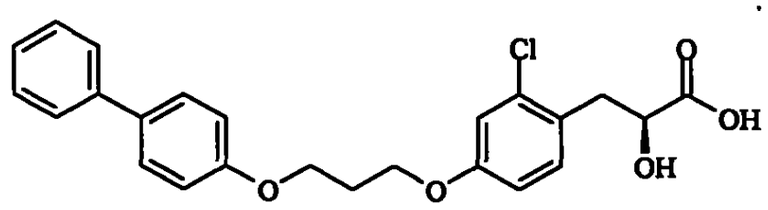
Ejemplo 281

Ácido (2*S*)-3-{4-[3-(bifenil-4-iloxi)propoxi]-2-clorofenil}-2-etoxipropiónico



Etapa A

Éster etílico del ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-clorofenil}-2-hidroxipropiónico



Se añadió tribromuro de boro (0,03 mmol, 0,03 mL) a una solución de ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-clorofenil}-2-metoxipropiónico (0,06 mmol, 25,5 mg) (Ejemplo 191) en CH_2Cl_2 (0,4 mL) a -78°C. Se calentó la mezcla a temperatura gradualmente y se agitó durante 12 horas. Se concentró el solvente a sequedad para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): δ 7,56-7,18 (m, 8H), 6,99-6,95 (m, 3H), 6,79-6,75 (m, 1H), 4,58-4,42 (m, 1H), 4,25-4,12 (m, 4H), 3,34-2,92 (m, 2H), 2,30-2,22 (m, 2H).

Etapa B

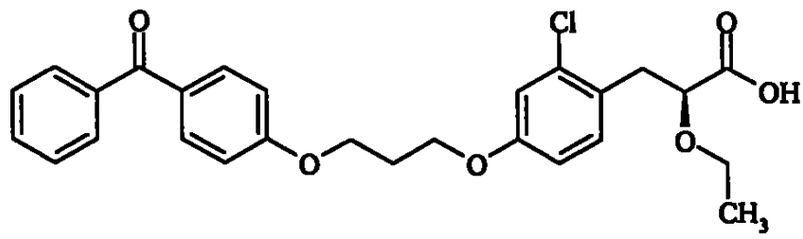
Ácido 3-{4-[3-(bifenil-4-iloxi)propoxi]-2-clorofenil}-2-etoxipropiónico

Se añadió yoduro de etilo (0,6 mmol, 0,05 mL) a una solución de ácido 3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-clorofenil}-2-hidroxipropiónico (Etapa A) y Ag_2O (0,09 mmol, 21 mg) en DMF (0,5 mL). Se calentó la mezcla a 50°C durante 24 horas. Se calentó la mezcla a temperatura ambiente y se añadió HCl 1N hasta pH 3. Se extrajo la fase acuosa con acetato de etilo (3 x 10 mL). Se secaron las capas orgánicas combinadas (Na_2SO_4), se filtraron y se evaporaron. Se purificó el producto bruto por cromatografía en gel de sílice (CH_2Cl_2), para obtener el compuesto del título. ^{1}H-RMN ($CDCl_3$, 300,15 MHz): δ 7,56-7,51 (m, 4H), 7,44-7,39 (m, 2H), 7,30 (t, 1H, J= 7,3), 7,20 (d, 1H, J= 8,5), 6,99 (d, 2H, J= 8,7), 6,95 (d, 1H,

J= 2,4), 6,77 (dd, 1H, J= 8,5, 2,4), 4,21-4,13 (m, 5H), 3,64-3,54 (m, 1H), 3,44-3,34 (m, 1H), 3,29 (dd, 1H, J= 14,1, 4,2), 3,01 (dd, 1H, J= 14,1, 8,7), 2,28 (q, 2H, J= 6,0), 1,12 (t, 3H, J= 6,9).

Ejemplo 282

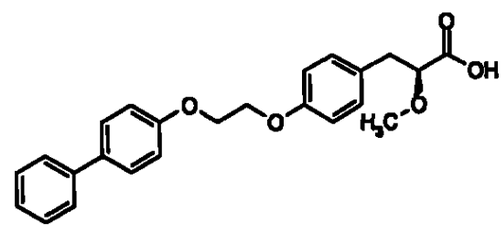
Ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-2-clorofenil}-2-etoxipropiónico



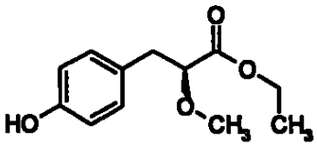
Se preparó el compuesto del título a partir de ácido 3-{4-[3-(4-benzoilfenoxi)propoxi]-2-cloro-fenil}-2-metoxipropiónico (Ejemplo 193) siguiendo el mismo procedimiento que en el Ejemplo 281 (Etapas A y B). ^{1}H-RMN ($CDCl_3$, 300,15 MHz): δ 7,82 (d, 2H, J= 8,7), 7,76 (d, 2H, J= 8,1), 7,61-7,55 (m, 1H), 7,50-7,45 (m, 2H), 7,18 (d, 1H, J= 8,5), 6,99-6,95 (m, 3H), 6,77 (dd, 1H, J= 8,5, 2,4), 4,25 (t, 2H, J= 5,9), 4,17-4,14 (m, 3H), 3,61-3,38 (m, 2H), 3,29 (dd, 1H, J= 14,1, 4,9), 3,02 (dd, 1H, J= 14,1, 8,1), 2,31 (q, 2H, J= 5,9), 1,14 (t, 3H, J= 7,1).

Ejemplo 283

Ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico

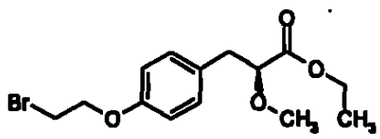


Etapa 1: éster etílico de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico



Se disolvió el compuesto ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico (5,1 mmol) en 50 ml. de etanol y se añadieron 0,3 ml (5,6 mmol) de ácido sulfúrico. Se agitó la mezcla a temperatura ambiente durante 18 horas y se concentró después. Se diluyó la mezcla con agua (55 ml) y se añadió $NaHCO_3$ (310 mg, 3,7 mmol). Se extrajo esta mezcla con acetato de etilo (4 x 20 mL) y se secaron las capas orgánicas combinadas ($MgSO_4$) y se concentraron después para producir un aceite amarillo. ^1H-RMN ($CDCl_3$, 200,15 MHz): 7,07 (d, 2H, J=8,6), 6,72 (d, 2H, J=8,6), 5,42 (s a, 1H), 4,18 (c, 2H, J=7,3), 3,92 (dd, 1H, J=6,7, 5,9), 3,36 (s, 3H), 2,95 (d, 2H, J=6,7), 1,23 (t, 3H, J=7,3).

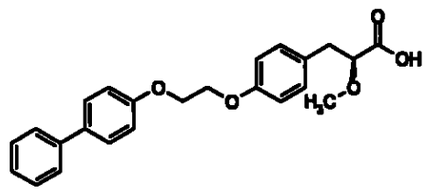
Etapa 2: éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)-fenil]-2-metoxipropiónico



Se calentó una mezcla que contenía el éster etílico de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico obtenido en la Etapa 1 (0,223 mol, 50 mg), carbonato de potasio (0,446 mol, 50 mg), sulfato de magnesio (en polvo, 50 mg, 1 g/g), dibromuro de etileno (3,35 mol, 628 mg) y EtOH (25 mL) a reflujo (78-76°C) durante 24 horas y se enfrió a temperatura ambiente. Se calentó la mezcla de nuevo a reflujo (76,5-77°C) y se añadieron 2 mL de dibromuro de etileno. Se calentó la mezcla durante otras 12

horas a 79,5-80,1°C y se enfrió después a la temperatura ambiente y se filtró a vacío. Se concentró el filtrado a vacío y se purificó el residuo por cromatografía en columna (gel de sílice, hexanos/acetato de etilo 6:1, Rf 0,27), para producir un aceite incoloro. MS (ES) para $C_{14}H_{19}BrO_4$ $[M+Na]^+$: 353,0.

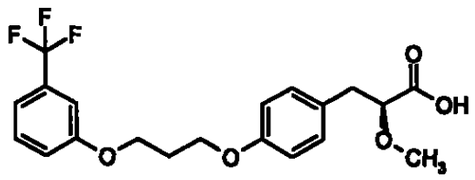
Etapa 3: ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico



Se trató una solución de bifenil-4-ol (0,39 mmol, 68 mg) en 10 ml de DMF con el éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico obtenido en la Etapa 2 (0,33 mmol, 100 mg) y carbonato de cesio (0,66 mmol, 214 mg) en un matraz de fondo redondo. Se filtraron los reactivos y se lavaron con DMF varias veces y se evaporó el solvente a vacío. Se reconstituyó el residuo en una mezcla de etanol (20 ml) y NaOH (1M, 8 ml) se agitó después a temperatura ambiente hasta que la TLC indicó la desaparición del material de partida. Se eliminó el etanol a vacío y se diluyó la solución acuosa con 20 mL de salmuera y se lavó con éter dietílico (3 x 15 mL). Se acidificó la fase acuosa con HCl 1N (pH 1-2) y se extrajo con acetato de etilo (3 x 15 mL). Se secó la capa orgánica ($MgSO_4$) y se concentró a vacío, para obtener el compuesto del título. MS (ES) para $C_{24}H_{24}O_5$ $[M+Na]^+$: 415,4.

Ejemplo 284

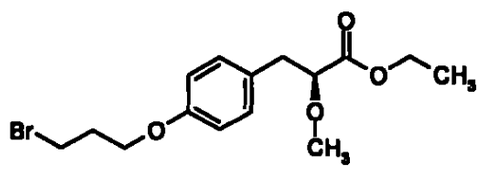
Ácido (2S)-2-metoxi-3-{4-[3-(3-trifluorometilfenoxi)propoxi]fenil}propiónico



Etapa 1: 3-bromopropan-1-ol

Se disolvió el compuesto 1,3-propanodiol (10,26 g, 134,8 mmol) en benceno (150 mL) y se añadió HBr al 48% (16,84 mL). Se sometió la mezcla a reflujo bajo eliminación azeotrópica de agua durante 24 horas. Se destiló el solvente a la presión atmosférica y se diluyó el residuo con éter (150 mL) y se lavó con agua (3 x 50 mL). Se secó la capa orgánica sobre $MgSO_4$ y se concentró, para obtener un aceite amarillento. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 3,80 (t, 2H, J=6,4), 3,54 (t, 2H, J=6,5), 2,10 (q, 2H, J=6,4).

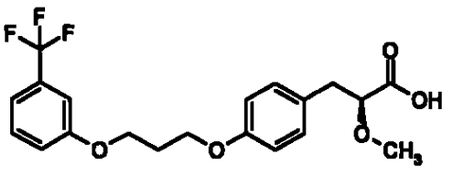
Etapa 2: éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico



Se trató una solución de trifenilfosfina (4,77 mmol, 1.250 mg) en 50 mL de tolueno seco a 0°C con azodicarboxilato de diisopropilo (4,77 mmol, 964,5 mg) y se agitó durante aproximadamente 20 minutos. Se añadió una solución de éster etílico de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico (Ejemplo 283, Etapa 1) (4,46 mmol, 1.000 mg) y 3-bromopropan-1-ol (4,77 mmol, 663 mg) en 10 mL de THF seco y se agitó la mezcla a temperatura ambiente durante la noche. Se concentró la mezcla a se-

quedad a vacío y se purificó por cromatografía en gel de sílice (gel de sílice, hexanos/acetato de etilo 6:1). Se combinó la fracción con Rf de 0,4 correspondiente al compuesto acoplado y se concentró a sequedad para obtener un aceite amarillo. MS (ES) para $C_{15}H_{21}BrO_4$ $[M+Na]^+$: 367,2.

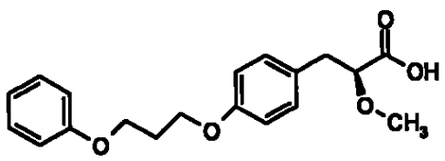
Etapa 3: ácido (2S)-2-metoxi-3-{4-[3-(3-trifluorometilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 3-trifluorometilfenol mediante el mismo procedimiento que el utilizado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3), para producir un sólido amarillo. MS (ES) para $C_{20}H_{21}F_3O_5$ $[M+NH_4]^+$: 421,4.

Ejemplo 285

<u>Ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico</u>

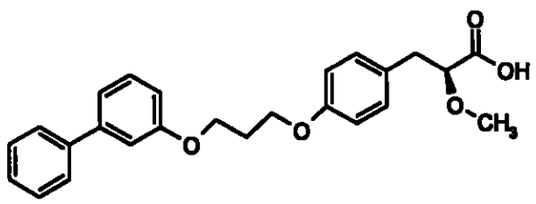


Se trató una solución de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) (0,1 mmol, 32 mg) en 0,7 ml de DMF, en un tubo de 16 x 100 mm, con fenol (0,15 mmol, 15 mg) y carbonato de cesio (0,3 mmol, 95 mg). Se agitó la mezcla a temperatura ambiente durante la noche, y se filtraron los reactivos y se lavaron con DMF varias veces.

Se evaporó el solvente a vacío y se reconstituyó el residuo en una mezcla de etanol (2 ml) y NaOH (1M, 1 ml), la cual fue agitada a temperatura ambiente hasta completarse la reacción por HPLC-MS. Tras completarse, se añadió HCl (1M) (pH=3) y se eliminaron los solventes a vacío. Se reconstituyó el residuo en CH_2Cl_2/H_2O y se filtró a través de una jeringa hidrofóbica. Se separó la capa orgánica, se concentró y se purificó por HPLC-MS, para obtener el compuesto del título como un aceite incoloro. MS (ES) para $C_{19}H_{22}O_5$ $[M+NH_4]^+$: 348,4.

Ejemplo 286

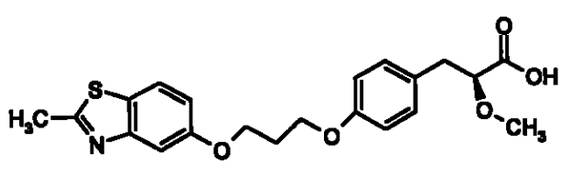
Ácido (2S)-3-{4-[3-(bifenil-3-iloxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y bifenil-3-ol mediante el mismo procedimiento que el utilizado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{25}H_{26}O_5$ $[M+Na]^+$: 429,4.

Ejemplo 287

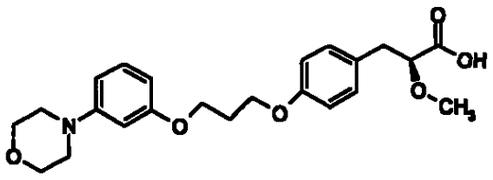
Ácido (2S)-2-metoxi-3-{4-[3-(2-metilbenzotiazol-5-iloxi)-propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 2-metilbenzotiazol-5-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{21}H_{23}NO_5S$ $[M+H]^+$: 402,4.

Ejemplo 288

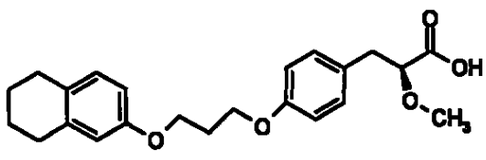
Ácido (2S)-2-metoxi-3-{4-[3-(3-morfolin-4-ilfenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 3-morfolin-4-ilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{23}H_{29}NO_6$ $[M+H]^+$: 416,4.

Ejemplo 289

Ácido (2S)-2-metoxi-3-{4-[3-(5,6,7,8-tetrahidronaftalen-2-iloxi)propoxi]fenil}propiónico

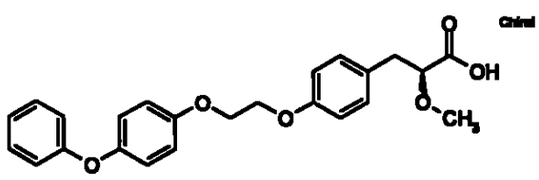


Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 5,6,7,8-

tetrahidronaftalen-2-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3), para producir un sólido blanco. MS (ES) para $C_{23}H_{28}O_5$ $[M+Na]^+$: 402,4.

Ejemplo 290

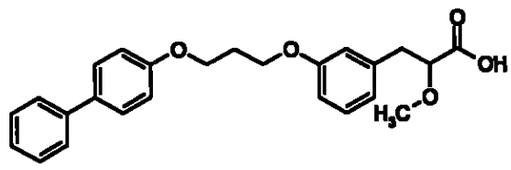
Ácido 2-metoxi-3-{4-[2-(4-fenoxifenoxi)etoxi]fenil}propiónico



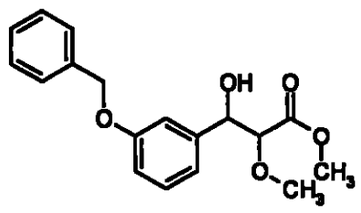
Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 4-fenoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)-etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3) para producir un sólido blanco. MS (ES) para $C_{24}H_{24}O_6$ $[M+NH_4]^+$: 426,0.

Ejemplo 291

Ácido 3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico (isómero 1)

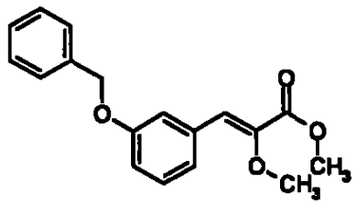


Etapa 1: éster metílico del ácido 3-(3-benciloxifenil)-3-hidroxi-2-metoxipropiónico



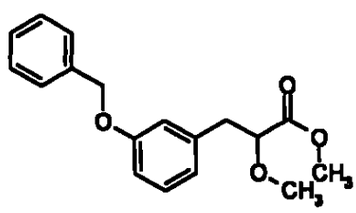
Se añadió trimetilsililamiduro de sodio 1M en THF (20,73 mL, 20,73 mmol) a un matraz de fondo redondo de 2 cuellos bajo nitrógeno. Se puso el matraz en un baño de acetona enfriado a aproximadamente -78°C. Se añadió una solución de 2-metoxiacetato de metilo (2,34 mL, 23,55 mmol) y 3-benciloxibenzaldehído (4,0 g, 18,85 mmol) en THF seco (24 mL) por goteo mediante una cánula a lo largo de 10 minutos. Se agitó la mezcla a -78°C durante 3 horas. La HPLC-MS mostró la presencia del aldehído de partida en este punto. Se añadieron 10 mL de NaHDMS adicionales y se agitó la mezcla durante otra hora más y luego se añadió HCl 3N (50 mL) a la mezcla a -78°C. Se retiró el baño y se extrajo la mezcla con éter dietílico (4 x 50 mL). Se secaron las capas orgánicas combinadas sobre $MgSO_4$ y se concentraron para obtener un aceite, que fue purificado por cromatografía (gel de sílice, hexanos/acetato de etilo 3:1). Rf 0,13. (Dos isómeros) ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,45-7,22 (m, 12H), 7,05-6,89 (m, 6H), 5,07 (d, 4H, J=1,1), 4,93 (dd, 2H, J=11,8, 5,9), 3,97 (d, 1H, J=5,6), 3,89 (d, 1H, J=5,4), 3,67 (s, 3H), 3,65 (s, 3H), 3,40 (s, 3H), 3,37 (s, 3H), 2,92 (s a, 1H), 2,83 (s a, 1H).

Etapa 2: éster metílico del ácido 3-(3-benciloxifenil)-2-metoxiacrílico



Se disolvieron los compuestos éster metílico de ácido 3-(3-benciloxifenil)-3-hidroxi-2-metoxipropiónico (Ejemplo 291, Etapa 1) (4,06 g, 12,84 mmol), trietilamina (7,15 mL, 51,33 mmol) y 4-(N,N-dimetilamino)piridina (0,157 g, 1,28 mmol) en diclorometano (20 mL) en un matraz de fondo redondo y se enfriaron luego a 0°C en un baño de hielo. Se añadió cloruro de mesilo (1,093 mL, 14,1 mmol) por goteo mediante una jeringa y se agitó la mezcla a temperatura ambiente hasta que no se observó nada de aldol de partida por HPLC-MS (4 días, se añadieron 0,2 mL adicionales de MsCl cada día). Se diluyó la mezcla con 200 mL de éter dietílico, se lavó con HCl (1N, 3 x 40 mL) y 40 mL de salmuera y se secó sobre $MgSO_4$. La concentración de la mezcla dio 3,96 g de una mezcla 2,5:1 del acrilato y un isómero simple del intermediario mesilato, que fue directamente usada en la siguiente Etapa. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,46-7,26 (m, 8H), 6,99-6,93 (m, 1H), 5,10 (s, 2H), 3,85 (s, 3H), 3,72 (s, 3H).

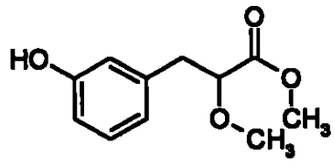
Etapa 3: éster metílico del ácido 3-(3-benciloxifenil)-2-metoxipropiónico



Se puso una solución de éster metílico de

ácido 3-(3-benciloxifenil)-2-metoxiacrílico (Ejemplo 291, Etapa 2) (3,96 g) en metanol (10 mL) en un matraz de fondo redondo equipado con un condensador de reflujo. Se enfrió la mezcla a 0°C y se añadieron virutas de Mg (6,45 g). Se agitó la mezcla inicialmente de forma vigorosa y luego se agitó a temperatura ambiente durante aproximadamente una hora. Se evaporó el solvente a vacío y se añadieron 100 mL de éter dietílico al sólido resultante. Se añadió HCl (3N, 100 mL) y se agitó la solución durante un minuto. Se separó la capa orgánica de la suspensión y se añadieron 100 mL de éter dietílico y HCl (3N, 100 mL) al resto de la suspensión. Se repitió el procedimiento hasta disolverse todo el sólido. Se lavaron los extractos etéreos combinados con salmuera y se secaron sobre $MgSO_4$. La concentración de la mezcla dio un aceite amarillo, que era aproximadamente un 90% puro por RMN. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,45-7,17 (m, 6H), 6,88-6,81 (m, 3H), 5,05 (s, 2H), 3,97 (dd, 1H, J=7,3, 5,4), 3,72 (s, 3H), 3,34 (s, 3H), 3,00 (d, 1H, J=5,1), 2,99 (d, 1H, J=7,8).

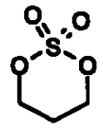
Etapa 4: éster metílico del ácido 3-(3-hidroxifenil)-2-metoxipropiónico



Se pusieron los compuestos éster metílico de ácido 3-(3-benciloxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 3) (3,15 g, 10,49 mmol) y Pd al 10% sobre carbono activado (0,558 g, 0,524 mmol) en un matraz de 250 ml de fondo redondo equipado con una barra agitadora magnética. Se añadieron 100 mL de metanol y se burbujeó hidrógeno a través de la solución durante 10 minutos. Se selló el matraz con un septo de caucho y se conectó un balón que contenía 250 mL de hidrógeno al matraz a través

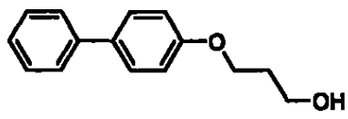
de una aguja. Se agitó la mezcla a temperatura ambiente durante 5 horas y se concentró después a sequedad a vacío. Se recogió el residuo en acetato de etilo y se filtró a través de una almohadilla de celita. La concentración de la mezcla dio un aceite. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,15 (dt, 1H, J=1,1, 7,0), 6,79-6,68 (m, 3H), 5,27 (s a, 1H), 3,98 (dd, 1H, J=7,5, 5,6), 3,73 (s, 3H), 3,35 (s, 3H), 2,97 (d, 1H, J=3,8), 2,97 (d, 1H, J=9,1).

Etapa 5: 2,2-dióxido de [1,3,2]dioxatiano



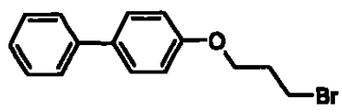
Se añadió cloruro de tionilo (36 mL, 491 mmol) a una solución de 1,3-propanodiol (30 g, 394 mmol) en CCl_4 (278 mL) mediante jeringa. Se calentó la mezcla a reflujo durante 1,5 horas y se enfrió a 0°C para evaporar el solvente a vacío. Se disolvió el residuo en una mezcla de $CCl_4/CH_3CN/H_2O$ (2:2:3=500 mL) y se enfrió a 0°C. Se añadió tricloruro de rutenio trihidrato (0,556 g, 2,68 mmol), seguido de adición de $NaIO_4$ sólido (14,35 g, 197 mmol). Se agitó la mezcla a temperatura ambiente durante 1 hora y se añadió luego H_2O (1 L). Se extrajo la fase acuosa con éter dietílico (4 x 300 mL). Se lavaron las capas orgánicas combinadas con salmuera (2 x 100 mL), se secaron ($MgSO_4$) y se filtraron a través de una almohadilla gel de sílice, para eliminar las sales de rutenio. Se evaporó el solvente y se añadieron hexanos (200 mL) al aceite resultante. Después de enfriar, precipitó un sólido gris, el cual fue filtrado y lavado con hexanos. La recristalización a partir de hexanos/éter dio lugar a un sólido blanco cristalino. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 4,73 (t, 4H, J=5,6), 2,13 (q, 2H, J=5,6).

Etapa 6: 3-(bifenil-4-iloxi)propan-1-ol



Se agitó una solución de 4-fenilfenol (4,9 g, 29,0 mmol) y terc-butóxido de potasio (3,64 g, 30,3 mmol) en THF (100 mL) a temperatura ambiente durante 30 minutos. Se enfrió la solución a 0°C y se añadió 2,2-dióxido de [1,3,2]dioxatiano (Ejemplo 291, Etapa 5) (3,6 g, 26,34 mmol) en THF (25 mL). Se agitó la mezcla a temperatura ambiente durante 5 horas y se eliminó el solvente a vacío. Se disolvió el residuo en HCl 6N (15 mL) y se calentó a 100°C durante 16 horas. Se enfrió la mezcla a temperatura ambiente y se extrajo la fase acuosa con acetato de etilo (3 x 30 mL). Se lavaron las capas orgánicas combinadas con H_2O (3 x 25 mL) y salmuera (25 mL), se secaron ($MgSO_4$), se filtraron y se concentraron para producir un sólido blanco. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,49 (m, 4H), 7,45-7,37 (m, 3H), 6,98 (dd, 2H, J=6,72, 2,14), 4,17 (t, 2H, J=5,9), 3,88 (c, 2H, J=5,9), 2,07 (q, 2H, J=5,9).

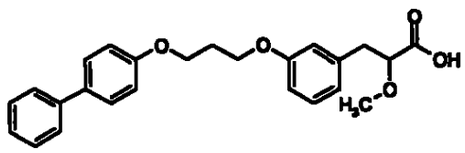
Etapa 7: 4-(3-bromopropoxi)bifenilo



Se añadió trifenilfosfina (1,61 g, 6,14 mmol) a una solución de 3-(bifenil-4-iloxi)propan-1-ol (Ejemplo 291, Etapa 6) (1,00 g, 4,38 mmol) y tetrabromuro de carbono (1,81 g, 5,47 mmol) en CH_2Cl_2 (20 mL) a 0°C. Se calentó la mezcla a temperatura ambiente y se agitó durante una hora y se extrajo después con acetato de etilo (50 mL). Se lavó la capa orgánica con H_2O (3 x 50 mL) y salmuera (3 x 25 mL) y se secó después ($MgSO_4$), se filtró y

se concentró. Se purificó el producto bruto por cromatografía en columna de gel de sílice (gel de sílice, hexanos/acetato de etilo, 9:1), para producir 4-(3-bromopropoxi)bifenilo. ^{1}H-RMN (200,15 MHz, $CDCl_3$): δ 7,57-7,29 (m, 7H), 6,98 (dd, 2H, J=6,72, 1,88), 4,15 (t, 2H, J=5,92), 3,62 (t, 2H, J=6,44), 2,34 (q, 2H, J=5,92).

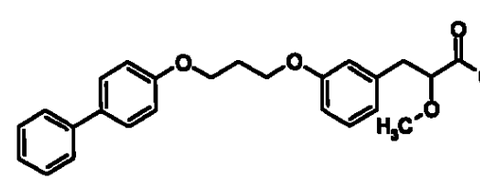
Etapa 8: ácido 3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico (isómero 1)



Se preparó el compuesto del título a partir de 4-(3-bromopropoxi)bifenilo (Ejemplo 291, Etapa 7) y éster metílico de ácido 3-(3-hidroxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 4) (0,3 g, 1,42 mmol) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3). Se sometió el material bruto a separación por HPLC quiral para obtener el enantiómero simple del isómero 1. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,57-7,17 (m, 7H), 6,99 (dd, 2H, J=6,7, 2,2), 6,85-6,80 (m, 3H), 4,19 (dd, 4H, J=13,4, 6,4), 4,03 (dd, 1H, J=7,3, 4,3), 3,40 (s, 3H), 0,14 (dd, 1H, J=14,0, 4,3), 2,98 (dd, 1H, J=14,8, 7,5), 2,28 (q, 2H, J=5,9).

Ejemplo 292

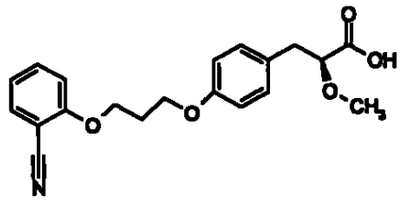
Ácido 3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico (isómero 2)



Se preparó el compuesto del título a partir de 4-(3-bromopropoxi)bifenilo (Ejemplo 291, Etapa 7) y éster metílico de ácido 3-(3-hidroxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 4) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3). Se sometió el material bruto a separación por HPLC quiral para obtener el enantiómero simple del isómero 2. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,57-7,17 (m, 7H), 6,99 (dd, 2H, J=6,7, 2,2), 6,85-6,80 (m, 3H), 4,19 (dd, 4H, J=13,4, 6,4), 4,03 (dd, 1H, J=7,3, 4,3), 3,40 (s, 3H),,14 (dd, 1H, J=14,0, 4,3), 2,98 (dd, 1H, J=14,8, 7,5), 2,28 (q, 2H, J=5,9).

Ejemplo 293

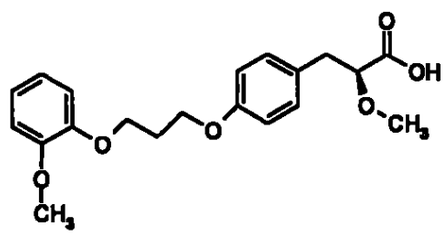
Ácido (2S)-3-{4-[3-(2-cianofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 2-hidroxibenzonitrilo mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{20}H_{21}NO_5$ $[M+NH_4]^+$: 373,4.

Ejemplo 294

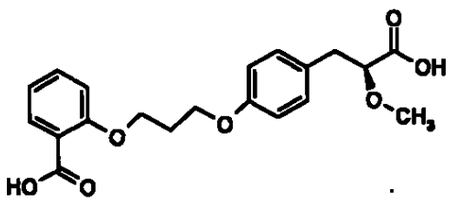
Ácido (2S)-2-metoxi-3-{4-[3-(2-metoxifenoxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 2-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{20}H_{24}O_6$ $[M+NH_4]^+$: 378,4.

Ejemplo 295

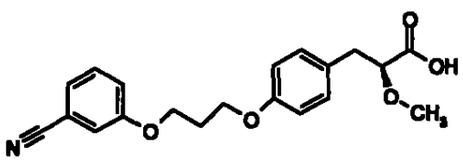
Ácido (2S)-2-{3-[4-(2-carboxi-2-metoxietil)fenoxi]propoxi}benzoico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y éster metílico de ácido 2-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{20}H_{22}O_7$ $[M+H]^+$: 375,2.

Ejemplo 296

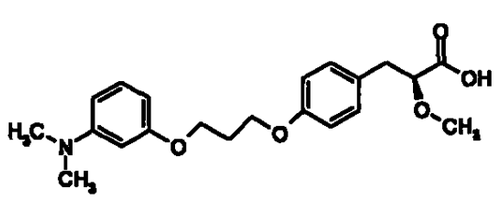
Ácido (2S)-3-{4-[3-(3-cianofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 3-hidroxibenzonitrilo mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{20}H_{21}NO_5$ $[M+NH_4]^+$: 373,4.

Ejemplo 297

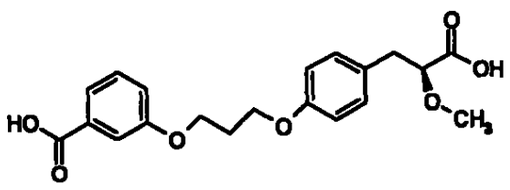
Ácido (2S)-3-{4-[3-(3-dimetilaminofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 3-dimetilaminofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{21}H_{27}NO_5$ $[M+H]^+$: 374,4.

Ejemplo 298

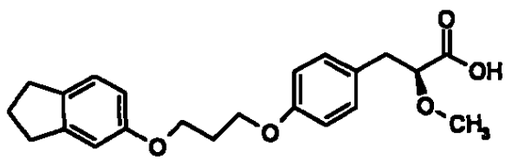
Ácido (2S)-3-{3-[4-(2-carboxi-2-metoxietil)fenoxi]propoxi}benzoico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)-fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y éster metílico de ácido 3-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{20}H_{22}O_7$ $[M+Na]^+$: 397,4.

Ejemplo 299

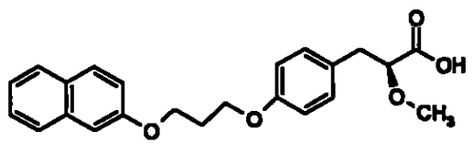
Ácido (2S)-3-{4-[3-(indan-5-iloxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y indan-5-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{22}H_{26}O_5$ $[M+Na]^+$: 393,4.

Ejemplo 300

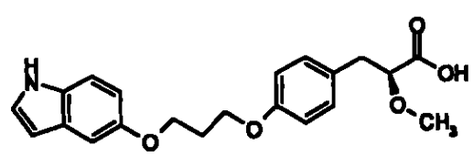
Ácido (2S)-2-metoxi-3-{4-[3-(naftalen-2-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y naftalen-2-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{23}H_{24}O_5$ $[M+Na]^+$: 403,4.

Ejemplo 301

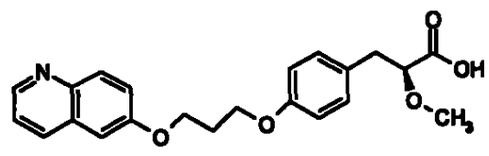
Ácido (2S)-3-{4-[3-(1H-indol-5-iloxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 1H-indol-5-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{21}H_{23}NO_5$ $[M+H]^+$: 370,4.

Ejemplo 302

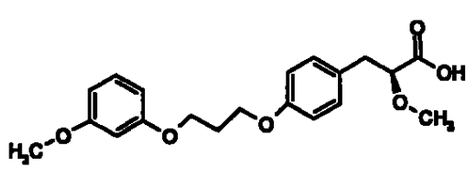
Ácido (2S)-2-metoxi-3-{4-[3-(quinolin-6-iloxi)propoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y quinolin-6-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{22}H_{23}NO_5$ $[M+H]^+$: 382,4.

Ejemplo 303

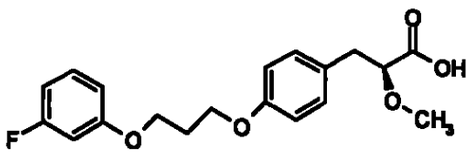
Ácido (2S)-2-metoxi-3-{4-[3-(3-metoxifenoxi)propoxi]fenil} propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 3-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{20}H_{24}O_6$ $[M+H]^+$: 361,4.

Ejemplo 304

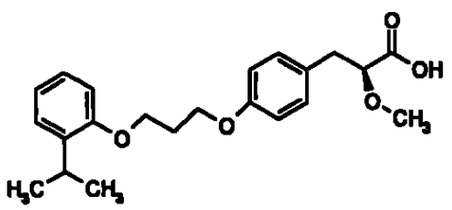
Ácido (2S)-3-{4-[3-(3-fluorofenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)-fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 3-fluorofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{19}H_{21}FO_5$ $[M+Na]^+$: 371,4.

Ejemplo 305

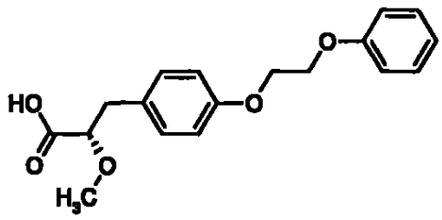
Ácido (2S)-3-{4-[3-(2-isopropilfenoxi)propoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(3-bromopropoxi)-fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2) y 2-isopropilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{22}H_{28}O_5$ $[M+NH_4]^+$: 390,4.

Ejemplo 306

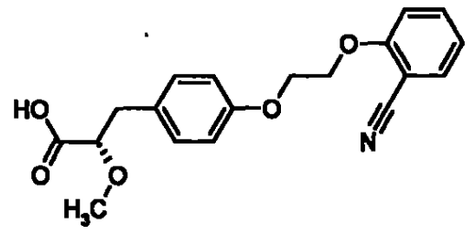
Ácido (2S)-2-metoxi-3-[4-(2-fenoxietoxi)fenil]propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y fenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{18}H_{20}O_5$ $[M+Na]^+$: 339,3.

Ejemplo 307

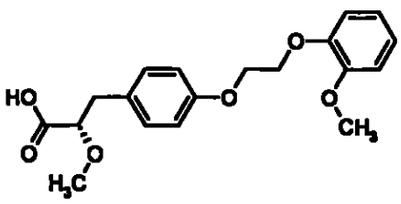
Ácido (2S)-3-{4-[2-(2-cianofenoxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 2-hidroxibenzonitrilo mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{19}H_{19}NO_5$ $[M-H]^-$: 340,3.

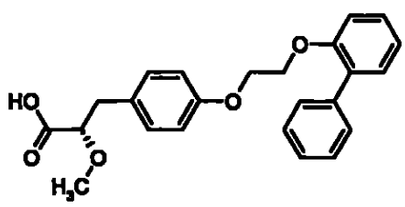
Ejemplo 308

Ácido (2S)-2-metoxi-3-{4-[2-(2-metoxifenoxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 2-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{19}H_{22}O_6$ Ejemplo 309: $[M+Na]^+$: 369,4.

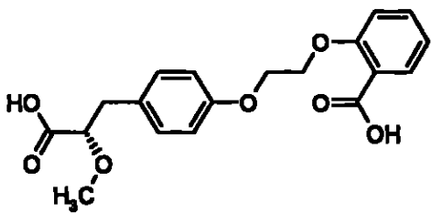
Ácido (2S)-3-{4-[2-(bifenil-2-iloxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y bifenil-2-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{24}H_{24}O_5$ $[M+Na]^+$: 415,4.

Ejemplo 310

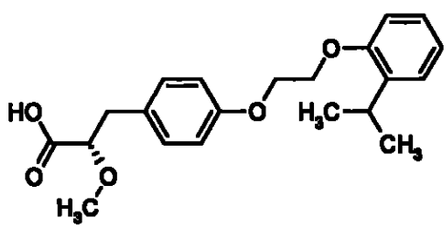
Ácido (2S)-2-{2-[4-(2-carboxi-2-metoxietil)fenoxi]etoxi}-benzoico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y éster metílico de ácido 2-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{19}H_{20}O_7$ $[M+Na]^+$: 383,3.

Ejemplo 311

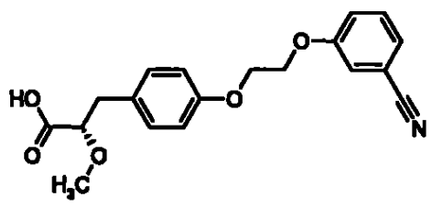
Ácido (2S)-3-{4-[2-(2-isopropilfenoxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 2-isopropilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{21}H_{26}O_5$ $[M+Na]^+$: 381,4.

Ejemplo 312

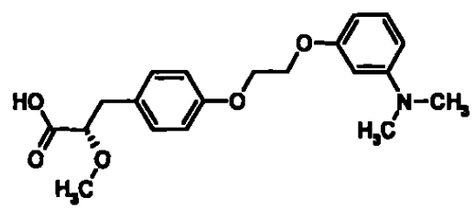
Ácido (2S)-3-{4-[2-(3-cianofenoxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 3-hidroxibenzonitrilo mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{19}H_{19}NO_5$ [M-H]$^-$: 340,3.

Ejemplo 313

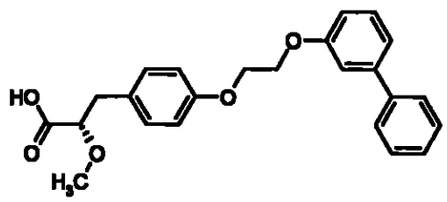
Ácido (2S)-3-{4-[2-(3-dimetilaminofenoxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 3-dimetilaminofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite amarillo. MS (ES) para $C_{21}H_{26}O_5$ [M+H]$^+$: 360,4.

Ejemplo 314

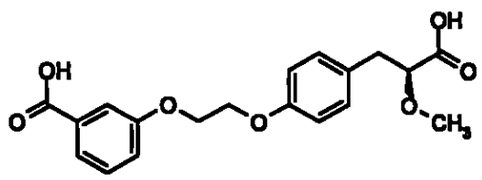
Ácido (2S)-3-{4-[2-(bifenil-3-iloxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y bifenil-3-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{24}H_{24}O_5$ $[M-H]^-$: 391,4.

Ejemplo 315

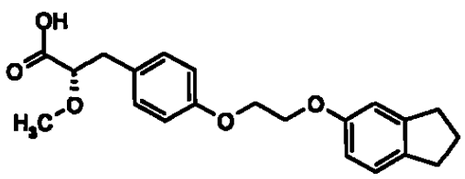
Ácido (2S)-3-{2-[4-(2-carboxi-2-metoxietil)fenoxi]etoxi}-benzoico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y éster metílico de ácido 3-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{19}H_{20}O_7$ $[M-H]^-$: 359,3.

Ejemplo 316

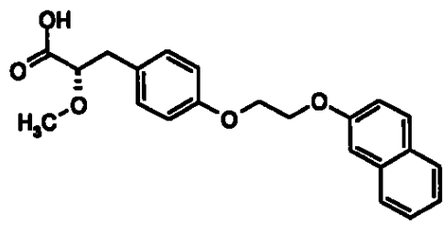
Ácido (2S)-3-{4-[2-(indan-5-iloxi)etoxi]fenil}-2-metoxi-propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y indan-5-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{21}H_{24}O_5$ $[M-H]^-$: 355,3.

Ejemplo 317

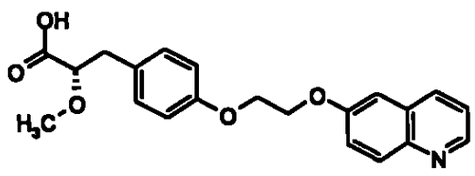
Ácido (2S)-2-metoxi-3-{4-[2-(naftalen-2-iloxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y naftalen-2-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{22}H_{22}O_5$ $[M+Na]^+$: 389,3.

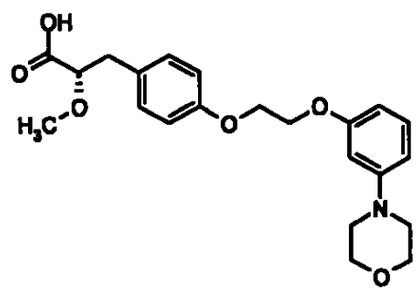
Ejemplo 318

Ácido (2S)-2-metoxi-3-{4-[2-(quinolin-6-iloxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y quinolin-6-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{21}H_{21}NO_5$ Ejemplo 368,3.

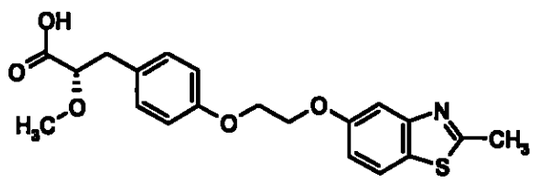
Ácido (2S)-2-metoxi-3-{4-[2-(3-morfolin-4-ilfenoxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 3-morfolin-4-ilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite amarillo. MS (ES) para $C_{22}H_{27}NO_6$ $[M+H]^+$: 402,4.

Ejemplo 320

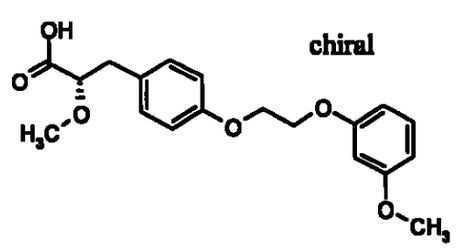
Ácido (2S)-2-metoxi-3-{4-[2-(2-metilbenzotiazol-5-iloxi)-etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 2-metil-benzotiazol-5-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite amarillo. MS (ES) para $C_{20}H_{21}NO_5S$ $[M+H]^+$: 388,3.

Ejemplo 321

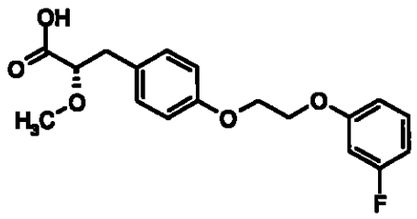
Ácido (2S)-2-metoxi-3-{4-[2-(3-metoxifenoxi)etoxi]fenil}-propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 3-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{19}H_{22}O_6$ $[M-H]^-$: 345,3.

Ejemplo 322

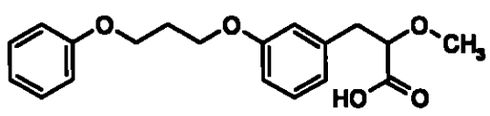
Ácido (2S)-3-{4-[2-(3-fluorofenoxi)etoxi]fenil}-2-metoxi-propiónico



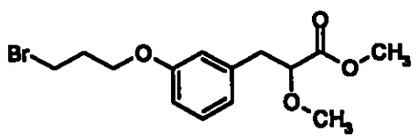
Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 3-fluorofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{18}H_{19}FO_5$ $[M-H]^-$: 333,3.

Ejemplo 323

Ácido 2-metoxi-3-[3-(3-fenoxipropoxi)fenil]propiónico (isómero 1)



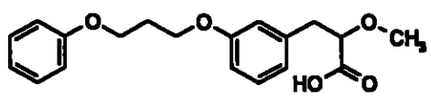
Etapa 1: éster metílico del ácido 3-[3-(3-bromopropoxi)-fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de 3-bromopropan-1-ol (Ejemplo 284, Etapa 1) y éster metílico de ácido 3-(3-hidroxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 4) mediante el mismo procedimiento que el usado para la preparación del éster etílico del

ácido (2S)-3-[4-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 284, Etapa 2). ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,26-7,16 (m, 1H), 6,80 (t, 3H, J=7,3), 4,09 (t, 2H, J=5,9), 3,97 (dd, 1H, J=7,3, 5,4), 3,73 (s, 3H), 3,60 (t, 2H, J=6,4), 3,36 (s, 3H), 3,00 (s, 1H), 2,97 (d, 1H, J=3,2), 2,31 (q, 2H, J=6,2).

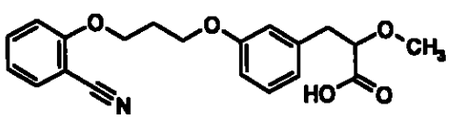
Etapa 2: (Isómero 1) Ácido 2-metoxi-3-[3-(3-fenoxipropoxi)fenil]propiónico



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y fenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{19}H_{22}O_5$ $[M+Na]^+$: 353,3.

Ejemplo 324

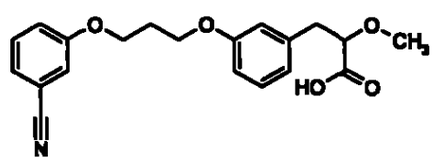
<u>Ácido 3-{3-[3-(2-cianofenoxi)propoxi]fenil}-2-metoxipropiónico (isómero 1)</u>



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-cianofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378,3.

Ejemplo 325

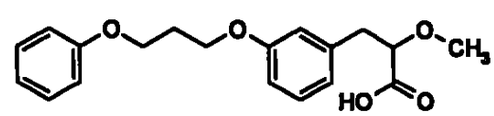
Ácido 3-{3-[3-(3-cianofenoxi)propoxi]fenil}-2-metoxipropiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 3-cianofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378,3.

Ejemplo 326

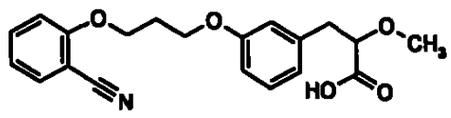
Ácido 2-metoxi-3-[3-(3-fenoxipropoxi)fenil]propiónico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y fenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{19}H_{22}O_5$ $[M+Na]^+$: 353,3.

Ejemplo 327

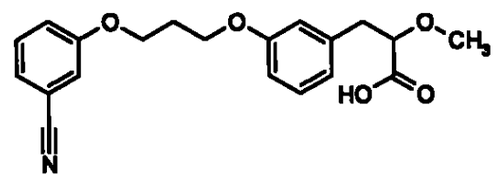
Ácido 3-{3-[3-(2-cianofenoxi)propoxi]fenil}-2-metoxipropiónico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-cianofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378,3

Ejemplo 328

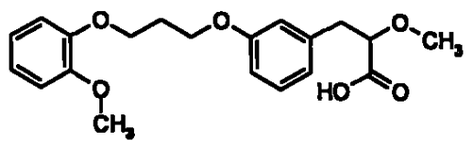
Ácido 3-{3-[3-(3-cianofenoxi)propoxi]fenil}-2-metoxipropiónico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 3-cianofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378,3

Ejemplo 329

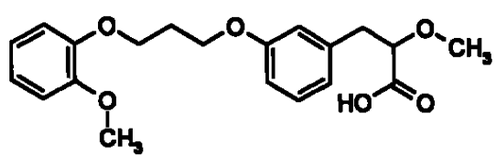
Ácido 2-metoxi-3-{3-[3-(2-metoxifenoxi)propoxi]fenil}propiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{24}O_6$ $[M+Na]^+$: 383,4.

Ejemplo 330

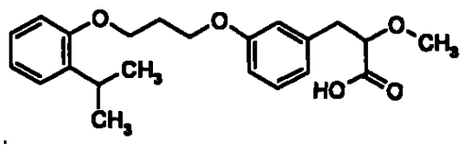
Ácido 2-metoxi-3-{3-[3-(2-metoxifenoxi)propoxi]fenil}-propiónico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{24}O_6$ $[M+Na]^+$: 383,4.

Ejemplo 331

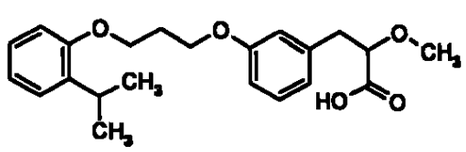
Ácido 3-{3-[3-(2-isopropilfenoxi)propoxi]fenil}-2-metoxi-propiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-isopropilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{22}H_{28}O_5$ $[M+Na]^+$: 395,4.

Ejemplo 332

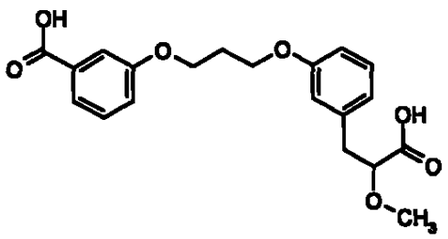
Ácido 3-{3-[3-(2-isopropilfenoxi)propoxi]fenil}-2-metoxi-propiónico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-isopropilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{22}H_{28}O_5$ $[M+Na]^+$: 395,4.

Ejemplo 333

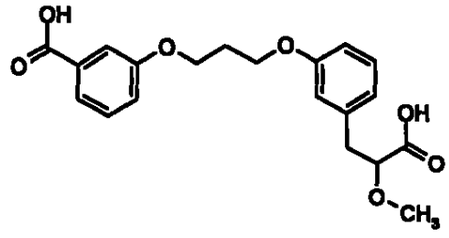
Ácido 3-{3-[3-(2-carboxi-2-metoxietil)fenoxi]propoxi}benzoico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y éster metílico de ácido 3-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{22}O_7$ $[M+Na]^+$: 397,4.

Ejemplo 334

Ácido 3-{3-[3-(2-carboxi-2-metoxietil)fenoxi]propoxi}benzoico (isómero 2)

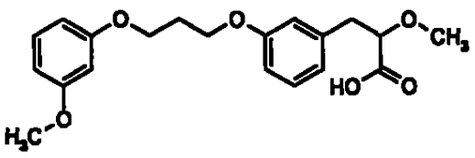


Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y éster metílico de ácido 3-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC

quiral. MS (ES) para $C_{20}H_{22}O_7$ $[M+Na]^+$: 397,4.

Ejemplo 335

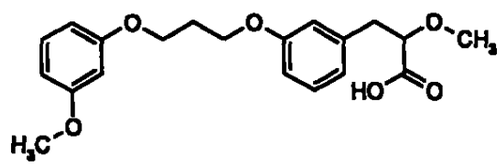
Ácido 2-metoxi-3-{3-[3-(3-metoxifenoxi)propoxi]fenil}propiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 3-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{24}O_6$ $[M+Na]^+$: 383,3.

Ejemplo 336

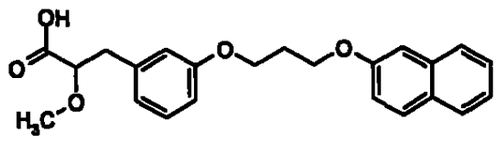
Ácido 2-metoxi-3-{3-[3-(3-metoxifenoxi)propoxi]fenil}propiónico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 3-metoxifenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{24}O_6$ $[M+Na]^+$: 383,3.

Ejemplo 337

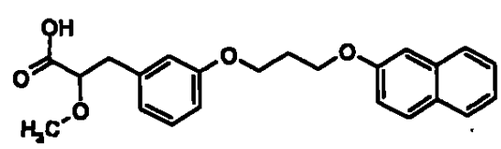
Ácido 2-metoxi-3-{3-[3-(naftalen-2-iloxi)propoxi]fenil}-propiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-naftol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,78-7,69 (m, 3H), 7,47-7,12 (m, 5H), 6,84-6,81 (m, 3H), 4,28 (t, 2H, J=5,9), 4,19 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,5, 4,0), 3,38 (s, 3H), 3,13 (dd, 1H, J=14,2, 4,3), 2,97 (dd, 1H, J=14,2, 7,5), 2,33 (q, 2H, J=6,2). MS (ES) para $C_{23}H_{24}O_5$ $[M+H]^+$: 381,2.

Ejemplo 338

Ácido 2-metoxi-3-{3-[3-(naftalen-2-iloxi)propoxi]fenil)-propiónico (isómero 2)

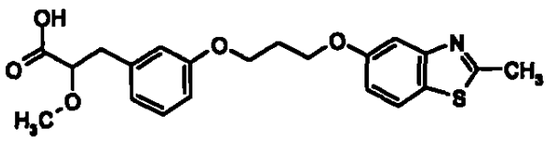


Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-naftol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,78-7,69 (m, 3H), 7,47-7,12 (m, 5H), 6,84-6,81 (m, 3H),

4,28 (t, 2H, J=5,9), 4,19 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,5, 4,0), 3,38 (s, 3H), 3,13 (dd, 1H, J=14,2, 4,3), 2,97 (dd, 1H, J=14,2, 7,5), 2,33 (q, 2H, J=6,2). MS (ES) para $C_{23}H_{24}O_5$ $[M+H]^+$: 381,2.

Ejemplo 339

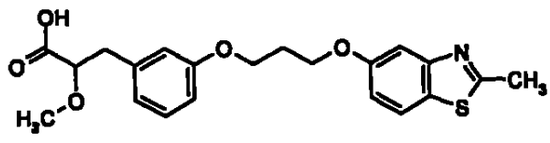
Ácido 2-metoxi-3-{3-[3-(2-metilbenzotiazol-5-iloxi)propoxi]fenil}propiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-metilbenzotiazol-5-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{21}H_{23}NO_5S$ $[M+H]^+$: 402,1.

Ejemplo 340

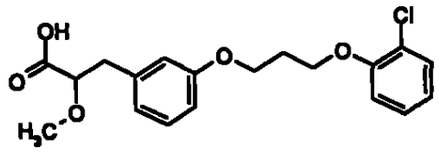
Ácido 2-metoxi-3-{3-[3-(2-metilbenzotiazol-5-iloxi)propoxi]fenil}propiónico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-metilbenzotiazol-5-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{21}H_{23}NO_5S$ $[M+H]^+$: 402,1.

Ejemplo 341

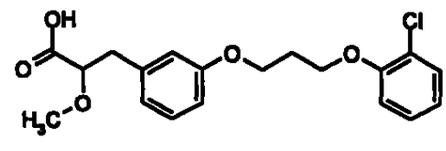
Ácido 3-{3-[3-(2-clorofenoxi)propoxi]fenil}-2-metoxipropiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-clorofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,35 (dd, 1H, J=8,1, 1,9), 7,24-7,16 (m, 2H), 6,97-6,80 (m, 5H), 4,22 (t, 2H, J=5,9), 4,20 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,3, 4,0), 3,39 (s, 3H), 3,13 (dd, 1H, J=14,2, 3,8), 2,97 (dd, 1H, J=14,0, 7,8), 2,30 (q, 2H, J=6,2). MS (ES) para $C_{19}H_{21}ClO_5$ $[M+Na]^+$: 387,2.

Ejemplo 342

Ácido 3-{3-[3-(2-clorofenoxi)propoxi]fenil}-2-metoxipropiónico (isómero 2)

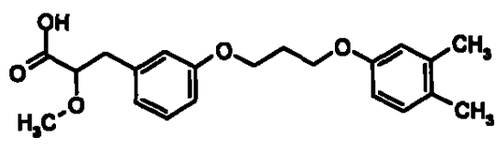


Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 2-clorofenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. ^{1}H-RMN ($CDCl_3$, 200,15 MHz):

7,35 (dd, 1H, J=8,1, 1,9), 7,24-7,16 (m, 2H), 6,97-6,80 (m, 5H), 4,22 (t, 2H, J=5,9), 4,20 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,3, 4,0), 3,39 (s, 3H), 3,13 (dd, 1H, J=14,2, 3,8), 2,97 (dd, 1H, J=14,0, 7,8), 2,30 (q, 2H, J=6,2). MS (ES) para $C_{19}H_{21}ClO_5$ $[M+Na]^+$: 387,2.

Ejemplo 343

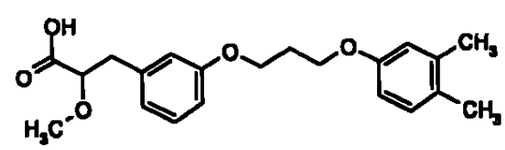
Ácido 3-{3-[3-(3,4-dimetilfenoxi)propoxi]fenil}-2-metoxi-propiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y 3,4-dimetilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,18 (d, 1H, J=7,5), 7,02 (d, 1H, J=8,3), 6,84-6,62 (m, 5H), 4,14 (t, 2H, J=6,4), 4,12 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,3, 4,0), 3,39 (s, 3H), 3,13 (dd, 1H, J=14,2, 4,6), 2,97 (dd, 1H, J=14,0, 7,5), 2,23 (c, 1H, J=6,2,1), 2,22 (s, 3H), 2,18 (s, 3H). MS (ES) para $C_{21}H_{26}O_5$ $[M+Na]^+$: 381,2.

Ejemplo 344

Ácido 3-{3-[3-(3,4-dimetilfenoxi)propoxi]fenil}-2-metoxi-propiónico (isómero 2)

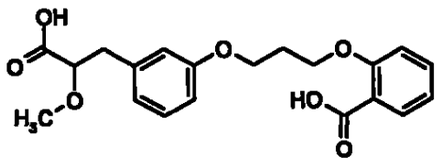


Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-

metoxipropiónico (Ejemplo 323, Etapa 1) y 3,4-dimetilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,18 (d, 1H, J=7,5), 7,02 (d, 1H, J=8,3), 6,84-6,62 (m, 5H), 4,14 (t, 2H, J=6,4), 4,12 (t, 2H, J=5,9), 4,02 (dd, 1H, J=7,3, 4,0), 3,39 (s, 3H), 3,13 (dd, 1H, J=14,2, 4,6), 2,97 (dd, 1H, J=14,0, 7,5), 2,23 (c, 1H, J=6,2,1), 2,22 (s, 3H), 2,18 (s, 3H). MS (ES) para $C_{21}H_{26}O_5$ $[M+Na]^+$: 381,2.

Ejemplo 345

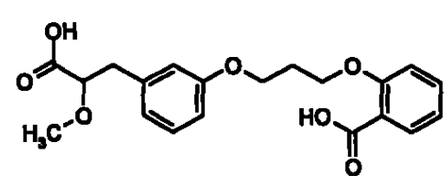
Ácido 2-{3-[3-(2-carboxi-2-metoxietil)fenoxi]propoxi}-benzoico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y ácido 2-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{22}O_7$ $[M+H]^+$: 375,2.

Ejemplo 346

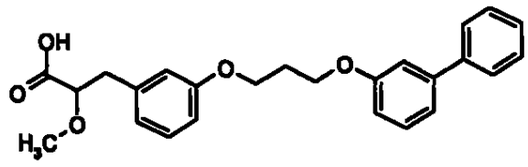
Ácido 2-{3-[3-(2-carboxi-2-metoxietil)fenoxi]propoxi}benzoico (isómero 2)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y ácido 2-hidroxibenzoico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{20}H_{22}O_7$ $[M+H]^+$: 375,2.

Ejemplo 347

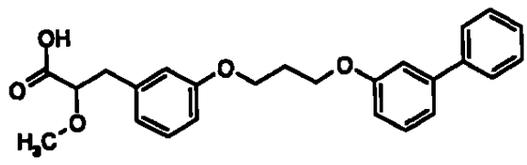
Ácido 3-{3-[3-(bifenil-3-iloxi)propoxi]fenil}-2-metoxipropiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y bifenil-3-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{25}H_{26}O_5$ $[M+Na]^+$: 429,2.

Ejemplo 348

Ácido 3-{3-[3-(bifenil-3-iloxi)propoxi]fenil}-2-metoxipropiónico (isómero 2)

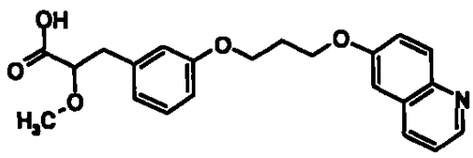


Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-

metoxipropiónico (Ejemplo 323, Etapa 1) y bifenil-3-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{25}H_{26}O_5$ $[M+Na]^+$: 429,2.

Ejemplo 349

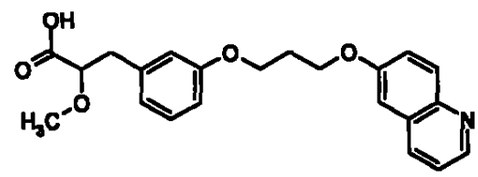
Ácido 2-metoxi-3-{3-[3-(quinolin-6-iloxi)propoxi]fenil}-propiónico (isómero 1)



Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y quinolin-6-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{22}H_{23}NO_5$ $[M+H]^+$: 382,2.

Ejemplo 350

Ácido 2-metoxi-3-{3-[3-(quinolin-6-iloxi)propoxi]fenil}-propiónico (isómero 2)

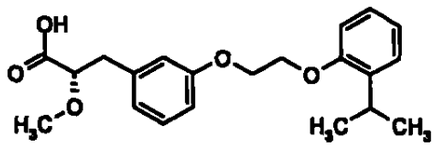


Se preparó el compuesto del título a partir de éster metílico de ácido 3-[3-(3-bromopropoxi)fenil]-2-metoxipropiónico (Ejemplo 323, Etapa 1) y quinolin-6-ol mediante el mismo procedimiento que el usado para la pre-

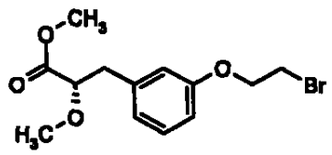
paración del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{22}H_{23}NO_5$ $[M+H]^+$: 382,2.

Ejemplo 351

Ácido 3-{3-[2-(2-isopropilfenoxi)etoxi]fenil}-2-metoxi-propiónico (isómero 2)

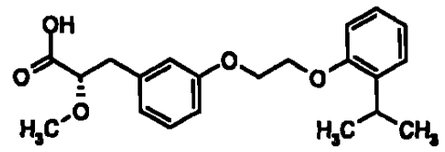


Etapa 1: éster metílico de ácido 3-[3-(2-bromoetoxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster metílico de ácido 3-(3-hidroxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 4) (4,76 mol, 1000 mg) mediante el mismo procedimiento que el usado para la preparación del éster etílico del ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2). MS (ES) para $C_{13}H_{17}BrO_4$ $[M+NH_4]^+$: 334,2.

Etapa 2: ácido 3-{3-[2-(2-isopropilfenoxi)etoxi]fenil}-2-metoxipropiónico (isómero 2)

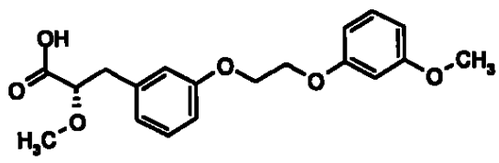


Se preparó el compuesto del título a partir de 2-isopropilfenol y éster metílico de ácido 3-[3-(2-

bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 351, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{21}H_{26}O_5$ $[M-H]^-$: 357,2.

Ejemplo 352

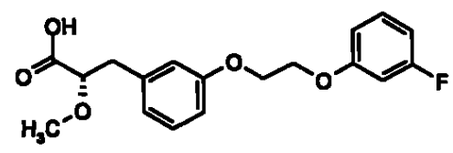
Ácido 2-metoxi-3-{3-[2-(3-metoxifenoxi)etoxi]fenil}propiónico (isómero 1)



Se preparó el compuesto del título a partir de 3-metoxifenol y éster metílico de ácido 3-[3-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 351, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{19}H_{22}O_6$ $[M-H]^-$: 345,1.

Ejemplo 353

Ácido 3-{3-[2-(3-fluorofenoxi)etoxi]fenil}-2-metoxipropiónico (isómero 1)

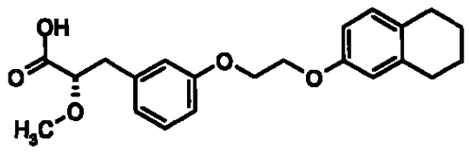


Se preparó el compuesto del título a partir de 3-fluorofenol y éster metílico de ácido 3-[3-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 351, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-

fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{18}H_{19}FO_5$ $[M-H]^-$: 333,1.

Ejemplo 354

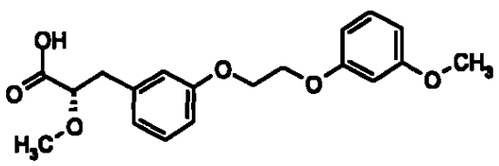
Ácido 2-metoxi-3-{3-[2-(5,6,7,8-tetrahidronaftalen-2-iloxi)etoxi]fenil}propiónico (isómero 1)



Se preparó el compuesto del título a partir de 5,6,7,8-tetrahidronaftalen-2-ol y éster metílico de ácido 3-[3-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 351, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{22}H_{26}O_5$ $[M-H]^-$: 369,2.

Ejemplo 355

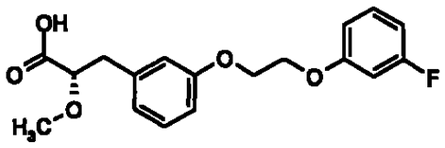
Ácido 2-metoxi-3-{3-[2-(3-metoxifenoxi)etoxi]fenil}propiónico (isómero 2)



Se preparó el compuesto del título a partir de 3-metoxifenol y éster metílico de ácido 3-[3-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 351, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{19}H_{22}O_6$ $[M-H]^-$: 345,1.

Ejemplo 356

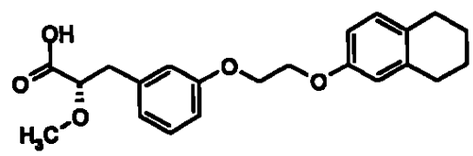
Ácido 3-{3-[2-(3-fluorofenoxi)etoxi]fenil}-2-metoxipropiónico (isómero 2)



Se preparó el compuesto del título a partir de 3-fluorofenol y éster metílico de ácido 3-[3-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 351, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{18}H_{19}FO_5$ $[M-H]^-$: 333,1.

Ejemplo 357

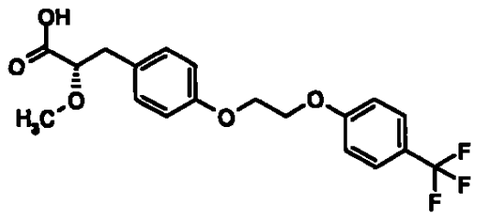
Ácido 2-metoxi-3-{3-[2-(5,6,7,8-tetrahidronaftalen-2-iloxi)etoxi]fenil}propiónico (isómero 2)



Se preparó el compuesto del título a partir de 5,6,7,8-tetrahidronaftalen-2-ol y éster metílico de ácido 3-[3-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 351, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1). Se separaron los enantiómeros por HPLC quiral. MS (ES) para $C_{22}H_{26}O_5$ $[M-H]^-$: 369,2.

Ejemplo 358

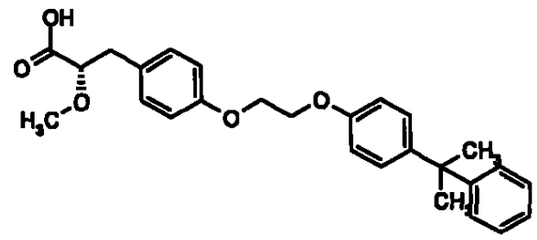
Ácido (2S)-2-metoxi-3-{4-[2-(4-trifluorometilfenoxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 4-trifluorometilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{19}H_{19}F_3O_5$ $[M+Na]^+$: 407,2.

Ejemplo 359

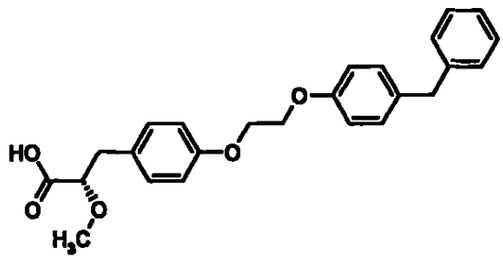
Ácido (2S)-2-metoxi-3-(4-{2-[4-(1-metil-1-feniletil)fenoxi]etoxi}fenil)propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 4-(1-metil-1-feniletil)fenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{27}H_{30}O_5$ $[M+Na]^+$: 457,2.

Ejemplo 360

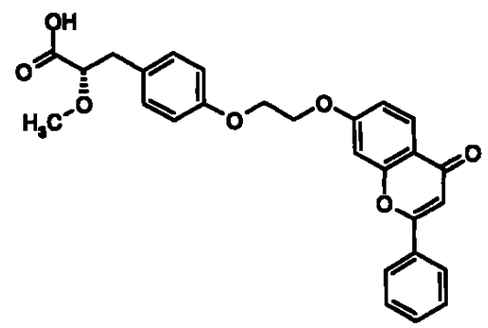
Ácido (2S)-3-{4-[2-(4-bencilfenoxi)etoxi]fenil}-2-metoxi-propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 4-bencilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{25}H_{26}O_5$ $[M+Na]^+$: 429,3.

Ejemplo 361

Ácido (2S)-2-metoxi-3-{4-[2-(4-oxo-2-fenil-4H-cromen-7-iloxi)etoxi]fenil}propiónico

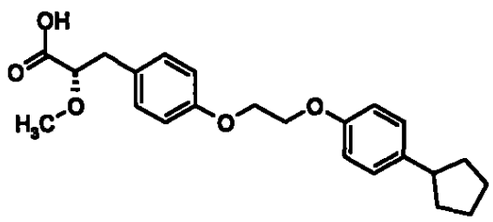


Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 7-hidroxi-2-fenilcromen-4-ona mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-

(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido amarillo. MS (ES) para $C_{27}H_{24}O_7$ $[M+H]^+$: 461,3.

Ejemplo 362

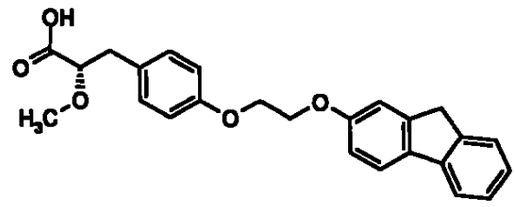
Ácido (2S)-3-{4-[2-(4-ciclopentilfenoxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 1-ciclopentil-4-metoxibenceno mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{23}H_{28}O_5$ $[M+Na]^+$: 407,3.

Ejemplo 363

Ácido (2S)-3-{4-[2-(9H-fluoren-2-iloxi)etoxi]fenil}-2-metoxipropiónico

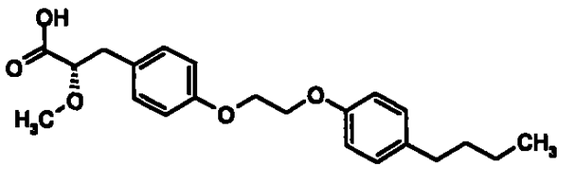


Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 9H-fluoren-2-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropo-

xi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{25}H_{24}O_5$ $[M+Na]^+$: 427,3.

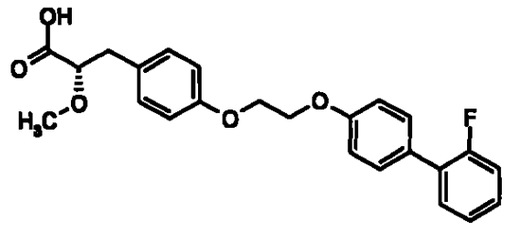
Ejemplo 364

Ácido (2S)-3-{4-[2-(4-butilfenoxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 4-butilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{22}H_{28}O_5$ [illegible]: 365,3.

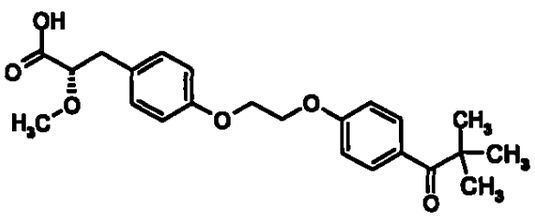
Ácido (2S)-3-{4-[2-(2'-fluorobifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 2'-fluorobifenil-4-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{24}H_{23}FO_5$ $[M+Na]^+$: 433,3.

Ejemplo 366

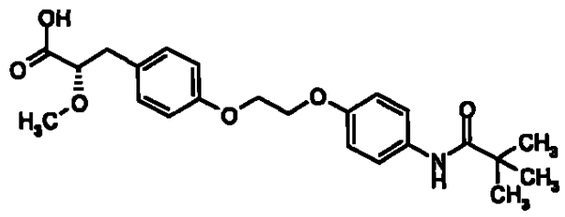
Ácido (2S)-3-(4-{2-[4-(2,2-dimetilpropionil)fenoxi]etoxi}fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 1-(4-hidroxifenil)-2,2-dimetilpropan-1-ona mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{23}H_{28}O_6$ $[M+H]^+$: 401,4.

Ejemplo 367

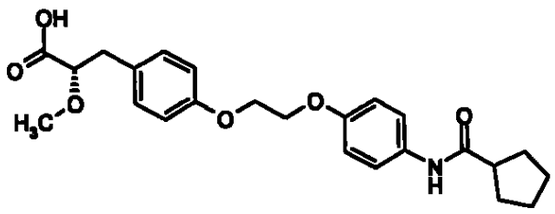
Ácido 3-(4-{2-[4-(2,2-dimetilpropionilamino)fenoxi]etoxi}fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y N-(4-hidroxifenil)-2,2-dimetilpropionamida mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{23}H_{29}NO_6$ $[M+H]^+$: 416,4.

Ejemplo 368

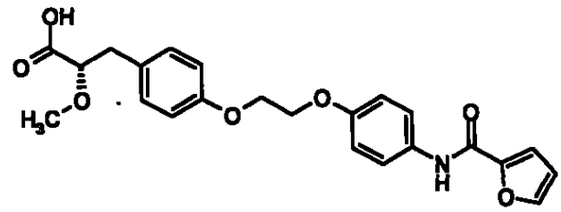
Ácido (2S)-3-{4-{2-[4-(ciclopentanocarbonilamino)fenoxi]-etoxi}fenil)-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y (4-hidroxifenil)amida del ácido ciclopentanocarboxílico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{24}H_{29}NO_6$ $[M+H]^+$: 428,3.

Ejemplo 369

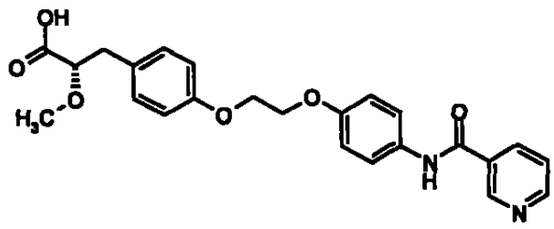
Ácido (2S)-3-[4-(2-{4-[(furan-2-carbonil)amino]fenoxi}-etoxi)fenil]-2-metoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y (4-hidroxifenil)amida del ácido furan-2-carboxílico mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{23}H_{23}NO_7$ $[M+H]^+$: 426,3.

Ejemplo 370

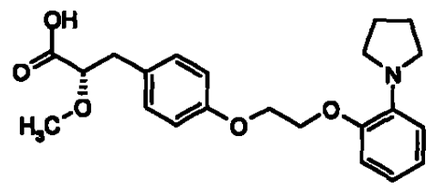
Ácido (2S)-2-metoxi-3-[4-(2-{4-[(piridina-3-carbonil)amino]fenoxi}etoxi)fenil]propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y N-(4-hidroxifenil)nicotinamida mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{24}H_{24}N_2O_6$ [M+H]+: 437,3.

Ejemplo 371

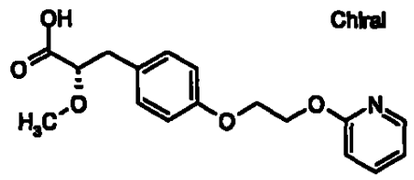
Ácido (2S)-2-metoxi-3-{4-[2-(2-pirrolidin-1-ilfenoxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 2-pirrolidin-1-ilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite amarillo. MS (ES) para $C_{22}H_{27}NO_5$ $[M+H]^+$: 386,3.

Ejemplo 372

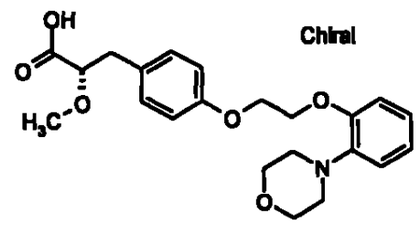
Ácido (2S)-2-metoxi-3-{4-[2-(piridin-2-iloxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y piridin-2-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)-fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{17}H_{19}NO_5$ $[M+H]^+$: 318,3.

Ejemplo 373

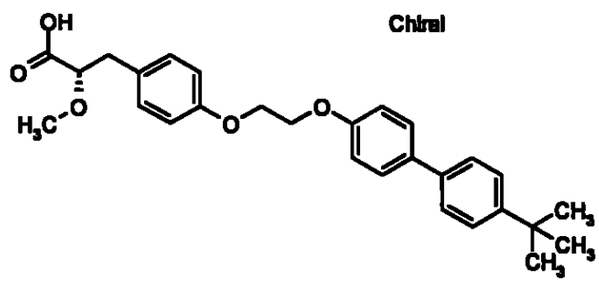
Ácido (2S)-2-metoxi-3-{4-[2-(2-morfolin-4-ilfenoxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 2-morfolin-4-ilfenol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un aceite incoloro. MS (ES) para $C_{22}H_{27}NO_6$ $[M+H]^+$: 402,3.

Ejemplo 374

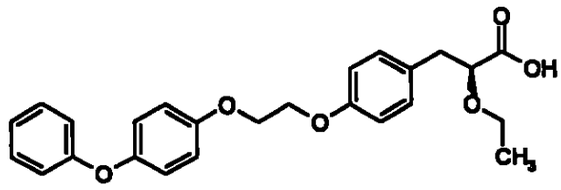
Ácido (2S)-3-{4-[2-(4'-terc-butilbifenil-4-iloxi)etoxi]-fenil}-2-metoxipropiónico



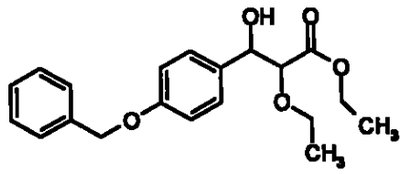
Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) y 4'-terc-butilbifenil-4-ol mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-2-metoxi-3-[4-(3-fenoxipropoxi)fenil]propiónico (Ejemplo 285, Etapa 1), para producir un sólido blanco. MS (ES) para $C_{28}H_{32}O_5$ [M-H]$^-$: 447,2.

Ejemplo 375

Ácido (2S)-2-etoxi-3-{4-[2-(4-fenoxifenoxi)etoxi]fenil}-propiónico

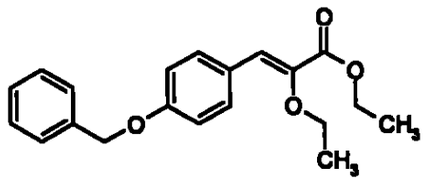


Etapa 1: éster etílico del ácido 3-(4-benciloxifenil)-2-etoxi-3-hidroxipropiónico



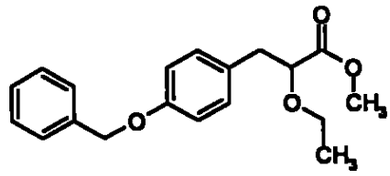
Se preparó el compuesto del título a partir de 4-benciloxibenzaldehído, diisopropilamiduro de litio y 2-etoxiacetato de etilo mediante el mismo procedimiento que el usado para la preparación del éster metílico del ácido 3-(3-benciloxifenil)-3-hidroxi-2-metoxipropiónico (Ejemplo 291, Etapa 1). MS (ES) para $C_{20}H_{24}O_5$ $[M+H_2O-H]^+$: 327, $[M+Na]^+$: 367,4.

Etapa 2: éster etílico del ácido 3-(4-benciloxifenil)-2-etoxiacrílico



Se preparó el compuesto del título a partir de éster etílico de ácido 3-(4-benciloxifenil)-2-etoxi-3-hidroxipropiónico (Ejemplo 375, Etapa 1) mediante el mismo procedimiento que el usado para la preparación del éster metílico del ácido 3-(4-benciloxifenil)-2-etoxiacrílico. MS (ES) para $C_{20}H_{22}O_4$ $[M+H]^+$: 327,2.

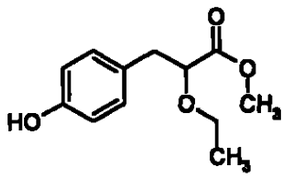
Etapa 3: éster metílico del ácido 3-(4-benciloxifenil)-2-etoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido 3-(4-benciloxifenil)-2-etoxiacrílico (Ejemplo 375, Etapa 2) (3,3 g, 10,12 mmol) mediante el mismo procedimiento que el usado para la preparación del éster metílico del ácido 3-(3-benciloxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 3) para producir un aceite, que fue purificado por cromatografía (gel de

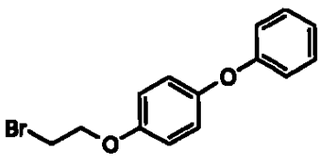
sílice, hexanos/acetato de etilo 6:1) para producir dos compuestos: éster metílico de ácido 3-(4-benciloxifenil)-propiónico (1,5 g, Rf aprox. 0,65) y el compuesto deseado (1,5 g, Rf aprox. 0,2). MS (ES) para $C_{19}H_{22}O_4$ $[M+NH_4]^+$: 332,3.

Etapa 4: éster metílico del ácido 2-etoxi-3-(4-hidroxifenil)propiónico



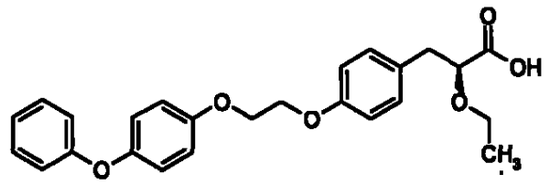
Se preparó el compuesto del título a partir de éster metílico de ácido 3-(4-benciloxifenil)-2-etoxipropiónico (Ejemplo 375, Etapa 3) mediante el mismo procedimiento que el usado para la preparación del éster metílico del ácido 3-(3-hidroxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 4), para producir un aceite amarillo. MS (ES) para $C_{12}H_{16}O_4$ $[M+H]^+$: 225,2, $[M+NH_4]^+$: 242,2, $[M+Na]^+$: 247,2.

Etapa 5: 4-(2-bromoetoxi)fenoxifenilo



Se preparó el compuesto del título a partir de 4-fenoxifenol mediante el mismo procedimiento que el usado para la preparación del éster etílico del ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2) para producir un sólido blanco. MS (ES) para $C_{14}H_{13}BrO_2$ $[M-H]^-$: 291,0.

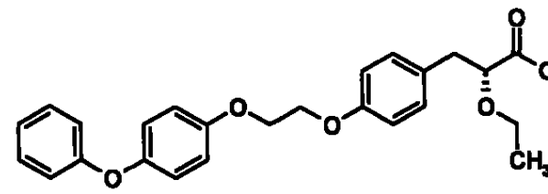
Etapa 6: ácido (2S)-2-etoxi-3-{4-[2-(4-fenoxifenoxi)etoxi]fenil}propiónico



Se preparó el compuesto del título a partir de éster metílico de ácido 2-etoxi-3-(4-hidroxifenil)propiónico (Ejemplo 375, Etapa 4) y 4-(2-bromoetoxi)fenoxifenilo (Ejemplo 375, Etapa 5) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3). Se sometió el material bruto a separación por HPLC quiral para obtener el isómero 2 del enantiómero simple. MS (ES) para $C_{25}H_{26}O_6$ $[M-H]^-$: 421,4.

Ejemplo 376

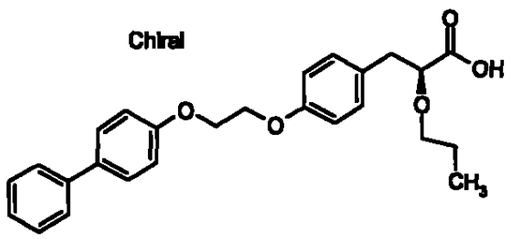
Ácido (2R)-2-etoxi-3-{4-[2-(4-fenoxifenoxi)etoxi]fenil}-propiónico



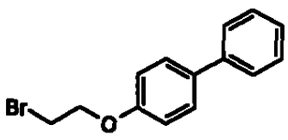
Se preparó el compuesto del título a partir de éster metílico de ácido 2-etoxi-3-(4-hidroxifenil)propiónico (Ejemplo 375, Etapa 4) y 4-(2-bromoetoxi)fenoxifenilo (Ejemplo 375, Etapa 5) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3). Se sometió el material bruto a separación por HPLC quiral para obtener el isómero 1 del enantiómero simple. MS (ES) para $C_{25}H_{26}O_6$ $[M-H]^-$: 421,4.

Ejemplo 377

Ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-propoxipropiónico

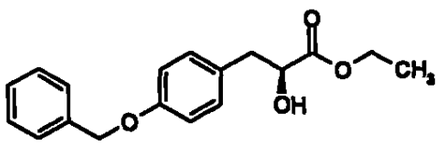


Etapa 1: 4-(2-bromoetoxi)bifenilo



Se preparó el compuesto del título a partir de bifenil-4-ol mediante el mismo procedimiento que el usado para la preparación del éster etílico de ácido (2S)-3-[4-(2-bromoetoxi)fenil]-2-metoxipropiónico (Ejemplo 283, Etapa 2), para producir un sólido blanco. MS (ES) para $C_{14}H_{13}BrO$ $[M-H]^-$: 279,1.

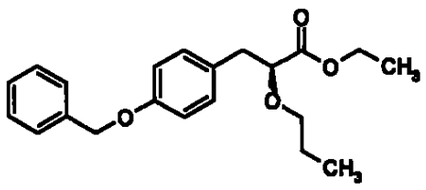
Etapa 2: éster etílico del ácido (2S)-3-(4-benciloxifenil)-2-hidroxipropiónico



Se preparó el compuesto del título a partir de ácido (2S)-3-(4-benciloxifenil)-2-hidroxipropiónico mediante el mismo procedimiento que el usado para la preparación del éster etílico de ácido (2S)-3-(4-hidroxifenil)-2-metoxipropiónico (Ejemplo 283, Etapa 1), para obtener el producto en forma de un aceite amarillo. ^1H-

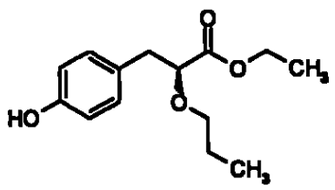
RMN ($CDCl_3$, 200,15 MHz): 7,35-7,55 (m, 5H), 7,20 (d, 2H, J = 8,3), 6,79 (d, 2H, J = 8,3), 4,99 (s, 2H), 4,41 (dd, 1H, J= 6,5, 4,4), 4,19 (c, 2H, J = 6,9), 2,92 (2dd, 2H, J= 16,1, 4,4), 1,23 (t, 3H, J= 6,9).

Etapa 3: éster etílico del ácido (2S)-3-(4-benciloxi-fenil)-2-propoxipropiónico



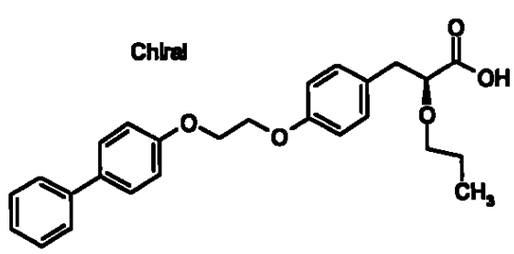
Se añadió yoduro de propilo (41,6 mmol) a temperatura ambiente a una solución de éster etílico de ácido (2S)-3-(4-benciloxifenil)-2-hidroxipropiónico (Ejemplo 377, Etapa 2) (8,3 mmol) y óxido de plata (12,45 mmol) en 40 mL de DMF. Se calentó la mezcla a 50°C durante 24 horas. Después de ello, se enfrió la mezcla a temperatura ambiente y se añadieron 300 ml de acetato de etilo y 200 ml de agua. Se separó la capa acuosa y se lavó la capa orgánica con salmuera (3 X 100 ml) y se secó después sobre $MgSO_4$, se filtró y se concentró a vacío. Se purificó el producto bruto por cromatografía (gel de sílice, hexanos/acetato de etilo 6:1), para producir un aceite amarillo. ^{1}H-RMN ($CDCl_3$, 200,15 MHz): 7,42-7,31 (m, 5 H), 7,17 (d, 2 H, J = 8,6 Hz), 6,90 (d, 2 H, J = 8,6 Hz), 5,05 (s, 2 H), 4,17 (c, 2 H, J = 7,0 Hz), 3,97 (dd, 1 H, J = 7,0, 6,2 Hz), 3,53 (dt, 1 H, J = 8,9, 6,4 Hz), 3,23 (dt, 1 H, J = 9,1, 6,7 Hz), 2,97 (d, 2 H, J = 6,7 Hz), 1,66-1,48 (m, 2 H), 1,23 (t, 3 H, J = 7,3 Hz), 0,86 (t, 3 H, J = 7,5 Hz).

Etapa 4: éster etílico del ácido (2S)-3-(4-hidroxifenil)-2-propoxipropiónico



Se preparó el compuesto del título a partir de éster etílico de ácido (2S)-3-(4-benciloxifenil)-2-propoxipropiónico (Ejemplo 377, Etapa 3) mediante el mismo procedimiento que el usado para la preparación del éster metílico de ácido 3-(3-hidroxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 4), para producir un aceite amarillo. MS (ES) para $C_{14}H_{20}O_4$ $[M+H]^+$: 253,1.

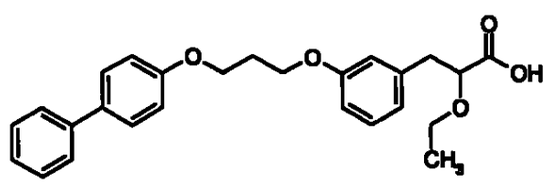
Etapa 5: ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-propoxipropiónico



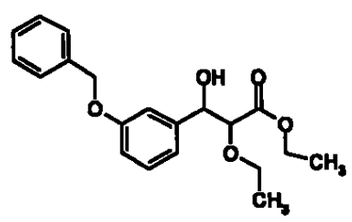
Se preparó el compuesto del título a partir de 4-(2-bromoetoxi)bifenilo (Ejemplo 377, Etapa 1) y éster etílico de ácido (2S)-3-(4-hidroxifenil)-2-propoxipropiónico (Ejemplo 377, Etapa 4) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3), para producir un sólido blanco. MS (ES) para $C_{26}H_{28}O_5$ $[M+H]^+$: 421,0, $[M+NH_4]^+$: 438,0, $[M+Na]^+$: 443,0, $[M-H]^-$: 3239,2.

Ejemplo 378

Ácido 3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-etoxipropiónico (isómero 1)

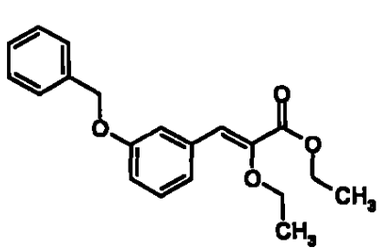


Etapa 1: éster etílico del ácido 3-(3-benciloxifenil)-2-etoxi-3-hidroxipropiónico



Se preparó el compuesto del título a partir de 3-benciloxibenzaldehído y etoxiacetato de etilo mediante el mismo procedimiento que el usado para la preparación del éster metílico del ácido 3-(3-benciloxifenil)-3-hidroxi-2-metoxipropiónico (Ejemplo 291, Etapa 1), para obtener el compuesto del título como un aceite incoloro.

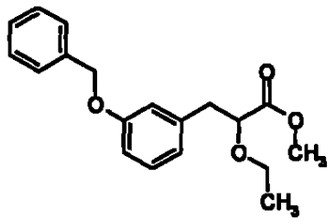
Etapa 2: éster etílico del ácido 3-(3-benciloxifenil)-2-etoxiacrílico



Se preparó el compuesto del título a partir de éster etílico de ácido 3-(3-benciloxifenil)-2-etoxi-3-hidroxipropiónico (Ejemplo 378, Etapa 1) mediante el mis-

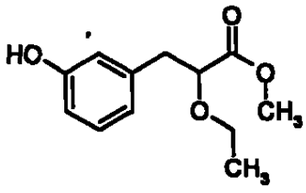
mo procedimiento que el usado para la preparación del éster metílico de ácido 3-(3-benciloxifenil)-2-metoxiacrílico (Ejemplo 291, Etapa 2), para obtener el compuesto del título como un aceite incoloro.

Etapa 3: éster metílico del ácido 3-(3-benciloxifenil)-2-etoxipropiónico



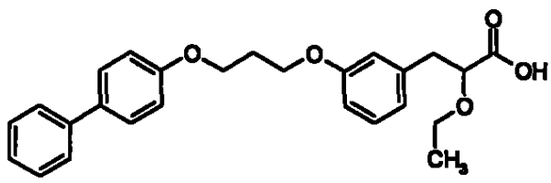
Se preparó el compuesto del título a partir de éster etílico de ácido 3-(3-benciloxifenil)-2-etoxiacrílico (Ejemplo 378, Etapa 2) mediante el mismo procedimiento que el usado para la preparación del éster metílico de ácido 3-(3-benciloxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 3), para obtener el compuesto del título como un aceite incoloro.

Etapa 4: éster metílico de ácido 2-etoxi-3-(3-hidroxifenil)propiónico



Se preparó el compuesto del título a partir de éster metílico de ácido 3-(3-benciloxifenil)-2-etoxipropiónico (Ejemplo 378, Etapa 3) mediante el mismo procedimiento que el usado para la preparación del éster metílico del ácido 3-(3-hidroxifenil)-2-metoxipropiónico (Ejemplo 291, Etapa 4), para obtener el compuesto del título como un aceite amarillo. MS (ES) para $C_{12}H_{16}O_4$ $[M+H]^+$: 225,1.

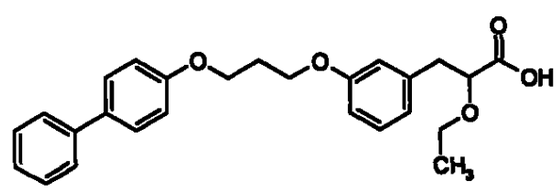
Etapa 5: ácido (3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-etoxipropiónico (isómero 1)



Se preparó el compuesto del título a partir de 3-(bifenil-4-iloxi)propan-1-ol (Ejemplo 291, Etapa 6) y éster metílico de ácido 2-etoxi-3-(3-hidroxifenil)propiónico (Ejemplo 378, Etapa 4) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3) para producir un sólido blanco. Se sometió el material bruto a separación por HPLC quiral, para obtener el isómero 1 del enantiómero simple. (ES) para $C_{26}H_{28}O_5$ $[M+NH_4]^+$: 438,0, $[M+Na]^+$: 443,0.

Ejemplo 379

Ácido 3-{3-[3-(bifenil-4-iloxi)propoxi]fenil}-2-etoxipropiónico (isómero 2)



Se preparó el compuesto del título a partir de 3-(bifenil-4-iloxi)propan-1-ol (Ejemplo 291, Etapa 6) y éster metílico de ácido 2-etoxi-3-(3-hidroxifenil)propiónico (Ejemplo 378, Etapa 4) mediante el mismo procedimiento que el usado para la preparación del ácido (2S)-3-{4-[2-(bifenil-4-iloxi)etoxi]fenil}-2-metoxipropiónico (Ejemplo 283, Etapa 3), para producir un sólido blanco. Se sometió el material bruto a separación por HPLC quiral

para obtener el isómero 2 del enantiómero simple. MS (ES) para $C_{26}H_{28}O_5$ $[M+NH_4]^+$: 438,0, $[M+Na]^+$: 443,0.

NOTA: En los Ejemplos anteriores, el término "chiral" que aparece en las fórmulas químicas significa "quiral".

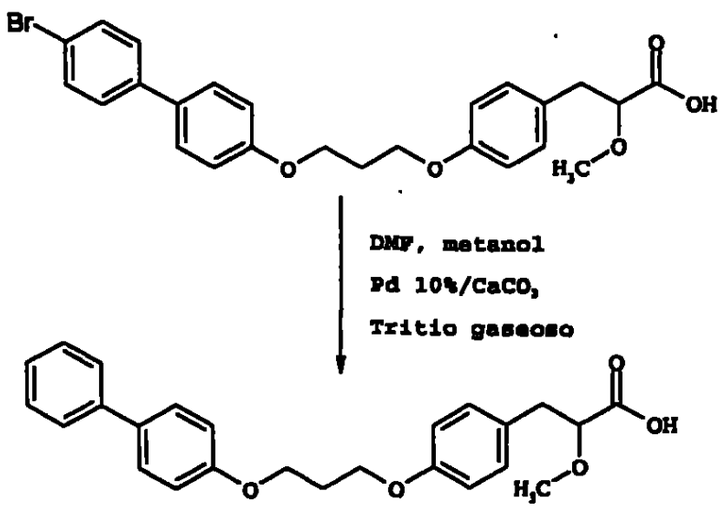
Ejemplo 380

Ensayo de unión:

Se llevó a cabo la unión dependiente de ADN usando la tecnología para Ensayo de proximidad de centelleo ("SPA"). Se preparó PPARγ, así como su compañero heterodimérico RXRα, usando un sistema de expresión de baculovirus. Se usó un dúplex oligonucleotídico complementario biotinilado que representaba el elemento de respuesta PPR de consenso humano para unir el dímero de receptores a perlas de SPA revestidas con silicato de itrio y estreptavidina. La hebra 5'-3' tenía la secuencia: $^{5'}$TAATGTAGGTAATAGTTCAATAGGTCAAAGG$^{3'}$ (SEC ID N°: 1); se unió biotina a la primera A en el extremo 3' de la hebra 3'-5' complementaria. El ligando marcado de PPARγ era ácido ^{3}H-(s)-3-{4-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico, con actividad específica de 24 Ci/mmol. Se llevó a cabo el ensayo de unión en placas de 96 pocillos. Se preincubaron 100 ng de oligonucleótido por pocillo con 3 µg de perlas de SPA en un tampón de unión que contenía HEPES 10 mM pH 7,8, KCl 80 mM, $MgCl_2$ 0,5 mM, DTT 1 mM, CHAPS 0,5% y 16,6 µg de seroalbúmina bovina durante 30 minutos a temperatura ambiente. Se centrifugó entonces la mezcla a 2.000 rpm durante 3 minutos para obtener una pella de la mezcla de perlas-oligo. Se eliminó el sobrenadante y se resuspendió la pella de perlas-oligo en el mismo tampón de unión que antes, pero que también contenía glicerol al 14%, 5 µg de ADN de esperma de salmón cortado y 2,5 µg de cada uno de los receptores, PPARγ y RXRα. Se llevo a cabo un ensayo de unión en saturación utilizando cantidades crecientes de ácido ^{3}H-(s)-3-{4-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico en la

reacción, para obtener 0,39 nM to 402 nM de ácido ^{3}H-(s)-3-{4-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico. Se midió la unión no específica en presencia de 10 µm de ácido (s)-3-{4-[3-(bifenil-4-iloxi)propoxi]fenil}-2-meto-xipropiónico no marcado. Se calculó un valor de A K_d a partir de los experimentos de unión en saturación después de representar la unión específica frente a la concentración de ligando marcado. Se llevaron a cabo reacciones de unión competitiva en presencia de 30.000 cpm de ácido ^{3}H-(s)-3-{4-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico y 5 nM a 10 µM de compuestos competitivos. Se calcularon los valores de CI_{50} (nM) para los compuestos competitivos después de restar la unión no específica (medida en presencia de 10µM de ácido ^{3}H-(s)-3-{4-[3-(bifenil-4-iloxi)propoxi]-fenil}-2-metoxipropiónico no marcado) y se normalizaron los datos para la unión total (en ausencia de cualquier compuesto no marcado). El ácido ^{3}H-(s)-3-{4-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico era efectivo para determinar la afinidad de unión de los subtipos de PPAR en el rango de 5 nM a 10.000 nM. Por ejemplo, los compuestos PPAR con valores de CI_{50} menores de 500 nM fueron identificados como ligandos para PPAR gamma.

Preparación de ácido ^{3}H-(s)-3-{4-[3-(bifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico



En un recipiente de reacción, se combinó ácido (s)-3-{4-[3-(4'-bromobifenil-4-iloxi)propoxi]fenil}-2-metoxipropiónico (6,1 mg) con Pd 10%/$CaCO_3$ (18,6 mg), DMF (0,5 ml) y metanol (0,5 ml). Se agitó la mezcla bajo 10 Ci de tritio gaseoso durante aproximadamente 4,5 horas. Se eliminó el catalizador por filtración y se eliminó la actividad lábil por evaporaciones rotatorias repetidas con metanol. Se disolvió el residuo final en etanol. Se purificó el producto bruto por HPLC de fase invertida eluyendo con un sistema en gradiente de agua/acetonitrilo/TFA. Se recogió el pico UV mayor y radioactivo y se evaporó rotatoriamente a sequedad. Se disolvió el residuo resultante en etanol (rendimiento: 102 mCi).

Ejemplo 381

Estudios de unión y cotransfección

Se determinó la potencia in vitro de los compuestos en la modulación de los receptores PPARα y PPARγ mediante el procedimiento detallado a continuación. Se llevó a cabo una unión dependiente de ADN (unión "ABCD")

utilizando tecnología de Ensayos de proximidad de centelleo ("SPA") con receptores PPAR. Se usaron los agonistas PPARα y PPARγ marcados con tritio como radioligandos para generar curvas de desplazamiento y los valores de CI_{50} con compuestos de la presente invención. Se realizaron ensayos de cotransfección en células CV-1. El plásmido informador contenía un promotor PPRE y TK de acilCoA oxidasa ("AOX") aguas arriba del ADNc informador de luciferasa. Se expresaron constitutivamente los PPAR y RXRα apropiados usando plásmidos que contenían el promotor CMV. Dado que, para PPARα y PPARβ/δ, la interferencia por el PPARγ endógeno en células CV-1 representa un problema, con objeto de eliminar dicha interferencia se usó un sistema quimérico GAL4 en el que el dominio de unión a ADN del PPAR transfectado está substituido por el de GAL4 y se utilizó el elemento de respuesta de GAL4 en lugar del PPRE AOX. Se determinó la eficacia de cotransfección en relación a los compuestos de referencia específicos para el isotopo PPAR. Se determinaron las eficacias por ajuste por ordenador a una curva de concentración-respuesta, o, en algunos casos, a una sola concentración elevada de agonista (10 μM). El rango típico para la determinación de la concentración CI_{50} es de 1 nM a 10 μM. Para los estudios de unión o cotransfección con receptores distintos de los PPARs, se realizaron ensayos similares usando ligandos, receptores y constructos informadores apropiados para ese receptor en particular.

Estos estudios fueron llevados a cabo para evaluar la capacidad de los compuestos de la presente invención para unirse a y/o activar varios factores de transcripción nucleares, en particular huPPARα ("hu" indica "humano") y huPPARγ. Estos estudios proporcionaron datos in vitro concernientes a la eficacia y selectividad de los compuestos de la presente invención. Más aún, se compararon los datos de unión y cotransfección para los

compuestos de la presente invención con los datos correspondientes para compuestos comercializados que actúan sobre huPPARα o sobre huPPARγ. Los datos de unión y cotransfección para compuestos representativos de la presente invención fueron comparados con los datos correspondientes para compuestos de referencia, con objeto de determinar la unión.

Se determinó la concentración de compuesto de ensayo necesaria para producir una activación máxima del 50% de PPARα ($CI_{50}\alpha$) y PPARγ ($CI_{50}\gamma$). Muchos de los compuestos de la presente invención son agonistas selectivos para PPARγ o son coagonistas de PPARα/PPARγ.

Evaluación de los niveles de triglicéridos y de colesterol en ratones transgénicos HuapoAI

Se albergaron ratones machos de cinco a seis semanas de edad, transgénicos para apoAI [C57Bl/6-tgn(apoa1)1rub humano, Jackson Laboratory, Bar Harbor, ME] a razón de cinco por jaula (10"x 20"x 8" con lecho de viruta álamo temblón) con alimento (Purina 5001) y agua disponibles en todo momento. Tras un período de aclimatación de 2 semanas, se identificó individualmente a los animales por muescas en la oreja, se los pesó y se los asignó a grupos en base al peso corporal. Comenzando a la mañana siguiente, se dosificó diariamente a los ratones por sondaje oral durante 7 días, utilizando una sonda de alimentación desechable curvada de calibre 20 y 1½". Los tratamientos consistían en los compuestos de ensayo (30 mg/kg), un control positivo (fenofibrato, 100 mg/kg) o vehículo [carboximetilcelulosa al 1% (p/v)/ Tween 80 al 0,25% (p/v); 0,2 ml/ratón]. Antes de finalizar el 7° día, los ratones fueron pesados y dosificados. Tres horas después de la dosificación, se anestesió a los animales por inhalación de isoflurano (2-4%) y se obtuvo sangre por punción cardíaca (0,7-1,0 ml). Se transfirió la sangre entera a tubos separadores de suero (Vacutainer SST), se

enfrió sobre hielo y se dejó que coagulara. Se obtuvo el suero tras centrifugar a 4°C y se congeló hasta el análisis de triglicéridos, colesterol total, niveles de compuesto y lipoproteínas séricas, obteniéndose el perfil por cromatografía líquida rápida de proteínas ("FPLC") acoplada a un sistema de detección en línea. Después de sacrificar por dislocación cervical, se extirparon y pesaron el hígado, el corazón y los cojinetes de grasa epididimal.

Los animales dosificados con vehículo tenían valores medios de triglicéridos de aproximadamente 60 a 80 mg/dl, los cuales resultaron reducidos por el control positivo de fenofibrato (33-58 mg/dl, con una reducción media del 37%). Los animales dosificados con vehículo tenían valores de colesterol total en suero de aproximadamente 140 a 180 mg/dl, los cuales aumentaron con el fenofibrato (aproximadamente 190 a 280 mg/dl, con una elevación media del 41%). Cuando se los sometió a análisis por FPLC, los sueros reunidos de los ratones transgénicos hu apoAI tratados con vehículo tenían un área pico de lipoproteína de alta densidad-colesterol (HDLc) que variaba en el rango de 47v-seg a 62v-seg. El fenofibrato aumentó la cantidad de HDLc (68-96v-seg, con un aumento medio de porcentaje del 48%). Los compuestos de ensayo fueron evaluados en términos de porcentaje de aumento en el área bajo la curva. Los compuestos representativos de la presente invención fueron estudiados usando el método anterior o métodos substancialmente similares.

<u>Evaluación de los niveles de glucosa en ratones db/db</u>

Se albergó a ratones machos de cinco semanas de edad diabéticos (db/db) [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] o compañeros de camada flacos (db+) a razón de 6 por jaula (10"x 20"x 8" con lecho de viruta de álamo temblón), con alimento (Purina 5015) y agua disponibles en todo momento. Después de un

período de aclimatación de 2 semanas, los ratones fueron individualmente identificados por muescas en la oreja, pesados y sangrados a través de la vena de la cola para la determinación de los niveles iniciales de glucosa. Se recogió la sangre (100 µl) de animales que no habían ayunado envolviendo a cada animal en una toalla, cortando la punta de la cola con un escalpelo y dejando gotear la sangre de la cola en un tubo capilar heparinizado equilibrado sobre el borde de la mesa. Se descargó la muestra en un microrrecipiente heparinizado con separador de gel (VWR) y se mantuvo sobre hielo. Se obtuvo el plasma tras centrifugación a 4°C y se midió la glucosa inmediatamente. Se congeló el resto del plasma hasta completarse el experimento y se estudiaron la glucosa y los triglicéridos en todas las muestras. Los animales fueron agrupados en base a los niveles iniciales de glucosa y a los pesos corporales. Comenzando a la mañana siguiente, se dosificó a los ratones diariamente por sondaje oral durante días, usando una sonda desechable de alimentación curvada de calibre 20 y 1½". Los tratamientos eran los compuestos de ensayo (30 mg/kg), un agente de control positivo (30 mg/kg) o vehículo [carboximetilcelulosa al 1% (p/v)/Tween 80 al 0,25% (p/v); 0,3 ml/ratón]. Al 7° día, los ratones fueron pesados y sangrados (vena de la cola) durante aproximadamente 3 horas tras la dosificación. A las 24 horas de la 7ª dosis (es decir, al 8° día), los animales fueron sangrados de nuevo (vena de la cola). Se estudiaron las muestras obtenidas de animales conscientes los días 0, 7 y 8 en cuanto a glucosa. A las 24 horas de la sangría, se pesó de nuevo a los animales y se los dosificó por última vez. Tres horas después de la dosificación al 8° día, se anestesió a los animales por inhalación de isoflurano y se obtuvo la sangre por punción cardíaca (0,5-0,7 ml). Se transfirió la sangre entera a tubos separadores de suero, se enfrió sobre hielo y se dejó que

coagulara. Se obtuvo el suero tras centrifugación a 4°C y se congeló hasta el análisis de los niveles de compuesto. Después del sacrificio por dislocación cervical, se extirparon y pesaron el hígado, el corazón y los cojinetes de grasa epididimal.

Los animales dosificados con vehículo tenían valores medios de triglicéridos de aproximadamente 170 a 230 mg/dl, los cuales resultaron reducidos por el control positivo PPARγ (aproximadamente 70 a 120 mg/dl, con una reducción media del 50%). Los ratones db/db machos son hiperglicémicos (glucosa media de aproximadamente 680 a 730 mg/dl al 7° día de tratamiento), mientras que los animales flacos tienen niveles medios de glucosa de entre aproximadamente 190 y 230 mg/dl. El tratamiento con el agente de control positivo redujo la glucosa significativamente (aproximadamente 350 a 550 mg/dl, con una disminución media hacia la normalización del 56%).

Se midió la glucosa colorimétricamente utilizando reactivos comprados comercialmente (Sigma #315-500). Según los fabricantes, los procedimientos fueron modificados con respecto al trabajo publicado (McGowan y col. *Clin. Chem.*, 20:470-5 (1974), y Keston, A. Specific colorimetric enzimatic analitical reagents for glucose. Abstract of papers 129th meeting ACS, 31C (1956)) y dependen de la liberación de un mol de peróxido de hidrógeno por cada mol de analito, junto con una reacción de color descrita por vez primera por Trinder (Trinder, P. *Ann. Clin. Biochem.*, 6:24 (1969)). Se relacionó linealmente la absorbancia del colorante producida con el analito en la muestra. Se modificaron además los ensayos para utilización en un formato de 96 pocillos. Se midieron los patrones (Sigma #339-11, Sigma #16-11 y Sigma #CC0534 para glucosa, triglicéridos y colesterol total, respectivamente), el plasma de control de calidad (Sigma # A2034) y las muestras (2 ó 5 µl/pocillo) por duplicado usando

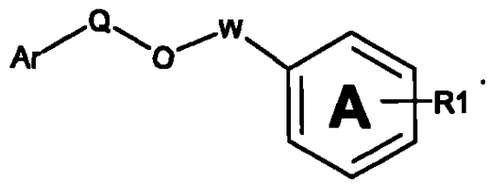
200 µl de reactivo. Una alícuota adicional de muestra, pipeteada en un tercer pocillo y diluida en 200 µl de agua, proporcionó un blanco para cada muestra. Las placas fueron incubadas a temperatura ambiente (18, 15 y 10 minutos para la glucosa, los triglicéridos y el colesterol total, respectivamente) en un agitador de placa y se leyó la absorbancia a 500 nm (glucosa y colesterol total) ó 540 nm (triglicéridos) en un lector de placas. Se comparó la absorbancia con una curva patrón (100-800, 10-500 y 100-400 mg/dl para glucosa, triglicéridos y colesterol total, respectivamente). Los valores para el control de calidad estaban consistentemente dentro del rango esperado y el coeficiente de variación para las muestras está por debajo del 10%. Todas las muestras de un experimento fueron estudiadas al mismo tiempo para minimizar la variabilidad entre ensayos.

Se separaron las lipoproteínas séricas y se cuantificó el colesterol con un sistema de detección en línea. Se aplicó la muestra a una columna de exclusión por tamaños Superose® 6 HR 10/30 (Amersham Pharmacia Biotech) y se eluyó con solución salina tamponada con fosfatos-EDTA a 0,5 ml/min. Se mezcló reactivo de colesterol (Roche Diagnostics Chol/HP 704036) a 0,16 ml/min con el efluente de la columna a través de una conexión en T y se pasó la mezcla a través de un reactor de tuberías reticuladas de 15 m x 0,5 mm de d.i. sumergido en un baño de agua a 37°C. Se monitorizó el producto coloreado producido en presencia de colesterol en la corriente de flujo a 505 nm y se convirtió el voltaje análogo del monitor en una señal digital para recogida y análisis. Se representó el cambio de voltaje correspondiente al cambio en la concentración de colesterol frente al tiempo y se calculó el área bajo la curva correspondiente a la elución de VLDL, LDL y HDL (programa Turbochrome de Perkin Elmer).

Mientras que esta invención ha sido particularmente mostrada y descrita en relación a realizaciones preferidas de la misma, los expertos en la técnica entenderán que se pueden hacer en ella diversos cambios en cuanto a forma y detalles sin desviarse del alcance de la invención amparado por las reivindicaciones adjuntas.

REIVINDICACIONES

1. Un compuesto representado por la siguiente fórmula estructural:



o las sales, hidratos, estereoisómeros y solvatos farmacéuticamente aceptables del mismo, donde:

Ar es un grupo aromático sustituido o no sustituido;

Q es a enlace covalente, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ o $-CH_2CH_2CH_2CH_2-$;

W es un grupo alquileno sustituido o no sustituido de dos a diez átomos de longitud o un grupo heteroalquileno sustituido o no sustituido, donde el grupo heteroalquileno es un grupo alquileno de dos a diez átomos de longitud en el que uno o más grupos metileno han sido reemplazados por un grupo funcional seleccionado entre $-CH=CH-$, $-C\equiv C-$, $-O-$, $-CO-$, $-NR_7-$, $-NR_7CO-$, $-C(=NOH)-$, $-S-$, $-S(O)-$, $-S(O)_2-$ o $-CH(NR_7R_8)-$;

el Anillo de fenilo **A** está sustituido opcionalmente con hasta cuatro sustituyentes además de R_1;

R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ o $-(CH)=C(Y)-(CH_2)_mE$; donde E es $COOR_3$, alquil(C_1-C_3)nitrilo, carboxamida, sulfonamida, acilsulfonamida o tetrazol y donde sulfonamida, acilsulfonamida y tetrazol están sustituidos opcionalmente con uno o más sustituyentes seleccionados independientemente entre: alquilo C1-C6, haloalquilo C1-C6 y arilalquilo C0-C4;

R_2 es -H, un grupo alifático, un grupo alifático sustituido, haloalquilo, un grupo aralquilo, un grupo

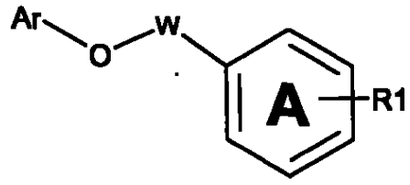
aralquilo sustituido, un grupo aromático, un grupo aromático sustituido, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ o $-C(S)NR_5R_6$;

Y es $-O-$, $-CH_2-$, $-CH_2CH_2-$ o un grupo $-CH=CH-$ que está unido a un átomo de carbono en el Anillo de Fenilo **A** que está en *orto* respecto a R_1;

R_3-R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido; y

n y m son independientemente 0, 1 o 2.

2. Un compuesto representado por la siguiente fórmula estructural



o las sales, hidratos, estereoisómeros y solvatos farmacéuticamente aceptables del mismo, donde:

Ar es un grupo aromático sustituido o no sustituido;

W es un grupo conector alquileno sustituido o no sustituido o un grupo conector heteroalquileno sustituido o no sustituido de dos a diez átomos de longitud;

el Anillo de fenilo **A** está sustituido opcionalmente con hasta cuatro sustituyentes además de R_1;

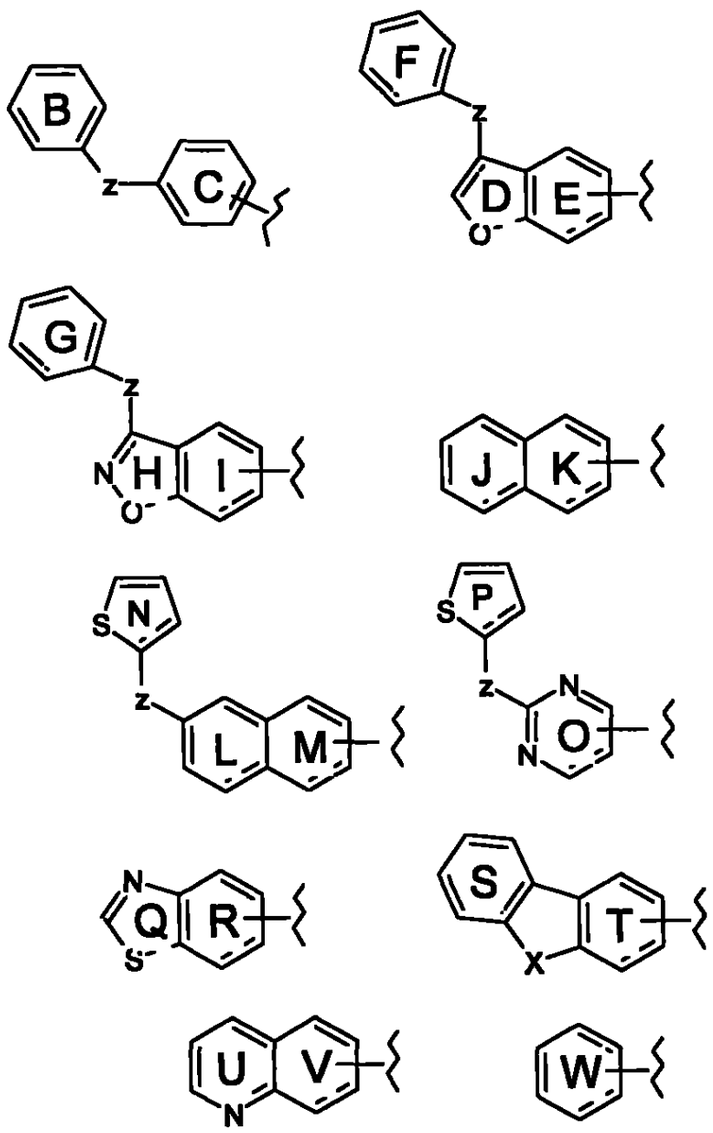
R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ o $-(CH)=C(Y)-(CH_2)_mCOOR_3$;

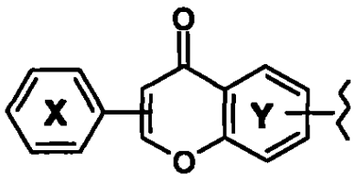
R_2 es -H, un grupo alifático, un grupo alifático sustituido, un grupo arilo, un grupo arilo sustituido, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ o $-C(S)NR_5R_6$;

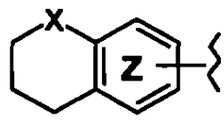
Y es $-O-$, $-CH_2-$, $-CH_2CH_2-$ o un grupo $-CH=CH-$ que está unido a un átomo de carbono en el Anillo de Fenilo **A** que está en *orto* respecto a R_1;

R_3-R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido; y
n y m son independientemente 0, 1 o 2.

3. El compuesto de la Reivindicación 1 o 2, donde Ar está representado por una fórmula estructural seleccionada entre:







donde:

los Anillos **B-Z** están independientemente sustituidos o no sustituidos;

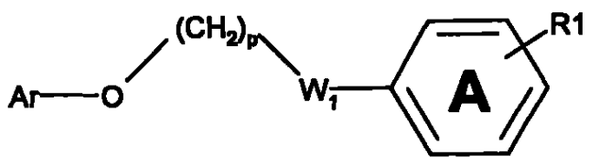
X es $-O-$, $-S-$, $-CH_2-$ o $-C(O)-$;

Z es un enlace covalente, $-O-$, $(-CH_2)_q-$, $-CH(CH_3)(CH_2)_q-$, $-C(CH_3)_2(CH_2)_q-$, $-(CH_2)_qCH(CH_3)-$, $-(CH_2)_qC(CH_3)_2-$, $-O(CH_2)_q-$, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, $-(CH_2)_qNH-$, $-(CH_2)_qCHR_{20}-$, $-CHR_{20}(CH_2)_q-$, $-(CH_2)_qCR_{20}R_{20}-$, $-(CH_2)_qCR_{20}R_{20}-$, $-(CH_2)_qNR_{20}-$, $-NR_{20}(CH_2)_q-$, $-(CH_2)_qC(=NOH)-$, $-C(=NOH)(CH_2)_q-$, $-CH(OH)-(CH_2)_q-$, $-(CH_2)_q-CH(OH)-$, $-CO-(CH_2)_q-$, $-(CH_2)_q-CO-$, $-COO-(CH_2)_q-$, $-OCO-(CH_2)_q-$, $-(CH_2)_q-OCO-$, $-(CH_2)_q-COO-$, $-(CH_2)_qCO-NH-$, $-(CH_2)_qNH-CO-$, $-(CH_2)_qCONR_{20}-$, $-CONR_{20}(CH_2)_q-$, $-(CH_2)_qNR_{20}CO-$ o $-NR_{20}CO(CH_2)_q-$;

q es 0, 1, 2 o 3; y

cada R_{20} es independientemente un grupo alquilo C1-C5 o un grupo alquilo C1-C5 halogenado.

4. El compuesto de la Reivindicación 3, donde el compuesto está representado por la siguiente fórmula estructural:



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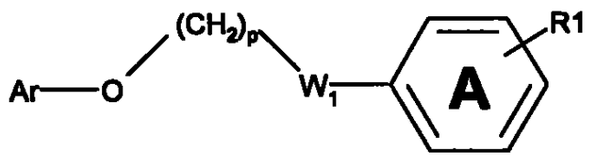
donde:

p es un entero de uno a nueve

W_1 es $-O-$, $-C(O)-$, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, $-C(=NOH)-$ o $-CH(NR_7R_8)-$; y

R_7 y R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

5. El compuesto de la Reivindicación 3, donde el compuesto está representado por la siguiente fórmula estructural:



;

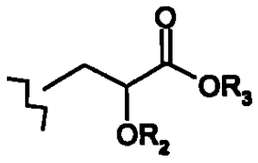
donde:

p es un entero de uno a cuatro;

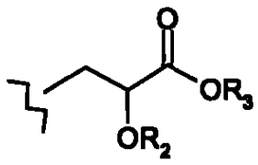
W_1 es -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- o $-CH(NR_7R_8)-$; y

R_7 y R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

6. El compuesto de la Reivindicación 5, donde R_1 está en *para* respecto a W_1 y está representado por la siguiente fórmula estructural:

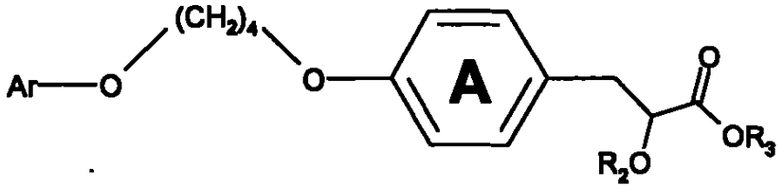


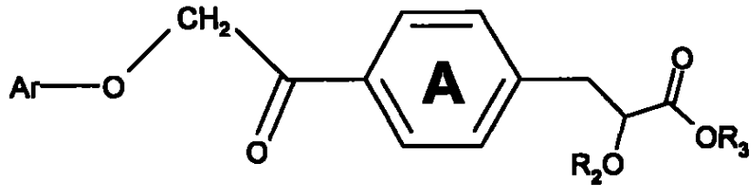
7. El compuesto de la Reivindicación 5, donde R_1 está en *meta* respecto a W_1 y está representado por la siguiente fórmula estructural:

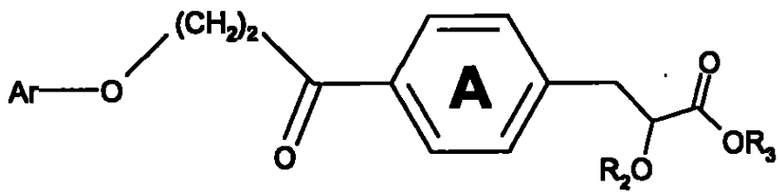


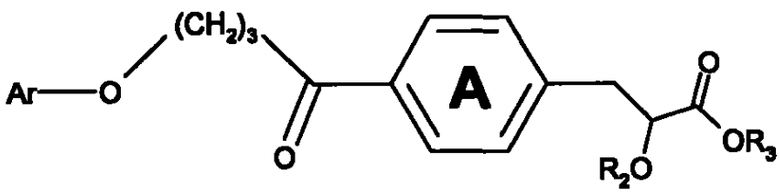
8. El compuesto de la Reivindicación 6, donde el compuesto está representado por una fórmula estructural seleccionada entre:

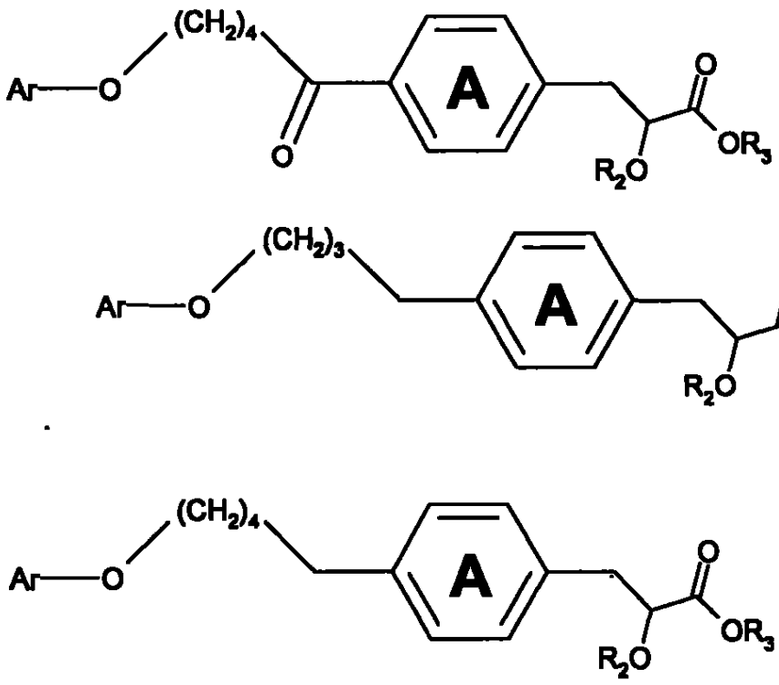






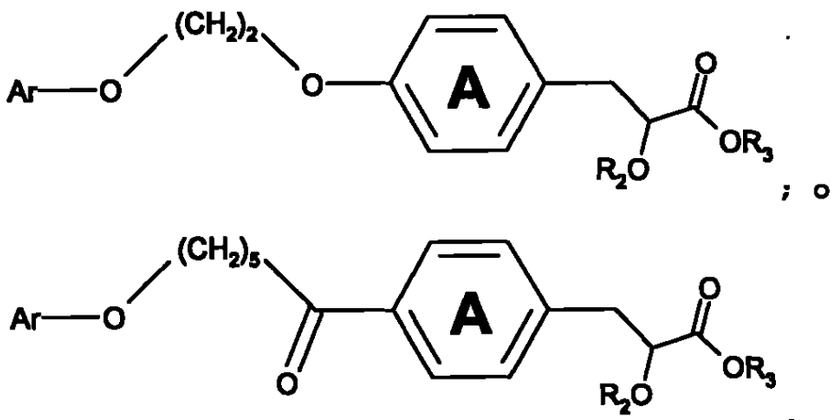






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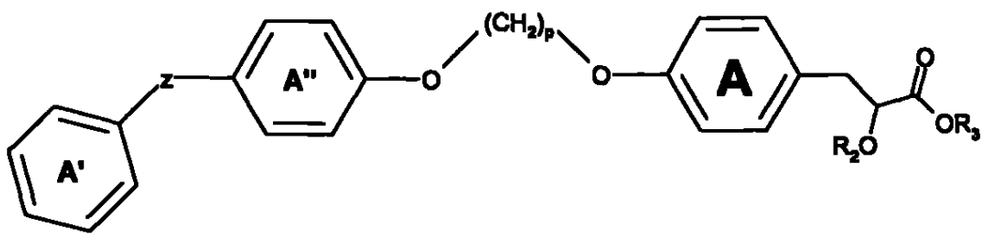
9. El compuesto de la Reivindicación 4, donde el compuesto está representado por una fórmula estructural seleccionada entre:



10

10. El compuesto de la Reivindicación 8 donde R_2 es un grupo alquilo C1-C6, fenilo, bencilo o benzoílo; y R_3 es -H o un grupo alquilo C1-C6.

11. El compuesto de la Reivindicación 10, donde el compuesto está representado por la siguiente fórmula estructural:



;

donde:

los Anillos de Fenilo **A'** y **A''** sustituidos independientemente o no sustituidos y Z es -O- o -CO- y p es 3 o 4.

12. El compuesto de la Reivindicación 11, donde Los Anillos de Fenilo **A'** y **A''** están sustituidos independientemente con uno o más grupos seleccionados entre halógeno, $-R_9$, $-OR_9$, $-COR_9$, $-COOR_9$, -CN, un grupo heterocíclico no aromático, un grupo alilo, $-(CH_2)_aCH(OR_{30})(CH_2)_bCOOR_{31}$, o $-NR_9C(O)R_9$, R_9 es -H, un grupo alquilo C1-C10, un grupo alquilo halogenado C1-C10, un grupo cicloalquilo o un grupo aromático, R_{30} es un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado, R_{31} es -H, un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado, y a y b son independientemente 0, 1 o 2.

13. El compuesto de la Reivindicación 12, donde los Anillos de Fenilo **A'** y **A''** están sustituidos independientemente con uno o más grupos seleccionados entre halógeno, alquilo de cadena lineal o ramificado C1-

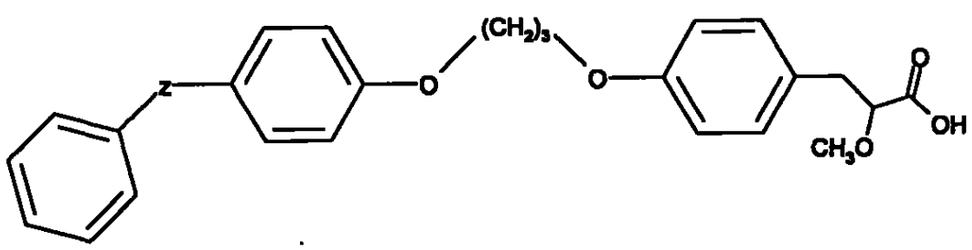
C8, cicloalquilo C3-C8, alcanoílo C1-C8 de cadena lineal o ramificado, alcoxi de cadena lineal o ramificado C1-C8, -Br, -F, *N*-morfolino, -CN, -COOH, -OH, $-CF_3$ o $-OCF_3$.

14. El compuesto de la Reivindicación 13, donde el Anillo de Fenilo **A** está sustituido con uno o más grupos seleccionados entre halógeno, $-OR_{10}$, $-R_{10}$, un grupo aromático, un grupo aromático sustituido, aralquilo, aralquilo sustituido, aralquenilo, aralquenilo sustituido, alilo o alilo sustituido y R_{10} es un grupo alquilo C1-C10 o un grupo alquilo C1-C10 halogenado.

15. El compuesto de la Reivindicación 14, donde el Anillo de Fenilo **A** está sustituido con uno o más grupos seleccionados entre -F, -Cl, $-OCH_3$, $-OCF_3$, $-CH_3$, etilo, *n*-propilo, *iso*-propilo, alilo, 2-feniletenilo, 2-feniletilo, fenilo, *-o*-bifenilo, *-m*-bifenilo, *-p*-bifenilo, $-o-C_6H_4OCH_3$, $-m-C_6H_4OCH_3$, $-p-C_6H_4OCH_3$, $-o-C_6H_4F$, $-m-C_6H_4F$ o $-p-C_6H_4F$.

16. El compuesto de la Reivindicación 11, donde R_2 es metilo y R_3 es hidrógeno.

17. Un compuesto representado mediante la siguiente fórmula estructural:

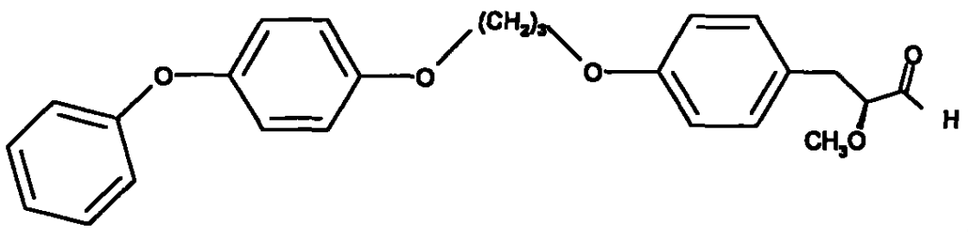


;

o las sales, hidratos, estereoisómeros, y solvatos farmacéuticamente aceptables del mismo, donde Z es -O- o

-CO-.

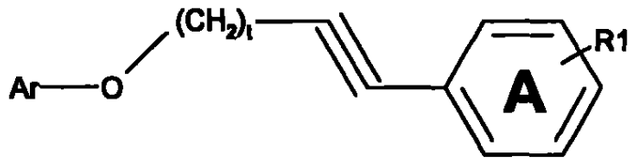
18. Un compuesto representado mediante la siguiente fórmula estructural



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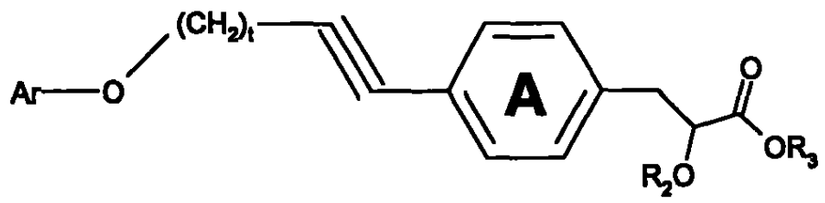
o las sales, hidratos y solvatos farmacéuticamente aceptables del mismo.

19. El compuesto de la Reivindicación 1 o 2, donde el compuesto está representado por la siguiente fórmula estructural:



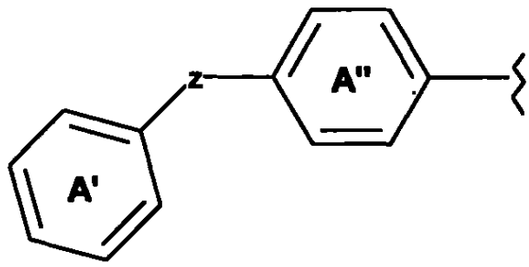
donde t es un entero de 1 a aproximadamente 5.

18. El compuesto de la Reivindicación 19 donde el compuesto está representado por la siguiente fórmula estructural:



21. El compuesto de la Reivindicación 20, donde R_2 es un grupo alquilo C1-C6, fenilo, bencilo o benzoílo; y R_3 es -H o un grupo alquilo C1-C6.

22. El compuesto de la Reivindicación 21, donde Ar está representado por la siguiente fórmula estructural:



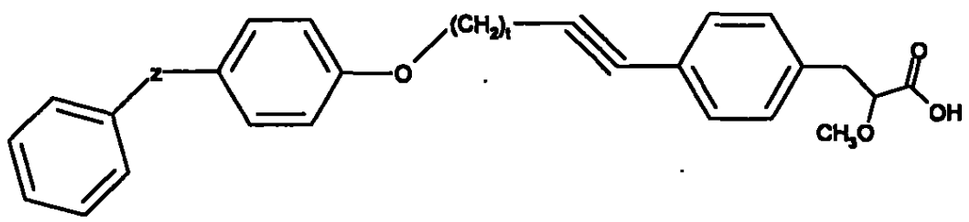
;

donde los Anillos de Fenilo A' y A'' están independientemente sustituidos o no sustituidos y Z es -O- o -CO-.

23. El compuesto de la Reivindicación 22, donde los Anillos de Fenilo A' y A'' están sustituidos independientemente con uno o más grupos seleccionados entre $-R_9$, $-OR_9$, $-COR_9$, $-COOR_9$, -CN, un grupo heterocíclico no aromático, un grupo alilo, $-(CH_2)_aCH(OR_{30})(CH_2)_bCOOR_{31}$, o $-NR_9C(O)R_9$, R_9 es -H, un grupo alquilo C1-C10, un grupo alquilo C1-C10 halogenado, un grupo cicloalquilo o un grupo aromático, R_{30} es un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado, R_{31} es -H, un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado, y a y b son independientemente 0, 1 o 2.

24. El compuesto de la Reivindicación 23, donde R_2 es metilo y R_3 es -H.

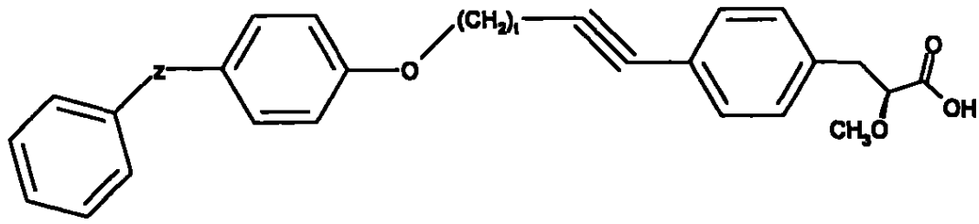
25. Un compuesto representado mediante la siguiente fórmula estructural:



;

o las sales, hidratos, estereoisómeros y solvatos farmacéuticamente aceptables del mismo, donde Z es -O-, -CO-, -C(=NOH) o un enlace y t es 1, 2 o 3.

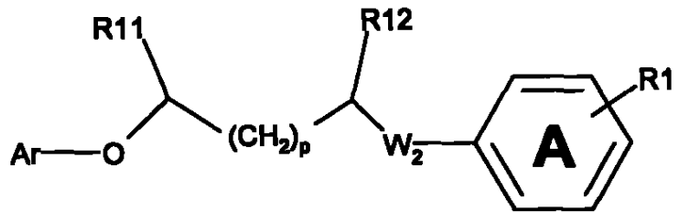
26. Un compuesto representado mediante la siguiente fórmula estructural:



;

o las sales hidratos, y solvatos farmacéuticamente aceptables del mismo, donde Z es -O-, -CO- o un enlace y t es 1, 2 o 3.

27. El compuesto de la Reivindicación 1 o 2, donde el compuesto está representado por la siguiente fórmula estructural:



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donde:

p es cero, uno o dos;

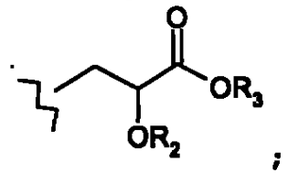
W_2 es -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- o $-CH(NR_7R_8)-$;

R_7 y R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido; y

R_{11} y R_{12} son independientemente un grupo alquilo C1-C6, o, tomados juntos son un grupo etileno, propileno o butileno sustituido o no sustituido.

28. El compuesto de la Reivindicación 27, donde W_2 es -O-.

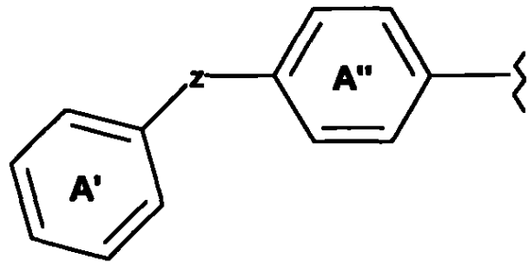
29. El compuesto de la Reivindicación 28, donde R_1 está en *para* respecto al átomo de carbono unido a W_2 y está representado por la siguiente fórmula estructural:



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donde R_2 es un grupo alquilo C1-C6, fenilo, bencilo o benzoílo; y R_3 es -H o un grupo alquilo C3-C6.

30. El compuesto de la Reivindicación 29, donde Ar está representado por la siguiente fórmula estructural:

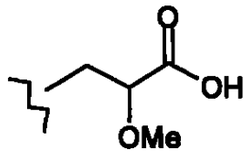


;

donde los Anillos de Fenilo **A' y A''** independientemente sustituidos o no sustituidos y Z es -O- o -CO-.

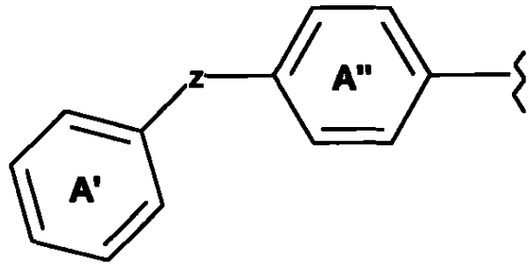
31. El compuesto de la Reivindicación 30, donde los Anillos de Fenilo **A'** y **A''** son sustituidos independientemente con uno o más grupos seleccionados entre $-R_9$, $-OR_9$, $-COR_9$, $-COOR_9$, $-CN$, un grupo heterocíclico no aromático, un grupo alilo, $-(CH_2)_aCH(OR_{30})(CH_2)_bCOOR_{31}$, o $-NR_9C(O)R_9$, y donde R_9 es -H, un grupo alquilo C1-C10, o un grupo alquilo C1-C10 halogenado, un grupo cicloalquilo o un grupo aromático, R_{30} es un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado, R_{31} es -H, un grupo alquilo C1-C6 o un grupo alquilo C1-C6 halogenado, y a y b son independientemente 0, 1 o 2.

32. El compuesto de la Reivindicación 31, donde R_1 está representado por la siguiente fórmula estructural:



33. El compuesto de la Reivindicación 27, donde: 1) p es uno y R_{11} y R_{12}, tomados juntos, son etileno o propileno; 2) p es cero y R_{11} y R_{12}, tomados juntos, son propileno o butileno; o 3) p es cero, uno o dos y R_{11} y R_{12} son independientemente metilo, etilo o propilo.

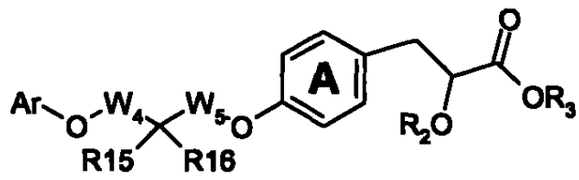
34. El compuesto de la Reivindicación 33, donde Ar está representado por la siguiente fórmula estructural:



;

los Anillos de Fenilo **A**, **A'** y **A''** no están sustituidos y Z es -O-, -C(O)- o un enlace.

35. El compuesto de la Reivindicación 1 o 2 donde el compuesto está representado por la siguiente fórmula estructural:



donde:

W_4 y W_5 son independientemente metileno o etileno;

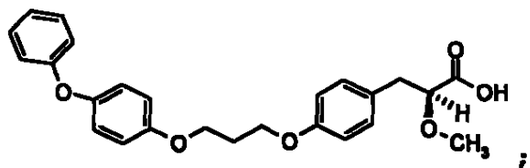
R_2 es un grupo alquilo C1-C6, fenilo, bencilo o benzoil;

R_3 es -H o un grupo alquilo C1-C3.

R_{15} es H y R_{16} es un grupo alquilo C1-C6, o R_{15} y R_{16}, tomados juntos, son =O o $=CH_2$.

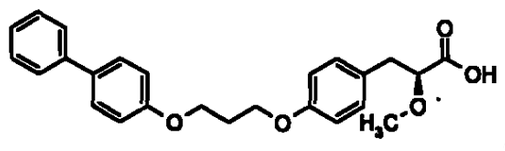
36. El compuesto de la Reivindicación 35, donde R_{15} es H y R_{16} es metilo, etilo o propilo, o R_{15} y R_{16}, tomados juntos, son =O o $=CH_2$.

37. Un compuesto seleccionado del grupo formado por Acido (S)-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



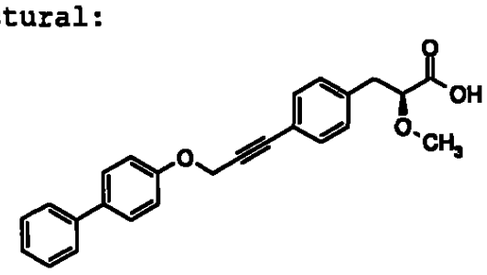
;

Acido (S)-3-{4-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



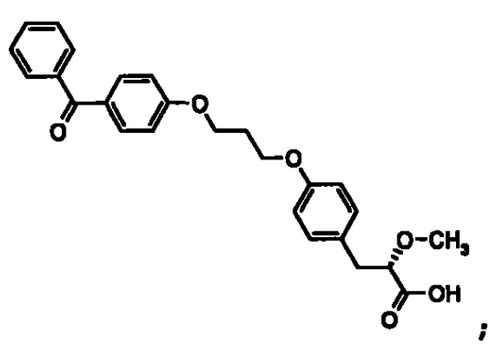
;

Acido (S)-3-{4-[3-(bifenil-4-iloxi)-prop-1-inil]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



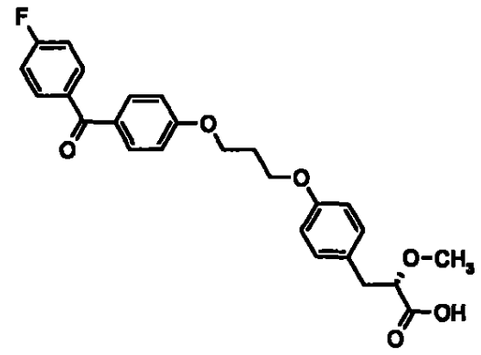
;

Acido (S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



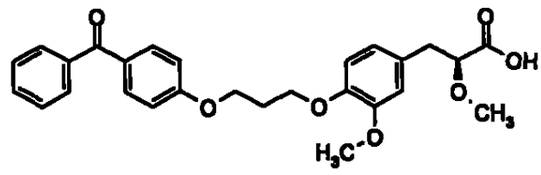
;

Acido (S)-3-(4-{3-[4-(4-fluoro-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



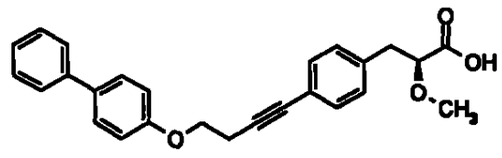
;

Acido (S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-metoxi-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



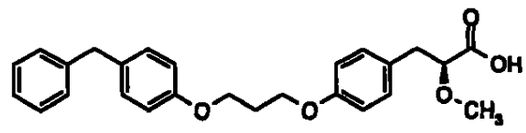
;

Acido (S)-3-{4-[4-(bifenil-4-iloxi)-but-1-inil]-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



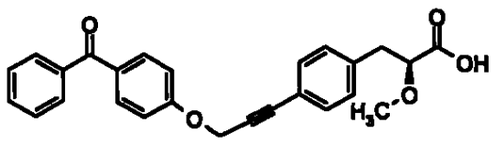
;

Acido (S)-3-{4-[3-(4-bencil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



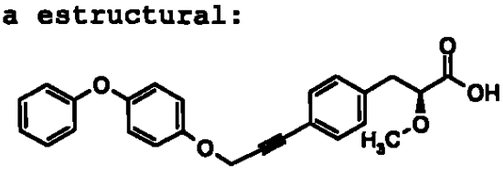
;

Acido (S)-3-{4-[3-(4-benzoil-fenoxi)-prop-1-inil]-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



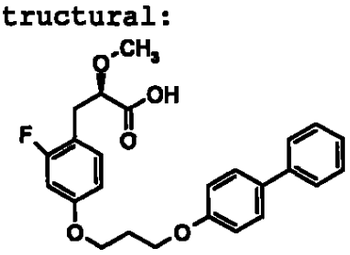
;

Acido (S)-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-prop-1-inil]-fenil}-propiónico, que está representado por la siguiente fórmula estructural:



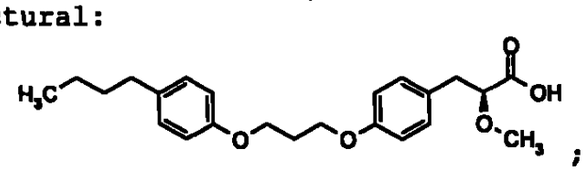
;

Acido (S)-3-{4-[3-(bifenil-4-iloxi)-propoxi]-2-fluoro-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



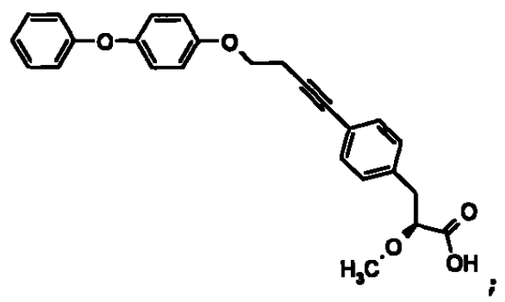
;

Acido (S)-3-{4-[3-(4-Butil-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



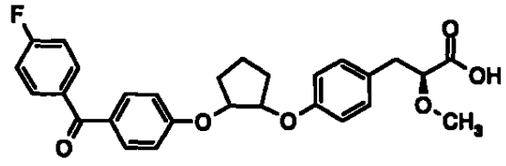
;

Acido (S)-2-metoxi-3-{4-[4-(4-fenoxi-fenoxi)-but-1-inil]-fenil}-propiónico, que está representado por la siguiente fórmula estructural:



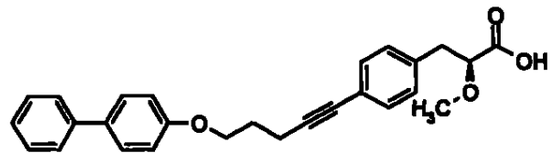
;

Acido (2S)-3-(4-{2-[4-(4-fluoro-benzoil)-fenoxi]-ciclopentiloxi}-fenil)-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



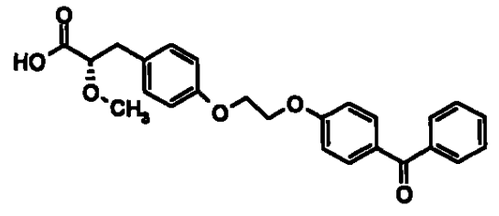
;

Acido (S)-3-{4-[5-(bifenil-4-iloxi)-pent-1-inil]-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:



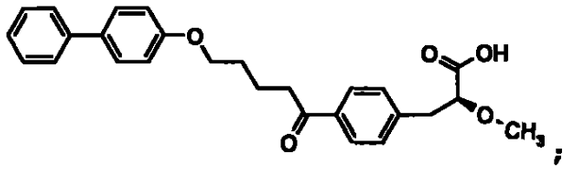
;

Acido (S)-3-{4-[2-(4-benzoil-fenoxi)-etoxi]-fenil}-2-metoxi-propiónico, que está representado por la siguiente fórmula estructural:

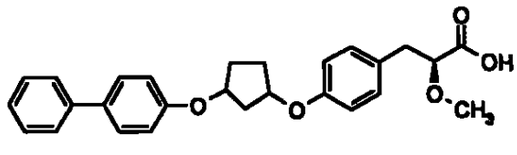


;

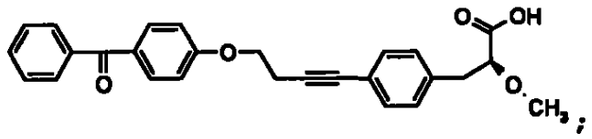
Acido (S)-3-{4-[5-(bifenil-4-iloxi)-pentanoil]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



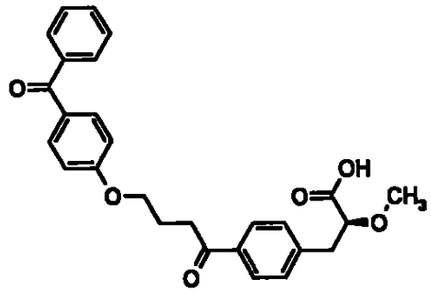
Acido (S)-3-{4-[3-(bifenil-4-iloxi)-ciclopentiloxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



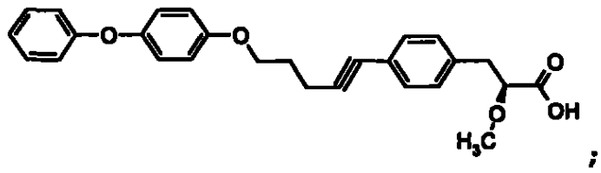
Acido (S)-3-{4-[4-(4-benzoil-fenoxi)-but-1-inil]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



Acido (S)-3-{4-[4-(4-benzoil-fenoxi)-butiril]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:

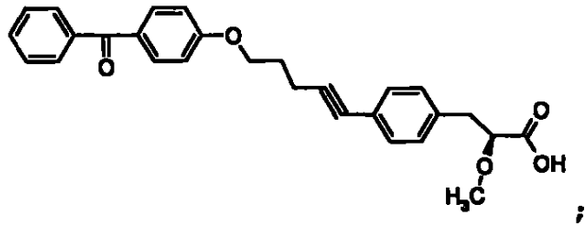


Acido (S)-2-metoxi-3-{4-[5-(4-fenoxi-fenoxi)-pent-1-inil]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



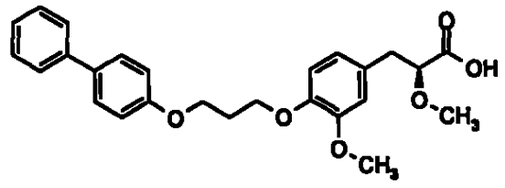
;

Acido (S)-3-{4-[5-(4-benzoil-fenoxi)-pent-1-inil]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



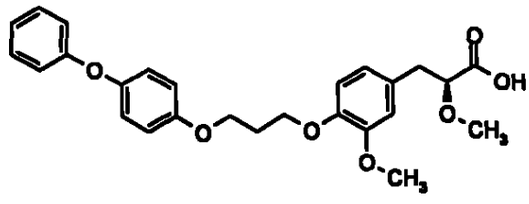
;

Acido (S)-3-{4-[3-(bifenil-4-iloxi)-propoxi]-3-metoxi-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



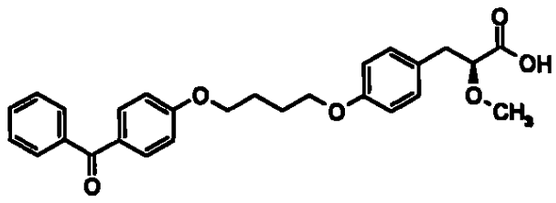
;

Acido (S)-2-metoxi-3-{3-metoxi-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



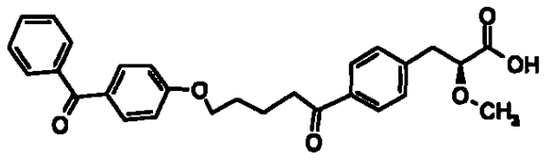
;

Acido (S)-3-{4-[4-(4-benzoil-fenoxi)-butoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



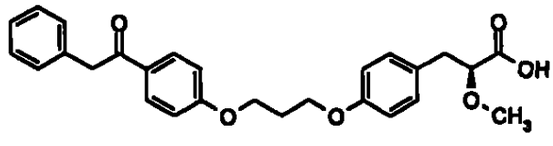
;

Acido (S)-3-{4-[5-(4-benzoil-fenoxi)-pentanoil]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



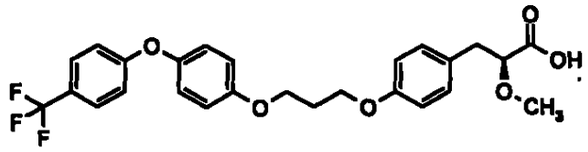
;

Acido (S)-2-metoxi-3-{4-[3-(4-fenilacetil-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



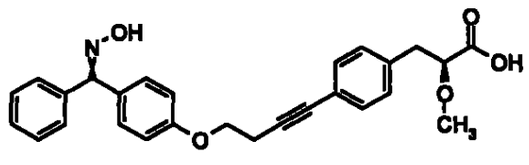
;

Acido 2-metoxi-3-(4-{3-[4-(4-trifluorometil-fenoxi)-fenoxi]-propoxi}-fenil)-propiónico, representado mediante la siguiente fórmula estructural:



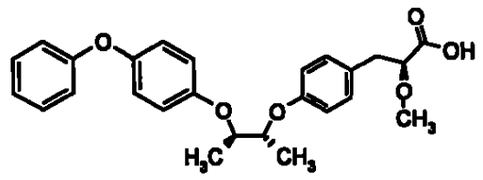
;

Acido 3-(4-{4-[4-(hidroxiimino-fenil-metil)-fenoxi]-but-1-inil}-fenil)-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



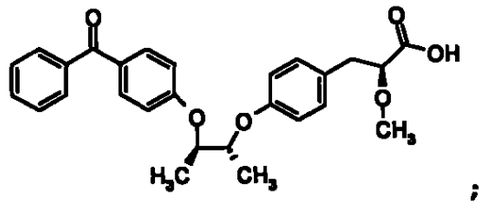
;

Acido 2-metoxi-3-{4-[1-metil-2-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



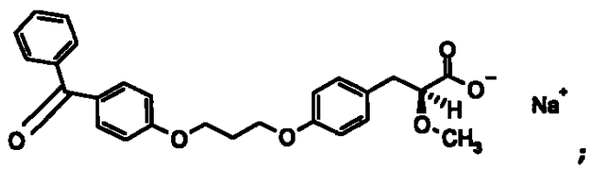
;

Acido 3-{4-[2-(4-benzoil-fenoxi)-1-metil-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



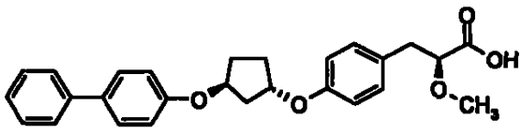
;

3-{4-[3-(4-Benzoil-fenoxi)-propoxi]-fenil}-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



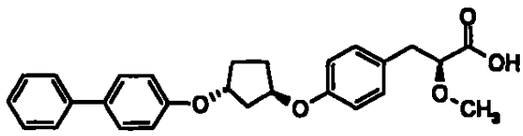
;

Acido 3-{4-[3-(bifenil-4-iloxi)-ciclopentiloxi]-fenil}-2*S*-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



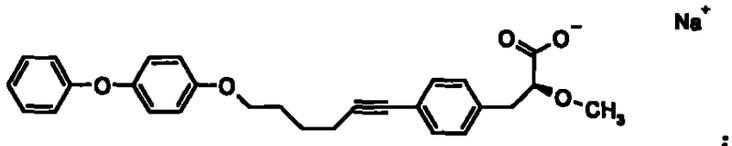
;

Acido 3-{4-[3-(bifenil-4-iloxi)-ciclopentiloxi]-fenil}-2*S*-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



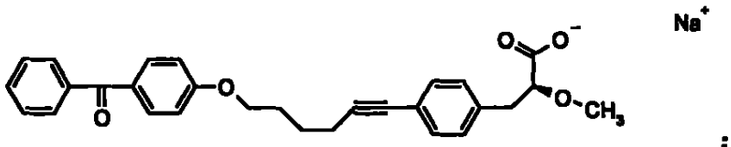
;

(S)-2-metoxi-3-{4-[6-(4-fenoxi-fenoxi)-hex-1-inil]-fenil}-propionato de sodio, representado mediante la siguiente fórmula estructural:



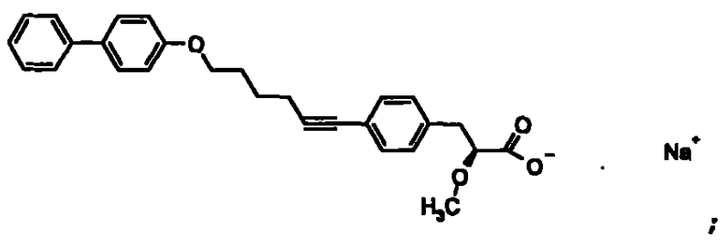
;

(S)-3-{4-[6-(4-benzoil-fenoxi)-hex-1-inil]-fenil}-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



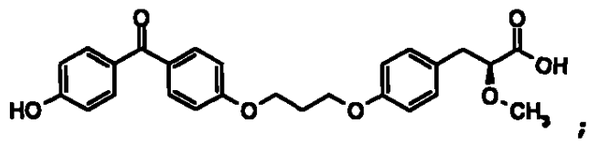
;

(S)-3-{4-[6-(bifenil-4-iloxi)-hex-1-inil]-fenil}-2-metoxi-propionate de sodio, representado mediante la siguiente fórmula estructural:



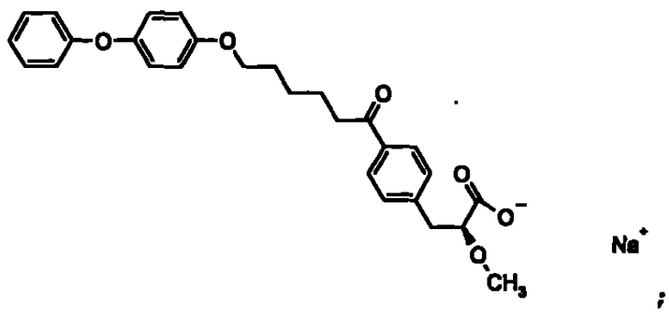
;

Acido (S)-3-(4-{3-[4-(4-hidroxi-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



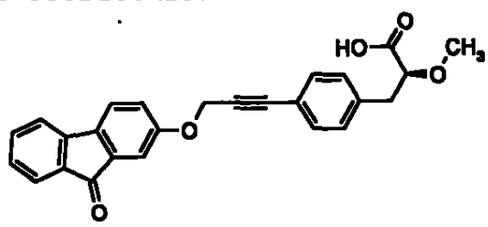
;

(S)-2-metoxi-3-{4-[6-(4-fenoxi-fenoxi)-hexanoil]-fenil}-propionato de sodio, representado mediante la siguiente fórmula estructural:



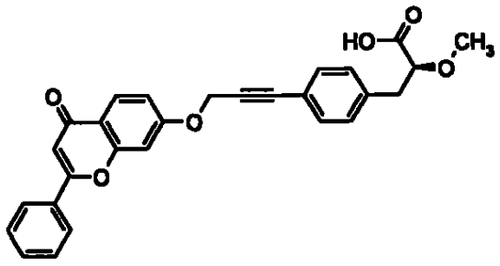
;

Acido (S)-2-metoxi-3-{4-[3-(9-oxo-9H-fluoren-2-iloxi)-prop-1-inil]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



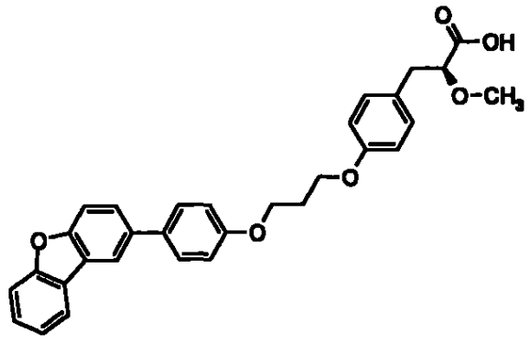
;

Acido (S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-7-iloxi)-prop-1-inil]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



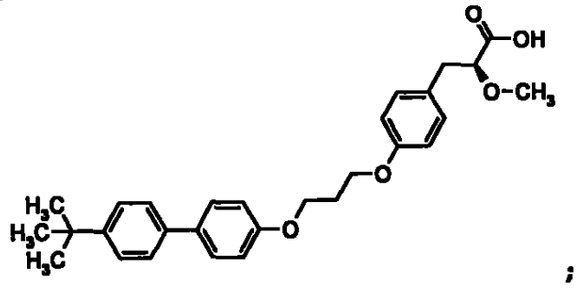
;

Acido (S)-3-{4-[3-(4-dibenzofuran-2-il-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



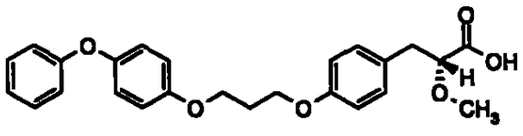
;

Acido (S)-3-{4-[3-(4'-tert-butil-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



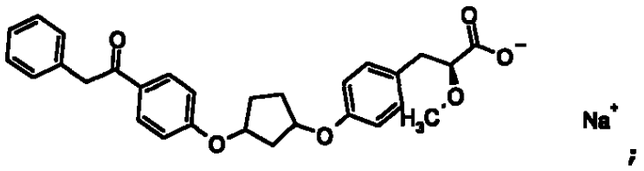
;

(R)-2-metoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



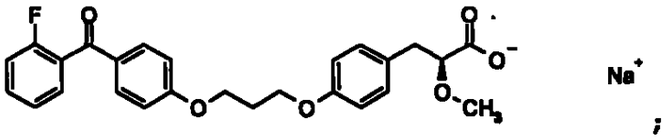
;

(S)-2-metoxi-3-{4-[3-(4-fenilacetil-fenoxi)-ciclopentiloxi]-fenil}-propionato de sodio, representado mediante la siguiente fórmula estructural:



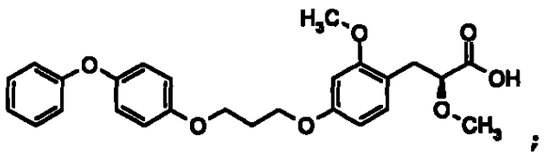
;

(S)-3-{4-{3-[4-(2-fluoro-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



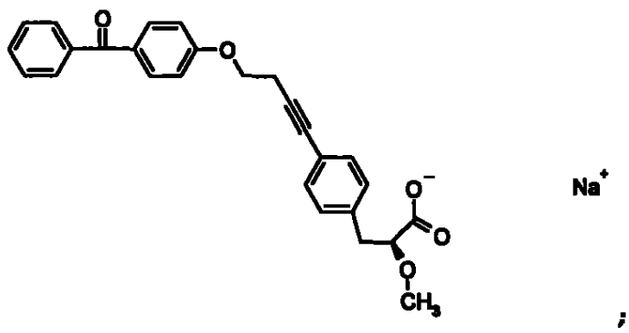
;

Acido (S)-2-metoxi-3-{2-metoxi-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



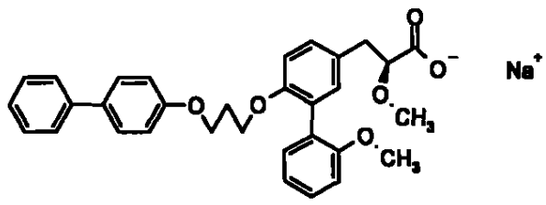
;

(S)-3-{4-[4-(4-benzoil-fenoxi)-but-1-inil]-fenil}-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



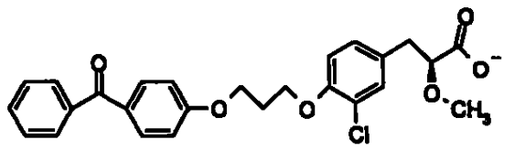
;

(S)-3-{6-[3-(bifenil-4-iloxi)-propoxi]-2'-metoxi-bifenil-3-il}-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



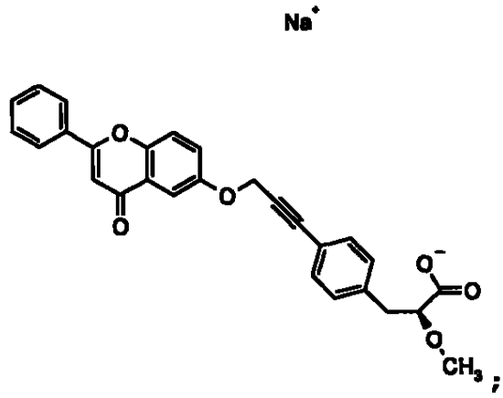
;

(S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-cloro-fenil}-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:

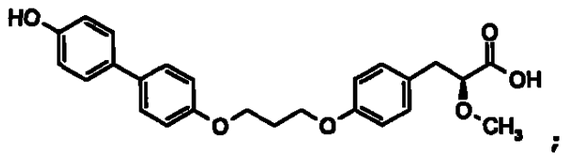


;

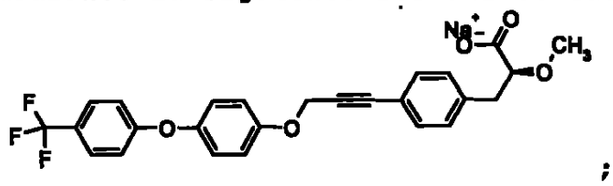
(S)-2-metoxi-3-{4-[3-(4-oxo-2-fenil-4H-cromen-6-iloxi)-prop-1-inil]-fenil}-propionato de sodio, representado mediante la siguiente fórmula estructural:



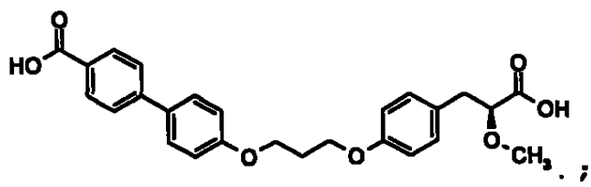
Acido (S)-3-{4-[3-(4'-hidroxi-bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



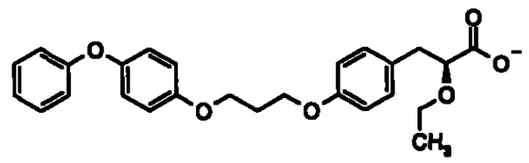
(S)-2-metoxi-3-(4-{3-[4-(4-trifluorometil-fenoxi)-fenoxi]-prop-1-inil}-fenil)-propionato de sodio, representado mediante la siguiente fórmula estructural:



Acido (S)-4'-{3-[4-(2-Carboxi-2-metoxi-etil)-fenoxi]-propoxi}-bifenil-4-carboxílico, representado mediante la siguiente fórmula estructural:

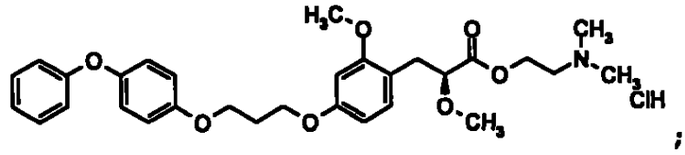


(S)-2-etoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propionato de sodio, representado mediante la siguiente fórmula estructural:



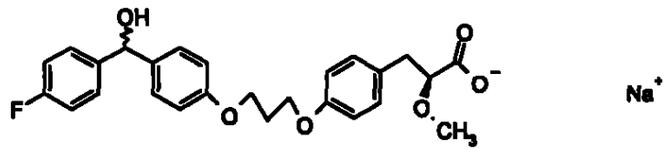
;

Ester 2-dimetilamino-etílico de ácido (S)-2-metoxi-3-{2-metoxi-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



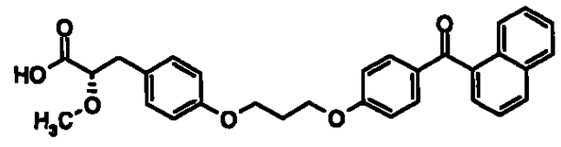
;

(S)-3-[4-(3-{4-[(4-fluoro-fenil)-hidroxi-metil]-fenoxi}-propoxi)-fenil]-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



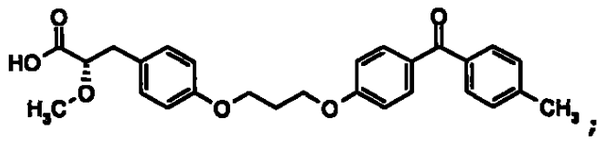
;

Acido (S)-2-metoxi-3-(4-{3-[4-(naftalene-1-carbonil)-fenoxi]-propoxi}-fenil)-propiónico, representado mediante la siguiente fórmula estructural:

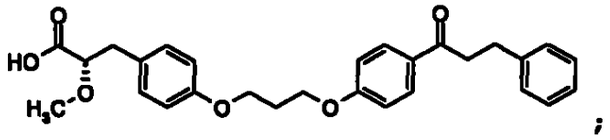


;

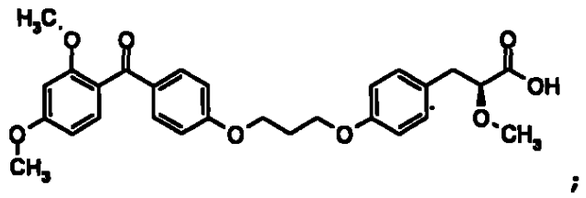
Acido (S)-2-metoxi-3-(4-{3-[4-(4-metil-benzoil)-fenoxi]-propoxi}-fenil)-propiónico, representado mediante la siguiente fórmula estructural:



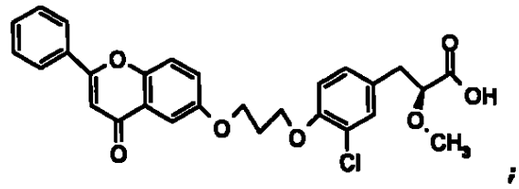
Acido (S)-2-metoxi-3-(4-{3-[4-(3-fenil-propionil)-fenoxi]-propoxi}-fenil)-propiónico, representado mediante la siguiente fórmula estructural:



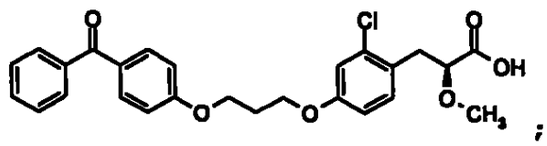
Acido (S)-3-(4-{3-[4-(2,4-dimetoxi-benzoil)-fenoxi]-propoxi}-fenil)-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



Acido (S)-3-{3-cloro-4-[3-(4-oxo-2-fenil-4H-cromen-6-iloxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:

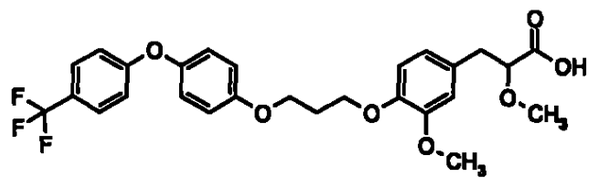


Acido (S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-cloro-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



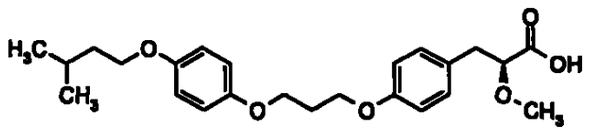
;

Acido (S)-2-metoxi-3-(3-metoxi-4-{3-[4-(4-trifluorometil-fenoxi)-fenoxi]-propoxi}-fenil)-propiónico, representado mediante la siguiente fórmula estructural:



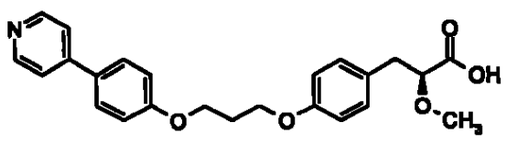
;

Acido (S)-2-metoxi-3-(4-{3-[4-(3-metil-butoxi)-fenoxi]-propoxi}-fenil)-propiónico, representado mediante la siguiente fórmula estructural:



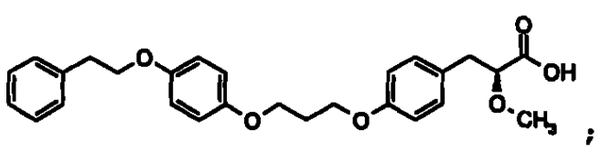
;

Acido (S)-2-metoxi-3-{4-[3-(4-piridin-4-il-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



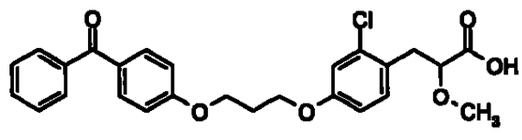
;

Acido (S)-2-metoxi-3-{4-[3-(4-fenetiloxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



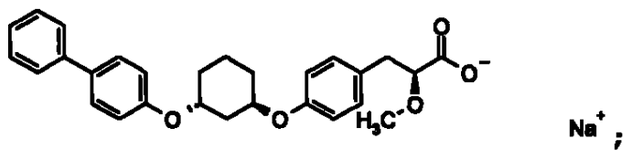
;

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-2-cloro-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



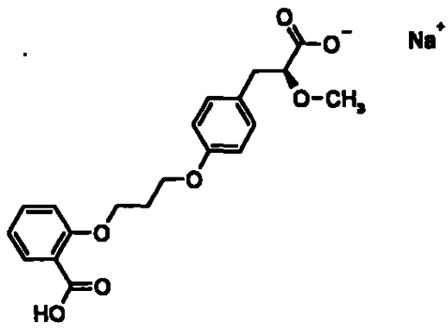
;

(S)-3-{4-[3-(bifenil-4-iloxi)-ciclohexiloxi]-fenil}-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



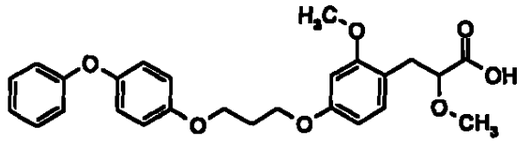
;

(S)-3-{4-[3-(2-carboxi-fenoxi)-propoxi]-fenil}-2-metoxi-propionato de sodio, representado mediante la siguiente fórmula estructural:



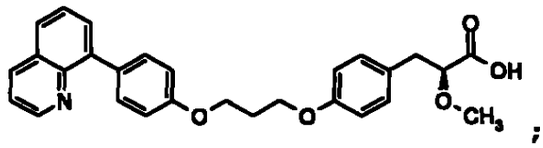
;

Acido 2-metoxi-3-{2-metoxi-4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



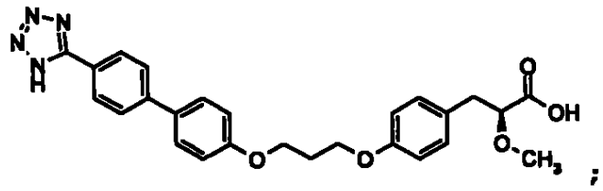
;

Acido (S)-2-metoxi-3-{4-[3-(4-quinolin-8-il-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



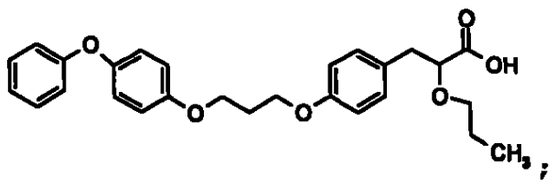
;

Acido (S)-2-metoxi-3-(4-{3-[4'-(1H-tetrazol-5-il)-bifenil-4-iloxi]-propoxi}-fenil)-propiónico, representado mediante la siguiente fórmula estructural:



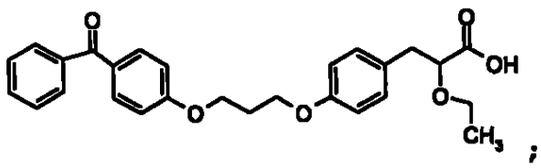
;

Acido 3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-2-propoxi-propiónico, representado mediante la siguiente fórmula estructural:



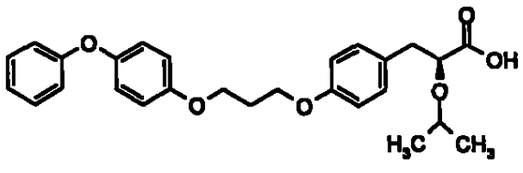
;

Acido 3-{4-[3-(4-benzoil-fenoxi)-propoxi]-fenil}-2-etoxi-propiónico, representado mediante la siguiente fórmula estructural:



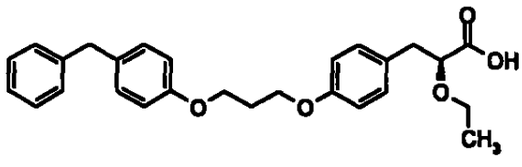
;

Acido (S)-2-isopropoxi-3-{4-[3-(4-fenoxi-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



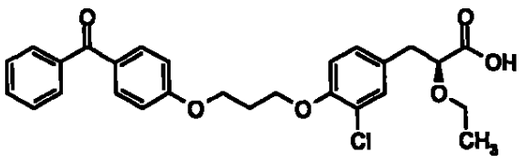
;

Acido (S)-3-{4-[3-(4-bencil-fenoxi)-propoxi]-fenil}-2-etoxi-propiónico, representado mediante la siguiente fórmula estructural:



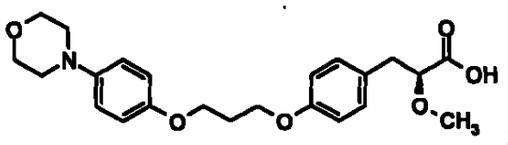
;

Acido (S)-3-{4-[3-(4-benzoil-fenoxi)-propoxi]-3-cloro-fenil}-2-etoxi-propiónico, representado mediante la siguiente fórmula estructural:



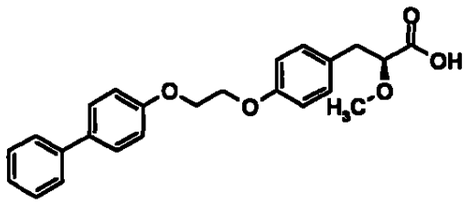
;

Acido (S)-2-metoxi-3-{4-[3-(4-morfolin-4-il-fenoxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



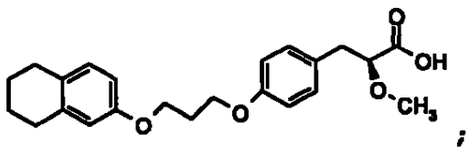
;

Acido (S)-3-{4-[2-(bifenil-4-iloxi)-etoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



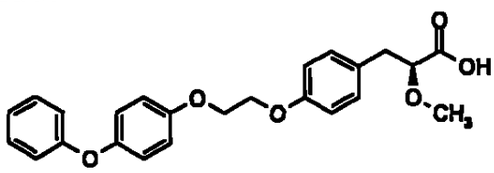
;

Acido (S)-2-metoxi-3-{4-[3-(5,6,7,8-tetrahidro-naftalen-2-iloxi)-propoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



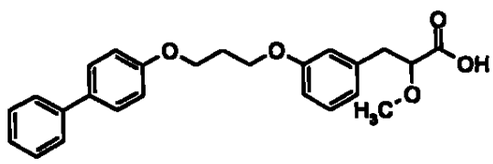
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Acido (S)-2-metoxi-3-{4-[2-(4-fenoxi-fenoxi)-etoxi]-fenil}-propiónico, representado mediante la siguiente fórmula estructural:



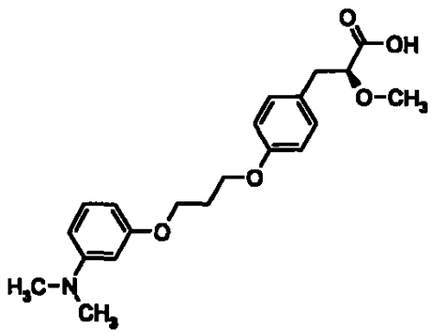
;

Acido 3-{3-[3-(bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



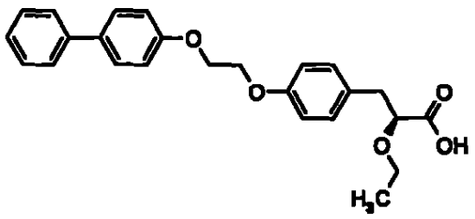
;

Acido (S)-3-{4-[3-(3-dimetilamino-fenoxi)-propoxi]-fenil}-2-metoxi-propiónico, representado mediante la siguiente fórmula estructural:



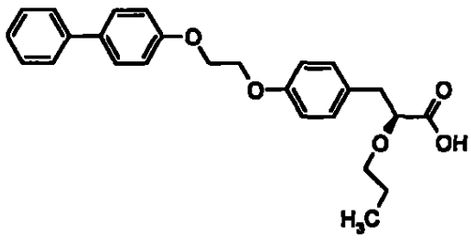
;

Acido (S)-3-{4-[2-(bifenil-4-iloxi)-etoxi]-fenil}-2-etoxi-propiónico, representado mediante la siguiente fórmula estructural:



; y

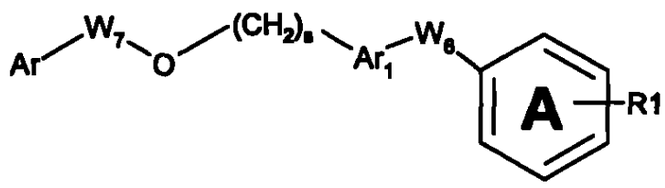
Acido (S)-3-{4-[2-(bifenil-4-iloxi)-etoxi]-fenil}-2-propoxi-propiónico, representado mediante la siguiente fórmula estructural:



,

o las sales, hidratos y solvatos farmacéuticamente aceptables de los compuestos anteriores.

38. Un compuesto representado mediante la siguiente fórmula estructural:



(XL)

o las sales, hidratos, estereoisómeros y solvatos farmacéuticamente aceptables del mismo, donde:

Ar es un grupo aromático sustituido o no sustituido;

R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ o $-(CH)=C(Y)-(CH_2)_mE$; donde E es $COOR_3$, alquil(C_1-C_3)nitrilo, carboxamida, sulfonamida, acilsulfonamida o tetrazol y donde sulfonamida, acilsulfonamida y tetrazol están sustituidos opcionalmente con uno o más sustituyentes seleccionados independientemente entre: alquilo C1-C6, haloalquilo y arilalquilo C0-C4;

R_2 es -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático, un grupo aromático sustituido, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ o $-C(S)NR_5R_6$;

Y es -O-, $-CH_2-$, $-CH_2CH_2-$ o -CH=CH- y está unido un átomo de carbono en el Anillo de Fenilo **A** que está en *orto* respecto a R_1;

R_3-R_6 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido;

n y m son independientemente 0, 1 o 2;

s es 0, 1 o 2;

Ar_1 es un grupo arileno sustituido o no sustituido;

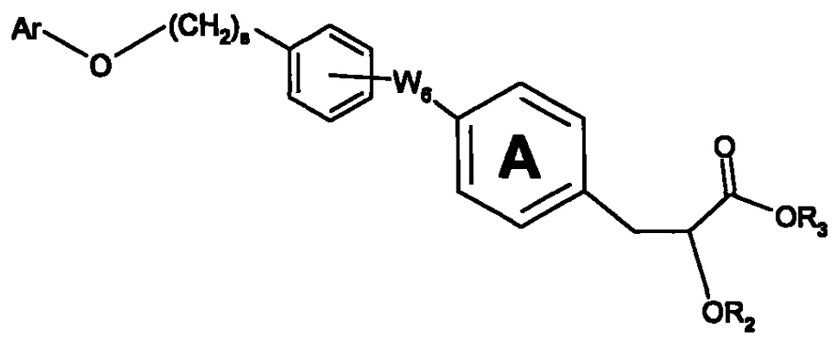
W_6 es un enlace covalente, $-W_1-$, $-CH_2W_1-$ o $-W_1CH_2-$;

W_7 es un enlace covalente o CH_2-; y

W_1 es -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- o $-CH(NR_7R_8)-$.

39. El compuesto de la Reivindicación 38, donde R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ o $-(CH)=C(Y)-(CH_2)_mCOOR_3$.

40. El compuesto de la Reivindicación 39, donde el compuesto está representado por la siguiente fórmula estructural:



;

donde s es 0 o 1 y W_6 es un enlace covalente, -O-, $-CH_2O-$ o $-OCH_2-$.

41. Una composición farmacéutica que comprende el compuesto de la Reivindicación 1 y un portador farmacéuticamente aceptable.

42. La composición farmacéutica de la Reivindicación 41, que comprende adicionalmente un segundo agente terapéutico seleccionado del grupo formado por sensibilizadores a la insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes para elevar HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acil CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes anti-hipercolesterolémicos, fibratos, vitaminas y aspirina.

43. Una composición farmacéutica que comprende el compuesto de una cualquiera de las Reivindicaciones 2-17 o 19-40 y un portador farmacéuticamente aceptable.

44. Una composición farmacéutica que comprende: 1) el compuesto de una cualquiera de las Reivindicaciones 2-17 o 19-40 o una sal, solvato, hidrato o estereoisómero farmacéuticamente aceptable del mismo; un segundo agente terapéutico seleccionado del grupo formado por sensibilizadores a la insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes para elevar HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acil CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes anti-hipercolesterolémicos, fibratos, vitaminas y aspirina; y 3) un portador farmacéuticamente aceptable.

45. Una composición farmacéutica que comprende el compuesto de la Reivindicación 18 o una sal, hidrato o solvato farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

46. La composición farmacéutica de la Reivindicación 45, que comprende adicionalmente un segundo agente terapéutico seleccionado del grupo formado por sensibilizadores a la insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes para elevar HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acil CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes anti-hipercolesterolémicos, fibratos, vitaminas y aspirina.

47. Un método para modular un receptor activado por proliferadores de peroxisomas (PPAR), que comprende la etapa de poner en contacto el receptor con al menos un compuesto de la Reivindicación 1.

48. El método de la Reivindicación 47, donde el PPAR es un receptor alfa.

49. El método de la Reivindicación 47, donde el PPAR es un receptor gamma.

50. Un método para modular un receptor activado por proliferadores de peroxisomas (PPAR), que comprende la etapa de poner en contacto el receptor con al menos un compuesto de la Reivindicación 2.

51. Un método para modular un receptor activado por proliferadores de peroxisomas (PPAR), que comprende la etapa de poner en contacto el receptor con el compuesto de la Reivindicación 18.

52. Un método para tratar una enfermedad o afección mediada por PPAR-gamma en un sujeto que comprende la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 1.

53. Un método para tratar una enfermedad o afección mediada por PPAR-gamma en un sujeto que comprende la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 2.

54. Un método para tratar una enfermedad o afección mediada por PPAR-gamma en un sujeto que comprende la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 18.

55. Un método para rebajar la glucosa en sangre en un sujeto que comprende la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 1.

56. Un método para rebajar la glucosa en sangre en un sujeto que comprende la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 2.

57. Un método para rebajar la glucosa en sangre en un sujeto que comprende la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 18.

58. Un método para tratar un sujeto con hiperglicemia, dislipidemia, diabetes de Tipo II, diabetes de Tipo I, hipertrigliceridemia, síndrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesteremia, hipertensión, obesidad, anorexia-bulimia, síndrome del ovario poliquístico, anorexia nerviosa, enfermedades cardiovasculares u otras enfermedades donde la resistencia a la insulina es un componente, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 1.

59. Un método para tratar un sujeto con hiperglicemia, dislipidemia, diabetes de Tipo II, diabetes de Tipo I, hipertrigliceridemia, síndrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesteremia, hipertensión, obesidad, anorexia-bulimia, síndrome del ovario poliquístico, anorexia nerviosa, enfermedades cardiovasculares u otras enfermedades donde la resistencia a la insulina es un

componente, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 2.

60. Un método para tratar un sujeto con hiperglicemia, dislipidemia, diabetes de Tipo II, diabetes de Tipo I, hipertrigliceridemia, sindrome X, resistencia a la insulina, insuficiencia cardíaca, dislipidemia diabética, hiperlipidemia, hipercolesteremia, hipertensión, obesidad, anorexia-bulimia, síndrome del ovario poliquístico, anorexia nerviosa, enfermedades cardiovasculares u otras enfermedades donde la resistencia a la insulina es un componente, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 18.

61. El método de la Reivindicación 58, que comprende adicionalmente la etapa de administrar al sujeto una cantidad eficaz de un segundo agente terapéutico seleccionado del grupo formado por sensibilizadores a la insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes para elevar HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acil CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina.

62. El método de la Reivindicación 59, que comprende adicionalmente la etapa de administrar al sujeto una cantidad eficaz de un segundo agente terapéutico seleccionado del grupo formado por sensibilizadores a la insulina, sulfonilureas, biguanidas, tiazolidinodionas,

inhibidores de la α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes para elevar HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acil CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina.

63. El método de la Reivindicación 60, que comprende adicionalmente la etapa de administrar al sujeto una cantidad eficaz de un segundo agente terapéutico seleccionado del grupo formado por sensibilizadores a la insulina, sulfonilureas, biguanidas, tiazolidinodionas, inhibidores de la α-glucosidasa, secretagogos de insulina, insulina, agentes antihiperlipidémicos, agentes para elevar HDL en plasma, inhibidores de la HMG-CoA reductasa, estatinas, inhibidores de la acil CoA:colesterol aciltransferasa, compuestos antiobesidad, agentes antihipercolesterolémicos, fibratos, vitaminas y aspirina.

64. Un método para tratar un sujeto con diabetes sacarina, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 1.

65. Un método para tratar un sujeto con diabetes sacarina, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 2.

66. Un método para tratar un sujeto con diabetes sacarina, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 18.

67. Un método para tratar un sujeto con enfermedades cardiovasculares, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 1.

68. Un método para tratar un sujeto con enfermedades cardiovasculares, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 2.

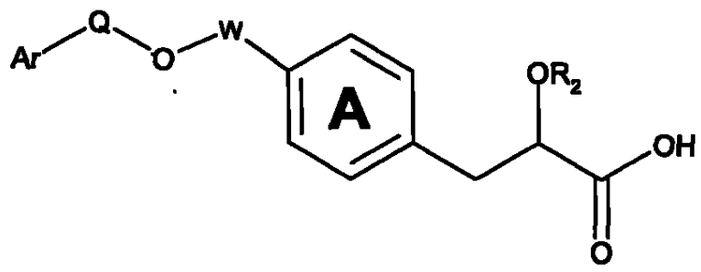
69. Un método para tratar un sujeto con enfermedades cardiovasculares, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 18.

70. Un método para tratar un sujeto con Síndrome X, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 1.

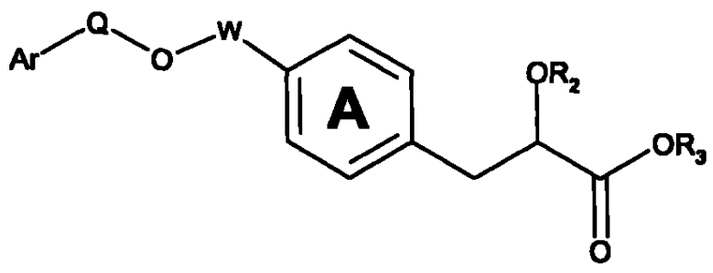
71. Un método para tratar un sujeto con Síndrome X, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 2.

72. Un método para tratar un sujeto con Síndrome X, comprendiendo dicho método la etapa de administrar al sujeto una cantidad eficaz del compuesto de la Reivindicación 18.

73. Un método para preparar un compuesto representado mediante la siguiente fórmula estructural:



a partir de un compuesto de partida representado mediante la siguiente fórmula estructural:



;

comprendiendo dicho método la etapa de hidrolizar el grupo éster en el computo de partida, donde:

Ar es un grupo aromático sustituido o no sustituido;

Q es un enlace covalente, $-CH_2-$ o $-CH_2CH_2-$;

W es un grupo conector alquileno o heteroalquileno sustituido o no sustituido de dos a diez átomos de longitud;

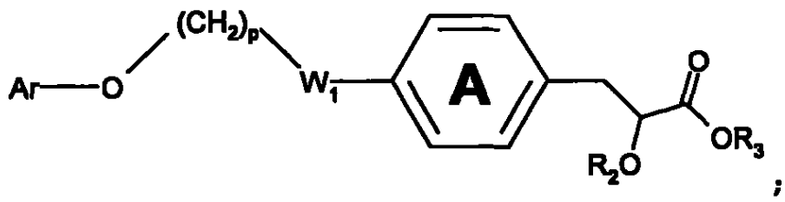
el Anillo de fenilo A está sustituido opcionalmente con hasta cuatro sustituyentes además de W y $-CH_2CHOR_2C(O)OR_3$;

R_2 es -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático, un grupo aromático sustituido;

R_3 un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

74. El método de la Reivindicación 73, donde Q es un enlace covalente.

75. El método de la Reivindicación 74, donde el compuesto de partida está representado por la siguiente fórmula estructural:



;

i. p es un entero de uno a cuatro;

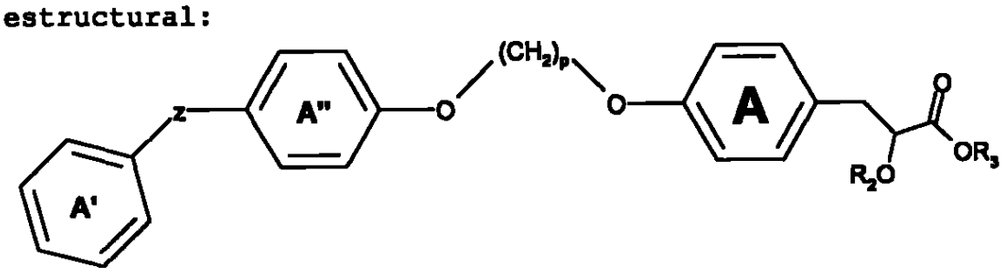
W_1 es -O-, -C(O)-, $-OCH_2-$, $-CH_2-$, $-NR_8-$, $-NR_8CO-$, $-NR_8CH-$, -C(=NOH)- o $-CH(NR_7R_8)-$;

R_2 es un grupo alquilo C1-C6, fenilo, bencilo o benzoílo;

R_3 -H o a C1-C3 un grupo alquilo; y

R_7 y R_8 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

76. El método de la Reivindicación 75 donde el compuesto está representado por la siguiente fórmula estructural:

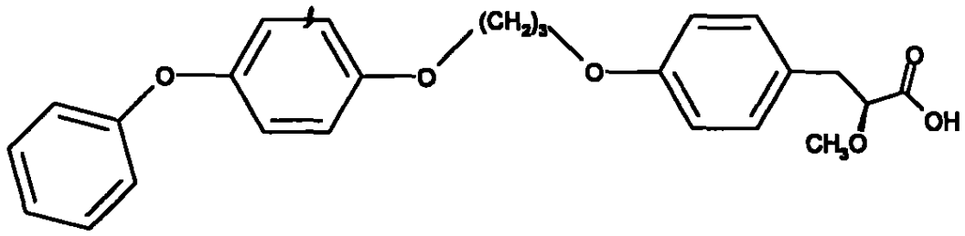


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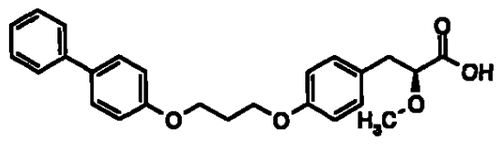
donde:

los Anillos de Fenilo **A'** y **A''** están independientemente sustituidos o no sustituidos y Z es -O- o -CO-.

77. El método de la Reivindicación 76, donde el compuesto está representado por la siguiente fórmula estructural:



78. Un compuesto, donde el compuesto es el ácido (S)-3-{4-[3-(Bifenil-4-iloxi)-propoxi]-fenil}-2-metoxi-propiónico radiomarcado, representado mediante la siguiente fórmula estructural:



79. El compuesto de la Reivindicación 78, donde la marca radiactiva es un átomo de tritio.

80. Un método para determinar si un compuesto inteacciona o no directamente con el receptor activado por proliferadores de peroxisomas, que comprende la etapa de unir específicamente el compuesto radiomarcado de la Reivindicación 78 al dominio de unión al ligando del receptor activado por proliferadores de peroxisomas.

81. El método de la Reivindicación 80, donde el receptor activado por proliferadores de peroxisomas es PPARγ.

82. El método de la Reivindicación 81, que comprende adicionalmente la etapa de poner en contacto el receptor

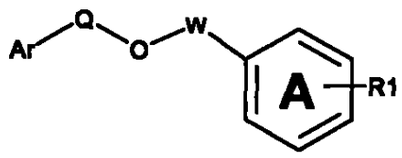
con un compuesto de ensayo y evaluar la cantidad de unión específica del compuesto radiomarcado al receptor, donde un descenso en la unión del compuesto radiomarcado indica que el compuesto de ensayo intecacciona directamente con el receptor activado por proliferadores de peroxisomas.

83. El método de la Reivindicación 82, donde el compuesto radiomarcado está tritiado.

MODULADORES DE LOS RECEPTORES ACTIVADOS POR PROLIFERADORES DE PEROXISOMAS

RESUMEN DE LA DESCRIPCION

Se ha descrito un compuesto representado por la Formula Estructural (I):



(I).

Ar es un grupo aromático sustituido o no sustituido.

Q es un enlace covalente, $-CH_2-$ o $-CH_2CH_2-$;

W es un grupo conector alquileno sustituido o no sustituido o un grupo conector heteroalquileno sustituido o no sustituido de dos a diez átomos de longitud, preferiblemente de dos a siete átomos de longitud.

el Anillo de Fenilo **A** está opcionalmente sustituido con hasta cuatro sustituyentes además de R_1 y W.

R_1 es $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ o $-(CH)=C(Y)-(CH_2)_mE$; donde E es $COOR_3$, alquil(C_1-C_3)nitrilo, carboxamida, sulfonamida, acilsulfonamida o tetrazol y donde sulfonamida, acilsulfonamida y tetrazol están opcionalmente sustituidos con uno o más sustituyentes seleccionados independientemente entre: alquilo C1-C6, haloalquilo y arilalquilo C0-C4; R_2 es -H, un grupo alifático, un grupo alifático sustituido, haloalquilo, un grupo aromático, un grupo aromático sustituido, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ o $-C(S)NR_5R_6$.

R_3 es -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

Y es -O-, $-CH_2-$, $-CH_2CH_2-$ o -CH=CH- y está unido a un átomo de carbono en el Anillo de Fenilo **A** que está en *orto* respecto a R_1.

R_4-R_6 son independientemente -H, un grupo alifático, un grupo alifático sustituido, un grupo aromático o un grupo aromático sustituido.

n y m son independientemente 0, 1 o 2.

PATENT COOPERATION TREATY

DOCKETED JAR 1028

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Brook, David E.
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 Virginia Road
P.O Box 9133
Concord, MA 01742-9133
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing (day/month/year)	18.07.2003
Applicant's or agent's file reference: 2947.1007002	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/16950	30.05.2002	07.06.2001

FOREIGN DOCKETING

Applicant: ELI LILLY AND COMPANY

no docketing required

Completed by: CRS

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Roche, S Tel. +49 89 2399-8031

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JUL 24 2003
Rec'd IFO
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

Form PCT/IPEA/416 (July 1992)

PATENT CO PERATION T. EATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2947.1007002	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/16950	International filing date *(day/month/year)* 30.05.2002	Priority date *(day/month/year)* 07.06.2001
International Patent Classification (IPC) or both national classification and IPC C07C59/68		
Applicant ELI LILLY AND COMPANY		

1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.12.2002	18.07.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Jardon Alvarez, J Telephone No. +49 89 2399-8325

Form PCT/IPEA/409 (Cover Sheet) (January 1994)

1618

1030

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/US02/16950

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-411	as originally filed

Claims, Numbers

3 (part),4-83	as originally filed
1,2,3 (part)	filed with telefax on 24.06.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

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6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-5,19,27,28,38,41-44,47-72

   because:

   ☒ the said international application, or the said claims Nos. 47-72 with respect to the industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-5,19,27,28,38,41-44,47-50,52,53

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-83
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-83
Industrial applicability (IA)	Yes:	Claims	1-46,73-83
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The International Preliminary Examination cannot be carried out in respect of subject-matter which is not covered by the search report (see Rule 66.1(e) PCT). Consequently claims 1- 5, 19, 27, 28, 38, 41- 44, 47-50, 52, 53, 55, 56, 58, 59, 61, 62, 64, 65, 67, 68, 70 and 71 are examined only to the extent that they have been searched (see International Search Report, Box I).

2. Claims 47 to 72 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO - A - 02 100812
D2: WO - A - 02 080899
D3: WO - A - 01 79150
D4: WO - A - 01 25181 (see also EP - 1 216 980, English translation of this document)
D5: WO - A - 01 16120
D6: WO - A - 02 16332
D7: Haigh, D. et al. Bioorganic & Medicinal Chemistry, (7), 1999, 821-830
D8: WO 97 31907

1. The present application claims priority rights from 07.06.2001. The International Preliminary Examination is carried out under the assumption that the claimed priority is valid. Therefore documents D1 - D3 and D6 are not considered as state of the art for the establishment of the present opinion (see Rule 64.3 PCT). Said documents will become relevant to assess the patentability of the present application when it enters the national/regional phases.

2. Novelty (Art. 33(2) PCT).

2.1. None of the pre-published prior art documents cited in the Search Report discloses compounds as claimed in the present claims and its use as modulators of peroxime proliferator activated receptors.

2.2. Document D4 discloses carboxylic acid derivatives of the formula (I) (see claim 1) which are modulators of peroxisome proliferator activated receptors (see claims 17 and 18) and therefor useful for the prevention or treatment of diseases such as hyperglycaemia and hyperlipemia. Examples 244a) and 244b) of this document disclose the preparation of 2-isopropoxy-3-(4-methoxy-3-2-[4-trifluoromethyl)-phenoxy]ethylphenyl)propanoic acid and its ethyl ester, two compounds falling within the scope of the claims as originally filed.

The definition of W in claims 1 and 2 of the application has been amended by way of a disclaimer to exclude such known compounds.

2.3. Consequently the subject-matter of the claims is novel (Art. 33(2) PCT).

3. Inventive step (Art. 33(3) PCT).

3.1. As pointed out above, D4 discloses carboxylic acid derivatives of the formula (I) (see claim 1) which are modulators of peroxisome proliferator activated receptors (see claims 17 and 18). The compounds now claimed fall in part within the scope of the general formula (I) of claim 1 of D4 and have the same use. Thus, in the absence of a surprising effect, the present claimed compounds appear to be no more than an arbitrary selection from the scope of D4 requiring no application of inventive step.

3.2. It is further noted that it is doubtful that all the compounds embraced by the present claims solve the problem underlying the present application (the provision of alternative compounds which are modulators of peroxisome proliferator activated receptors). The subject-matter of the claims embraces a huge number of compounds which have apparently not yet been explored (cf. activity examples in the application which do not state which of the claimed compounds show the desired activity). Having in mind that in the medicament field often small differences and changes in chemical structure can give rise to unexpected activity changes, the generalization of results obtained with a few compounds to compounds having a quite different structure does not appear to be justified. It is therefore doubtful that all the alternatives covered by the broad scope of the present claims achieve the claimed effect.

3.3. For these reasons the subject-matter of the claims does not involve an inventive step (Art. 33(3) PCT.

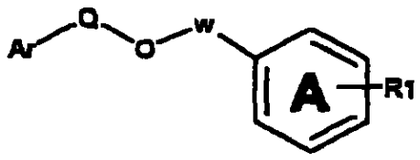
4. Industrial applicability (Art. 33(4) PCT).

For the assessment of the present claims 47 - 72 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

What is claimed is:

1. A compound represented by the following structural formula:



or pharmaceutically acceptable salts, hydrates, stereoisomers and solvates thereof, wherein:

Ar is a substituted or unsubstituted aromatic group;

Q is a covalent bond, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$;

W is a substituted or unsubstituted alkylene group two to ten atoms in length or a substituted or unsubstituted heteroalkylene group, wherein the heteroalkylene group is an alkylene group from two to ten atoms in length in which one or more methylene groups have been replaced with a functional group selected from $-CH=CH-$, $-C\equiv C-$, $-O-$, $-CO-$, $-NR_7-$, $-NR_7CO-$, $-C(=NOH)-$, $-S-$, $-S(O)-$, $-S(O)_2-$ or $-CH(NR_3R_4)-$, wherein when Ar is trifluoromethylphenyl ($CF_3C_6H_4$), W is not a C_2-C_3 alkylene group;

phenyl Ring A is optionally substituted with up to four substituents in addition to R_1;

R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mE$, $-(CH)=C(OR_2)-(CH_2)_mE$, $-(CH_2)_n-CH(Y)-(CH_2)_mE$ or $-(CH)=C(Y)-(CH_2)_mE$; wherein E is $COOR_2$, C_1-C_3-alkylnitrile, carboxamide, sulfonamide, acylsulfonamide or tetrazole and wherein sulfonamide, acylsulfonamide and tetrazole are optionally substituted with one or more substituents independently selected from: C1-C6 alkyl, C1-C6 haloalkyl and aryl-C0-4-alkyl;

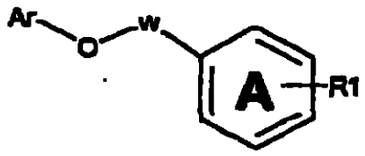
R_2 is -H, an aliphatic group, a substituted aliphatic group, haloalkyl, an aralkyl group, a substituted aralkyl group, an aromatic group, a substituted aromatic group, $-COR_4$, $-COOR_4$, $-CONR_3R_4$, $-C(S)R_4$, $-C(S)OR_4$ or $-C(S)NR_3R_4$;

Y is –O–, $-CH_2$–, $-CH_2CH_2$– or a –CH=CH– group which is bonded to a carbon atom in *Phenyl* Ring A that is *ortho* to R_1;

R_3-R_5 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group or a substituted aromatic group; and

n and m are independently 0, 1 or 2.

2. A compound represented by the following structural formula:



or pharmaceutically acceptable salts, hydrates and solvates thereof, wherein:

Ar is a substituted or unsubstituted aromatic group;

W is a substituted or unsubstituted alkylene linking group or a substituted or unsubstituted heteroalkylene linking group from two to ten atoms in length, wherein when Ar is trifluoromethylphenyl ($CF_3C_6H_4$), W is not a C_2-C_3 alkylene group;

phenyl Ring A is optionally substituted with up to four substituents in addition to R_1;

R_1 is $-(CH_2)_n-CH(OR_2)-(CH_2)_mCOOR_3$, $-(CH)=C(OR_2)-(CH_2)_mCOOR_3$, $-(CH_2)_n-CH(Y)-(CH_2)_mCOOR_3$ or $-(CH)=C(Y)-(CH_2)_mCOOR_3$,

R_2 is -H, an aliphatic group, a substituted aliphatic group, an aryl group, a substituted aryl group, $-COR_4$, $-COOR_4$, $-CONR_5R_6$, $-C(S)R_4$, $-C(S)OR_4$ or $-C(S)NR_5R_6$,

Y is –O–, $-CH_2$–, $-CH_2CH_2$– or a –CH=CH– group which is bonded to a carbon atom in Phenyl Ring A that is *ortho* to R_1;

R_3-R_6 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group; and

n and m are independently 0, 1 or 2.

3. The compound of Claim 1 or 2 wherein Ar is represented by a structural

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.TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
2947.1007002		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 02/16950	30/05/2002	07/06/2001
Applicant		
ELI LILLY AND COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. -

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

Int ternal Application No
PCT/US 02/16950

1038

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C59/68 C07C59/90 C07C59/72 C07C239/12 C07D311/30
C07D307/91 C07C219/10 C07D213/30 C07D215/14 C07D295/08
C07C217/94 A61K31/192 A61K31/195 A61P9/00 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 100812 A (CLARK RICHARD ;HIHARA TARO (JP); INOUE TAKASHI (JP); OHASHI KAYA () 19 December 2002 (2002-12-19) the whole document	1-83
E	WO 02 080899 A (CLARK RICHARD ;HIHARA TARO (JP); SEIKI TAKASHI (JP); EISAI CO LTD) 17 October 2002 (2002-10-17) the whole document	1-83
P,X	WO 01 79150 A (NOVO NORDISK AS) 25 October 2001 (2001-10-25) the whole document, especially example 1-6	1-3, 41-44,47
Y	WO 01 25181 A (MATSURA FUMIYOSHI ;CLARK RICHARD (JP); HIBARA TARO (JP); SEIKI HIS) 12 April 2001 (2001-04-12) the whole document	1-83

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2003	28/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Delanghe, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 02/16950 1039

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P3/06 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 16120 A (DOMINIANNI SAMUEL J ;MATTHEWS DONALD P (US); MICHELLYS PIERRE YVES) 8 March 2001 (2001-03-08) claims	1-83
P,Y	WO 02 16332 A (BROOKS DAWN ALISA ;GODFREY ALEXANDER GLENN (US); MANTLO NATHAN BRY) 28 February 2002 (2002-02-28) claims	1-83
A	HAIGH, D. ET AL: "Non-thiazolidinedione Antihyperglycaemic Agents. Part 3: The Effects of Stereochemistry on the Potency of alpha-Methoxy-beta-phenylpropanoic Acids." BIOORGANIC & MEDICINAL CHEMISTRY, vol. 7, - 1999 pages 821-830, XP002231306 the whole document	1-83

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Delanghe, P

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 31907 A (GLAXO GROUP LTD ;WILLSON TIMOTHY MARK (US); MOOK ROBERT ANTHONY JR) 4 September 1997 (1997-09-04) the whole document	1-83

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5, 19, 27, 28, 38, 41-44, 47-50, 52-53, 55-56, 58-59, 61-62, 64-65, 67-68, 70-71 (partially)

Present claims 1-5,19,27,28,38 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the formula in claims 1 and 38 wherein E is COOR3 or carboxamide (and R1-R8, Ar, Q, W, phenyl ring A, n, m and Y are as indicated).

The use claims 47-50, 52-53, 55-56, 58-59, 61-62, 64-65, 67-68, 70-71 have been similarly limited.
The composition claims 41-44 have been similarly limited.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 02/16950

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 47-72 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/16950

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 02100812	A	19-12-2002	WO	02100812 A1	19-12-2002
WO 02080899	A	17-10-2002	WO	02080899 A1	17-10-2002
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			SK	116398 A3	13-04-1999
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			US	6294580 B1	25-09-2001
			ZA	9701645 A	10-12-1997

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicación : 05SIC/AM/ 00000000 Folios: 1041
Fecha (AMD): 2004-12-03 17:00:12
Trámite : 001 PCT-PRIORI 379 PRIORIDAD 411 PRESENTACION
Dependencia: 05SIC DIVISION DE NUEVAS CREACIONES

1032

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓	MODELO DE UTILIDAD	( )	(✓)
- Indicación de que se solicita la concesión de una patente.		( )	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		( )	(✓)
- Descripción de la invención.		( )	(✓)
- Dibujos de ser estos pertinentes.		( )	(✓)
Comprobante de Pago de las tasas establecidas.			
COMPLETA (✓)	INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )			
- Indicación de que se solicita el registro de Diseño Industrial		( )	( )
- Datos de identificación del solicitante o de la persona que presenta		( )	( )
- la solicitud.			
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.		( )	( )
Comprobante de pago de las tasas establecidas		( )	( )
COMPLETA ( )	INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )			
- Indicación de que solicita el registro de un Esquema de trazado.		( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		( )	( )
- Representación gráfica del esquema de trazado		( )	( )
Comprobante de pago de las tasas establecidas.		( )	( )
COMPLETA ( )	INCOMPLETA	( )	( )

Firma Responsable:

fer

Fecha:

1045

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

1033

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO

REFERENCIA	Radicación No.	03 107407
	Solicitud internacional	US02/16950
	Fecha inicio fase nacional	07/07/2004
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	

8027

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. La solicitud no contiene las copias de los documentos en que constan las cesiones de los derechos a la patente de los inventores a los solicitantes o a sus causantes. (Art. 26-k) Decisión 486. Estan deben estar traducidas y legalizadas.

3. La solicitud no contiene el poder debidamente otorgado por la sociedad Ligand Pharmaceuticals, Inc., con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante.

4. Con el fin de escanear o digitalizar la solicitud posteriormente es importante que los documentos presentados se encuentren completos, por lo anterior debe presentar un nuevo capítulo reivindicatorio puesto que el aportado inicialmente contiene defectos en la numeración.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

1034

Radicación No.:3 107407

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 OCT. 2005
adpal