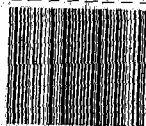


Industria y Comercio
SUPERINTENDENCIA



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SUPERINDUSTRIA Y COMERCIO

Radicación : 02084186 00000000

Folios: 1220 ación

Fecha (AMD): 2002-03-19 17:19:15

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

①

SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☐

Capítulo I.

☒ X

Capítulo II.

②

SOLICITANTE

(71)

Nombre: SCHERING CORPORATION

Dirección: 2000 Galloping Hill Road, Kenilworth, New Jersey 07033
Estados Unidos de América.

Nacionalidad o Domicilio: ESTADOUNIDENSE

Lugar de Constitución: New Jersey, Estados Unidos de América.

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Avda 82 No. 10-62 Piso 6

Teléfono: 634-1500

Fax: 376-2211

E-Mail: patents.bogota@bakernet.com

IDENTIFICACION

C.C.

☒ X

NIT

☐

C.E.

☐

Otro

☐

Cual

Número 79.782.747 Bta TP 74.295

④

INVENTOR (ES)
(72)

Nombre: ver documento adjunto

Dirección: ver documento adjunto

Nacionalidad o Domicilio: ver documento adjunto

⑤ PCT (85)

Solicitud Internacional No. PCT/US01/10869

Fecha Abril 3, 2001

Publicación Internacional No. WO 01/77113

Fecha Octubre 18, 2001

⑥

Título (54) INHIBIDORES MACROCICLICOS DE LA NS3-SERINA PROTEASA, DEL VIRUS DE LA HEPATITIS C, QUE
COMPRENDEN PARTES P2 N-CICLICAS.

⑦

Clasificación Internacional (51)

C07D 418/00; A61K38/06

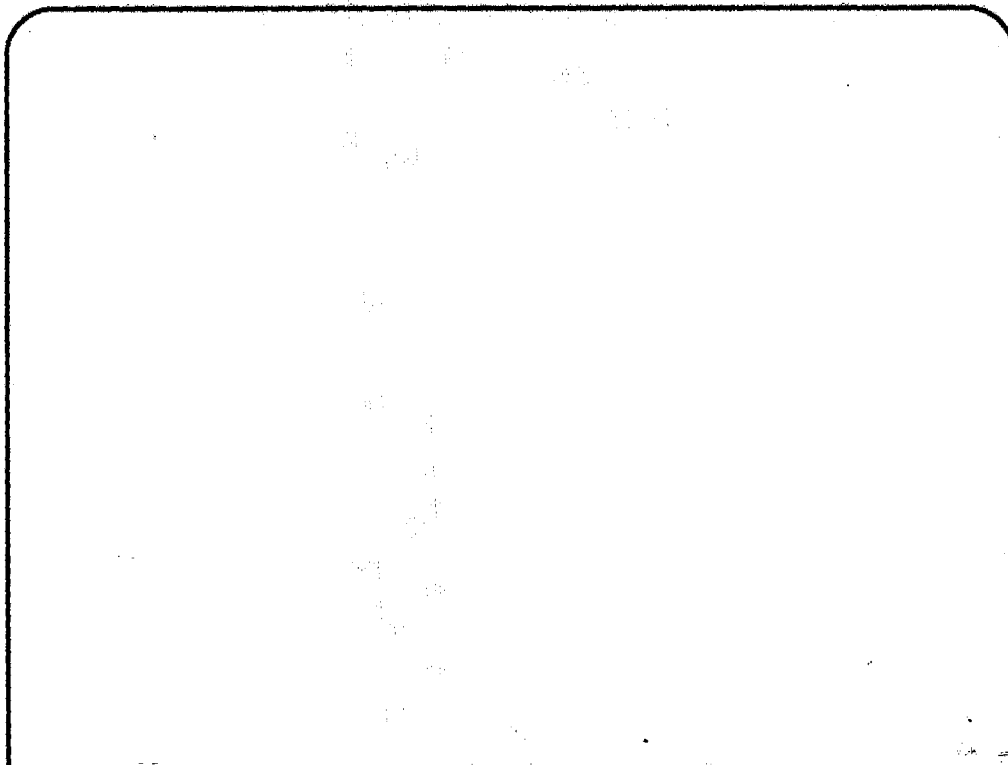
10

ANEXOS

- ☒ 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
- ☒ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ 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.
- ☒ Otros: Documento de Prioridad US No. 60/194,607 con su respectiva traducción, Búsqueda Internacional

11

FIGURA CARATERISTICA



P2002/000022

000013

Case No. IN01154K

Attachment "A"

Chen, Kevin X., citizen of the United States of America, residing at 44 Gill Lane, Apt. 1D, Iselin, New Jersey 08830, U.S.A.

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Parekh, Tejal N., citizen of India, residing at 39 Pikeview Lane, Woodbridge, New Jersey 07095, U.S.A.

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Saksena, Anil, citizen of the United States of America, residing at 53 Beverly Road, Upper Montclair, New Jersey 07043, U.S.A.

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Yao, Nanhua H., citizen of the United States of America, residing at 12 Santa Luzia Aisle, Irvine, California 92606, U.S.A.

Prongay, Andrew, J., citizen of the United States of America, residing at 104 Willow Grove Road, Stewartsville, New Jersey 08886, U.S.A.

Madison, Vincent S., citizen of the United States of America, residing at 12 Ronarm Drive, Mountain Lakes, New Jersey 07046, U.S.A.

Vibulbhan, Bancha, citizen of Thailand, residing at 201 North 24th Street, Kenilworth, New Jersey 07033, U.S.A.

NIT : 800176089-2

Radicación : 02084186 00000000 Folios: 1220
Fecha (AMD): 2002-09-19 17:19:15
Trasite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

CERTIFICACION DE EXCEDENTE : 02 - 51.147
FECHA : AGOSTO 5 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
JORGE LUIS GOMEZ	DEVOLUCION TASA			468	05/08/2002	300,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	
	99 OTROS SERVICIOS ADMINISTRATIVOS	300,000.00
	TOTAL :	\$ 300,000.00

SON: TRESCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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SUPERINDUSTRIA Y COMERCIO
 Radicacion : 02004186 00000000 Folios: 1220
 Fecha (AMD): 2002-09-19 17:19:15
 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
 Radicacion : 02004186 00000000 Folios: 1220
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 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
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 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Traducción Oficial No. 02-899

Efectuada el día 20 de agosto de 2002, de un documento escrito en Inglés, al cual para su identificación se le estampa el sello de María del Pilar Iglesias, Traductora e Intérprete Oficial por Resolución No. 819 del 15 de abril de 1971 expedida por el Ministerio de Justicia de la República de Colombia.

Traducción de las autenticaciones notariales y subsiguientes correspondientes a un Poder otorgado por **SCHERING CORPORATION** a **CARLOS REINALDO OLARTE Y/O ALVARO CORREA ORDOÑEZ**, documento éste que viene en español y se explica por sí solo.

La firma y cargo de Edward H. Mazer como Funcionario Autorizado de la compañía arriba citada fueron debidamente certificados por el Notario Público Norma Gallina del Estado de Nueva Jersey, según consta en la Certificación Notarial, que también viene en español y que fue firmada por dicho Notario el 2 de agosto de 2002, quien tuvo a la vista la Escritura de Constitución de la Compañía reformada el 4 de abril de 1996 y el Certificado de Constitución actualizado al 16 de junio de 1997.

COMO NOTARIO ONCE DE ESTE
CIRCULO HAGO CONSTAR QUE ESTA
COPIA CONCIDE CON EL
ORIGINAL QUE TENGO A LA VISTA.

21 AGO 2002

BOGOTÁ, D.C. - COLOMBIA
MARÍA DEL PILAR IGLESIAS
TRADUCTORA E
INTERPRETE OFICIAL
Resolución No. 819 de 1971

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APOSTILLA

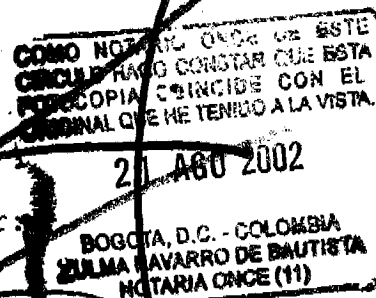
(Convención de La Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
El presente documento público
2. Fue firmado por Norma Gallina
3. Que actuó en su calidad de Notario Público del Estado de Nueva Jersey.
4. Lleva el sello del mencionado Notario Público
Se certificó
5. En Trenton, Nueva Jersey 6. El 9 de agosto de 2002
7. Por parte de John E McCormac, CPA, Tesorero de Nueva Jersey.
8. Bajo el Número A156329.
9. Sello del Estado de Nueva Jersey
10. Firmado por John E McCormac

Es traducción fiel y completa efectuada por:

Maria del Pilar Iglesias
María del Pilar Iglesias
C.C. 41.339.183 de Bogotá

Maria del Pilar Iglesias
María del Pilar Iglesias
C. C. 41.339.183 de Bogotá
Intérprete Oficial según Resolución No. 819
15 de Abril de 1971 del Ministerio de Justicia



8

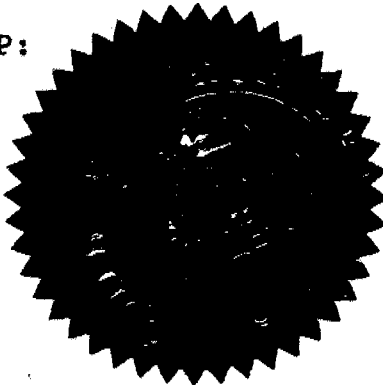
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
NORMA GALLINA
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
NORMA GALLINA, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 9TH DAY OF AUGUST 2002
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A156329
9. SEAL/STAMP:
10. SIGNATURE



RAISBRECK, LARA, RODRIGUEZ & RUEDA
MEMBERS OF THE FIRM
BAKER & MCKENZIE
ATTORNEYS AT LAW

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BOGOTA, D.C. COLOMBIA
TELEPHONE (57-1) 634-1500
FACSIMILE (57-1) 378-2211
NIT 860.068.840-3
OFFICE: BOGOTA@BAKERNET.COM
WWW.BAKERNET.COM

00019

POWER OF ATTORNEY

The undersigned.

SCHERING CORPORATION

located in
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
United States of America

declares that it hereby grants to

CARLOS REINALDO OLARTE AND/OR

ALVARO CORREA ORDOÑEZ

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of:

Patents of Invention, Patents for Utility Models, Industrial Design Registrations, mergers, changes of name, assignments, filing and prosecution of oppositions, changes of address.

to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds. To the said mandatories sufficient power is granted hereby to receive notifications for and 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 patents, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary.

Done and subscribed in
Kenilworth, New Jersey, USA

On the 2nd day of August

2002


(Signature)

Edward H. Mazer
Duly Authorized Officer

PODER

La abajo firmada.

SCHERING CORPORATION

domiciliada en
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
Estados Unidos de America

declara por el presente otorgar a

CARLOS REINALDO OLARTE Y/O

ALVARO CORREA ORDOÑEZ

poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de:

Patentes de invención, Patentes de Modelo de Utilidad, Registro de Diseños Industriales, fusiones, cambios de nombre, cesiones, presentación y trámite de oposiciones, cambios de dirección.

a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios 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 las patentes se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

COMO NOTARIO PORQUE DE ESTE
CIRCULO HAGO CONSTAR QUE ESTA
FOTOCOPIA COINCIDE CON EL
ORIGINAL QUE HE TENIDO EN MI OFICINA
Firmado en

21-08-2002
A los
BOGOTA, D.C. - COLOMBIA
JUAN VARGAS DE MENDIVIA
NOTARIO PUBLICO (11)
BOGOTA 2002

días del mes de

RAISBECK, LARA, RODRIGUEZ & RUEDA
MEMBERS OF THE FIRM
BAKER & MCKENZIE
ATTORNEYS AT LAW

AV 52 No. 10-32, 6TH FLOOR
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FACSIMILE (57-1) 378-2211
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WWW.BAKERNET.COM

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10

NOTARIAL CERTIFICATION

On this 2nd day of August
2002, the undersigned Notary

CERTIFIES

Edward H. Mazer

of legal age and domiciled in Millburn, New Jersey
United States of America

set his hand on the foregoing document.

2. That the grantor is to me personally know and that he/she has
legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Duly Authorized Officer

of the judicial person

4. That the judicial person

SCHERING CORPORATION

ing its home office in 2000 Galloping Hill Road,
Kenilworth, New Jersey 07033, USA

is duly organized, has present legal existence and that the purposes for
which the power of attorney is granted are within the scope of its corporate
purposes.

5. That the grantor has in fact the referred to authority and that his/her
representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic
documents for such purpose exhibited to me and which I mention specifically,
giving their dates and their origin or source:

Certificate of Incorporation, as amended, dated
April 4, 1996

Certificate of Restated Incorporation filed
June 16, 1997

Norma Gallina
Notary Public

CERTIFICACION NOTARIAL

A los _____ días del mes de _____
de 2002, el suscrito Notario

DA FE

1. Que

mayor y domiciliado en

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal
para el otorgamiento.

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

de la persona jurídica

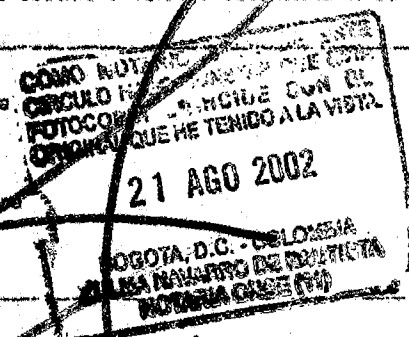
4. Que la persona jurídica

con sede en

está legalmente constituida, que tiene existencia legal actual y que
el acto para el cual se ha otorgado el poder está comprendido entre
los que constituyen su objeto social.

5. Que el otorgante tiene efectivamente la representación que
ostenta, y que esta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los
siguientes documentos auténticos que al efecto se me exhibieron y
que menciono específicamente con expresión de sus fechas y de su
origen o procedencia:



NORMA GALLINA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires June 27, 2005

22
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the pamphlet!

WO 01-77113
1/3

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(25) Filing Language: English

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(30) Priority Data:
60/194,607 5 April 2000 (05.04.2000) US

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(US).

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07095 (US). PAREKH, Tejal, N.; 39 Pikeview Lane,
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Jiang Chuan Load, Minhang, 200240 Shanghai (CN).
NJORGE, F., George; 2597 Juliet Place, Union, NJ
07083 (US). GIRIJAVALLABHAN, Viyyoor, M.; 10
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GULY, Ashit; 96 Cooper Avenue, Upper Montclair, NJ
07043 (US). SAKSENA, Anil; 53 Beverly Road, Upper

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Santa Luzia Aisle, Irvine, CA 92606 (US). PRONGAY,
Andrew, J.; 104 Willow Grove Road, Stewartville, NJ
08886 (US). MADISON, Vincent, S.; 12 Ronarm Drive,
Mountain Lakes, NJ 07046 (US). VIBULBHAN, Banacha;
201 North 24th Street, Kenilworth, NJ 07033 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID,
IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA,
MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU,
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(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, 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,
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CG, CI, CM, GA, GN, 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 "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MACROCYCLIC NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS C VIRUS COMPRISING N-CYCLIC P2
MOIETIES

(57) Abstract: The present invention discloses novel macrocyclic compounds which have HCV protease inhibitory activity as well
as methods for preparing such compounds. In another embodiment, the invention discloses pharmaceutical compositions comprising
such macrocycles as well as methods of using them to treat disorders associated with the HCV protease.

WO 01/77113 A2

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Macrocyclic NS3-Serine Protease Inhibitors of Hepatitis

C Virus Comprising N-Cyclic P2 Moieties

FIELD OF INVENTION

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention specifically discloses novel
5 macrocyclic compounds as inhibitors of the HCV NS3/NS4a serine protease.

Background of the Invention

Hepatitis C virus (HCV) is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH),
10 particularly in blood-associated NANBH (BB-NANBH)(see, International Patent Application Publication No. WO 89/04669 and European Patent Application Publication No. EP 381 216). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus
15 (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed; (see, e.g., U.S. Patent No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the
20 amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids;
25 and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and

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0001

(MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cV_HE2 (a "camelized" variable domain antibody fragment) (Martin et al. (1997) Protein Eng. 10:607-614), and α 1-antichymotrypsin (ACT)(Elzouki et al.) (1997) J. Hepat. 27:42-28). A ribozyme designed to selectively destroy hepatitis C virus RNA has recently been disclosed (see, BioWorld Today 9(217): 4 (November 10, 1998)).

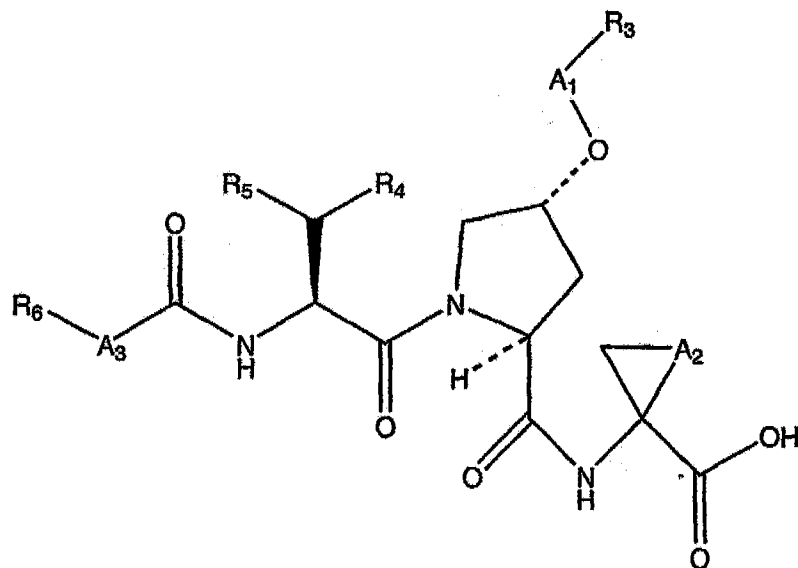
Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular carcinoma have a five-year survival rate of 10-30%, whereas those with localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.

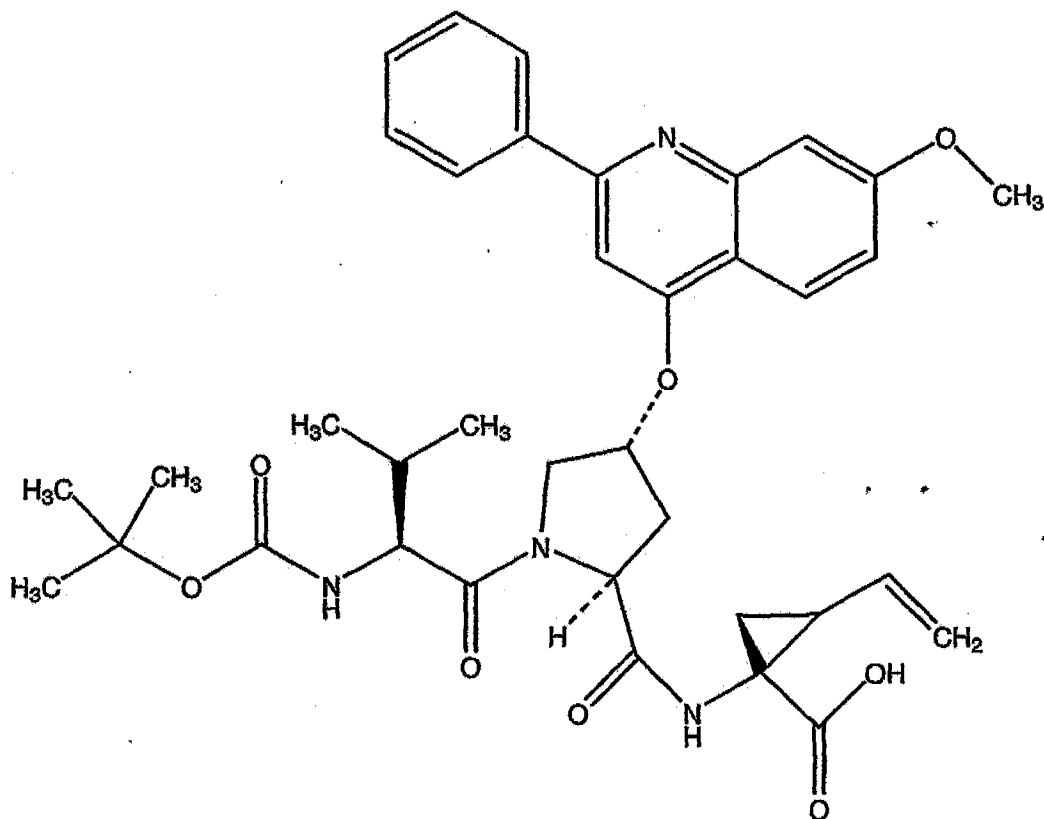
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:

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Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:

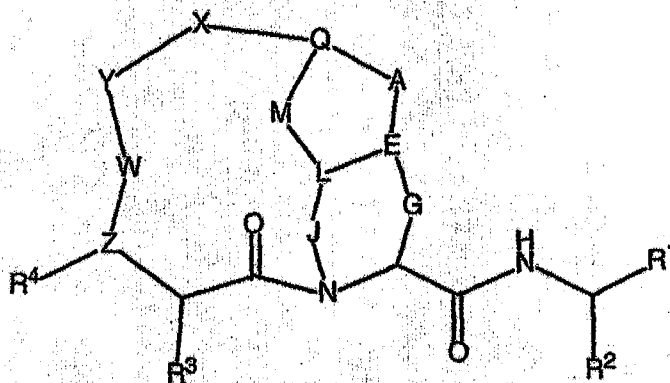


- 5 where the various elements are defined therein. An illustrative compound of that series is:



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In its principal embodiment, the present invention provides a macrocyclic compound of Formula I:



Formula I

wherein:

- X and Y are independently selected from the moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl sulfide, alkyl-aryl sulfide, aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, aryl sulfone, alkyl-alkyl sulfoxide, alkyl-aryl sulfoxide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl urea, alkyl-aryl urea, aryl urea, alkyl carbamate, alkyl-aryl carbamate, aryl carbamate, alkyl-hydrazide, alkyl-aryl hydrazide, alkyl hydroxamide, alkyl-aryl hydroxamide, alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylamino carbonyl or a combination thereof, with the proviso that X and Y may optionally be additionally substituted with moieties selected from the group consisting of aromatic, alkyl, alkyl-aryl, heteroalkyl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, alkyl sulfide, alkyl-aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, alkyl amide, alkyl-aryl amide, alkyl sulfonamide, alkyl amines, alkyl-aryl amines, alkyl-aryl sulfonamide, alkyl urea, alkyl-aryl urea, alkyl carbamate and alkyl-aryl carbamate;

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M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, SO₂,

5 (CH₂)_p, (CHR)_p, (CHR-CHR')_p, or (CRR')_p;

p is a number from 0 to 6; and

R, R', R², R³ and R⁴ are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; oxygen, nitrogen, sulfur, or phosphorus atoms with said oxygen, nitrogen, sulfur, or phosphorus atoms numbering zero to six; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl; with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Thus, for example, the term alkyl (including the alkyl portions of alkoxy) refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single atom having from 1 to 8 carbon atoms, preferably from 1 to 6;

30 aryl - represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic

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The invention also provides methods for preparing compounds of Formula I, as well as methods for treating diseases such as, for example, HCV and related disorders. The methods for treating comprise administering to a patient suffering from said disease or diseases a therapeutically effective amount of a compound of Formula I, or pharmaceutical compositions comprising a compound of Formula I.

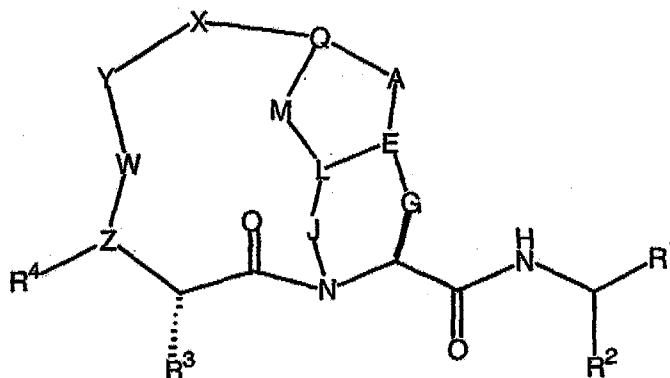
Also disclosed is the use of a compound of Formula I for the manufacture of a medicament for treating HCV and related disorders.

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Detailed Description of Preferred Embodiments

In one embodiment, the present invention discloses compounds of Formula I as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease. Among the compounds encompassed by Formula I, preferred compounds are those which have the Formula II:

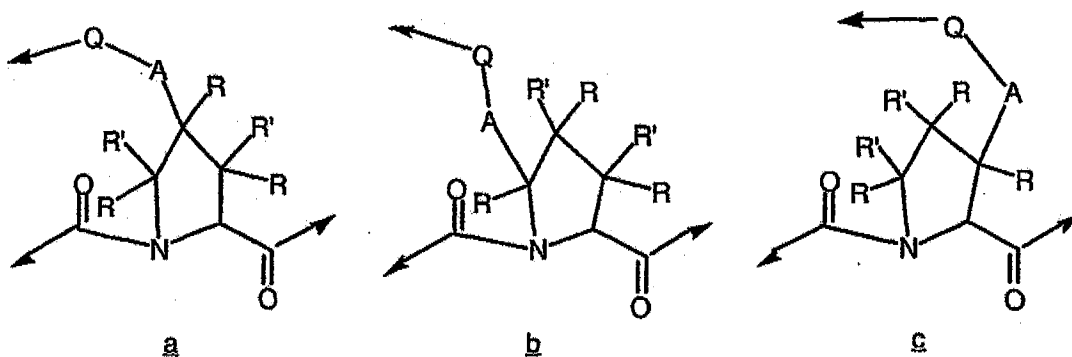
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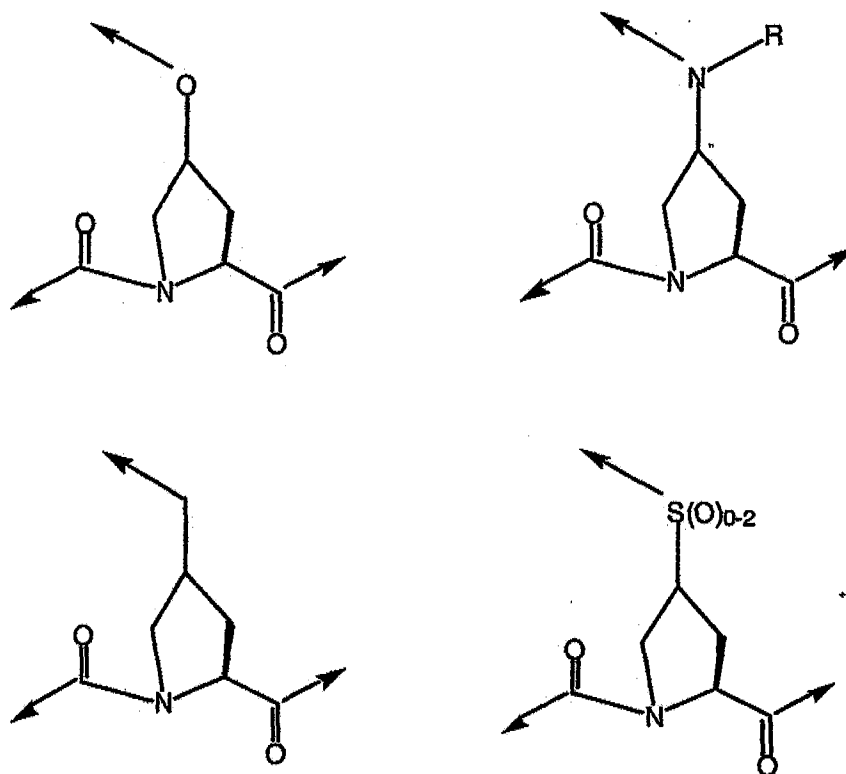
Formula II

or a pharmaceutically acceptable derivative thereof, where the various definitions are given above. Some of the preferred embodiments include, but are not limited to, the following definitions of the various functionalities in the above-noted general formulas I and II. Thus, for example, R² in formula I may be selected from the following moieties:

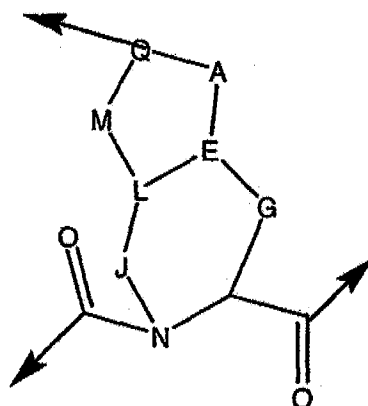
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The structure **a** may be selected from the following non-limiting types of structures:

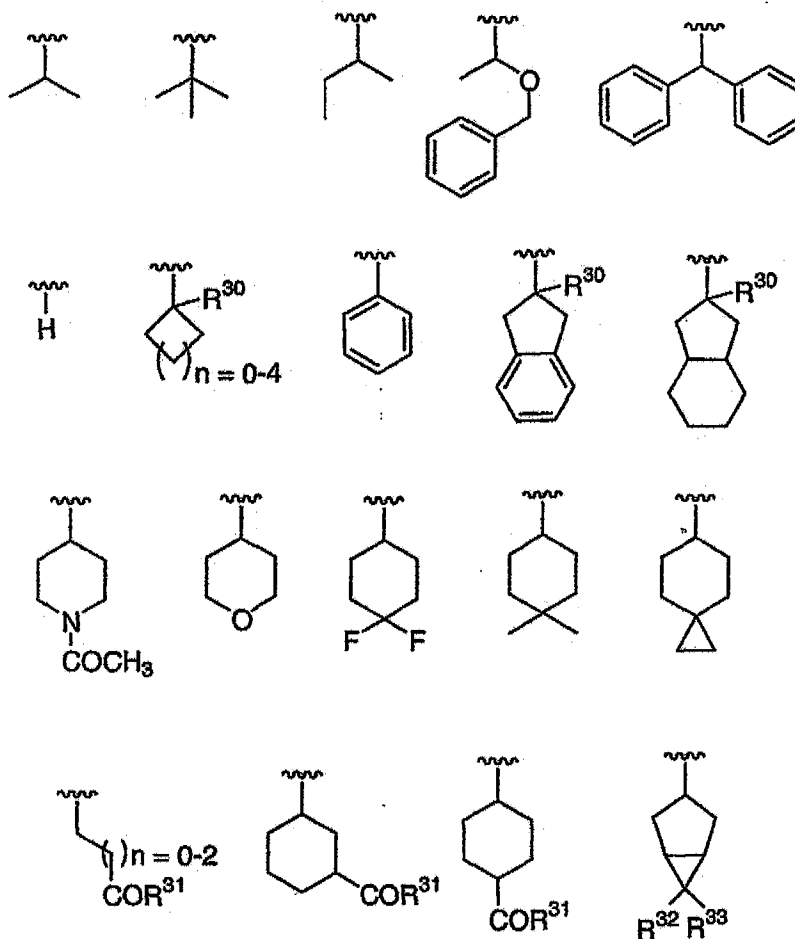


5 Other additional preferred embodiments are, for example, where the moiety:



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In other preferred embodiments, R^3 in formula I is selected from the following structures:



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Several additional and further refinements of the above-noted various definitions for the compounds represented by Formula I are noted in the **Claims** section of this application. They are also represented by the various compounds listed in the specification and claims. Such refinements, definitions and limitations are to be considered as representing the entire invention of this application.

Representative compounds of the invention which exhibit excellent HCV protease inhibitory activity are listed below along with their activity (ranges of K_i values in nanomolar, nM). The Example numbers refer to the numbers for the various structures in the **EXAMPLES** section found in the later parts of this application.

Table 1: HCV protease continuous assay results

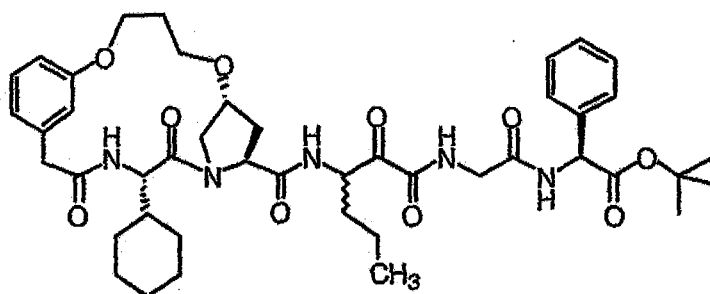
Example Number	K_i^* (nM)
1A	a
1B	b
2	b
3	b
4A	a
4B	b
5	b
6	b
7A	a
7B	b
8	a
9	b
10A	a
10B	b
11	a
12A	a
12B	b
13A	a
13B	b
14	b
15	b
16	b
17	b
18	b
19	b

22
00025

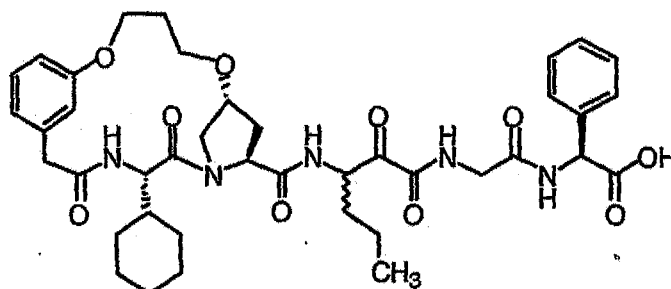
65	b
66A	a
66B	b
67A	a
67B	b
68	b
69A	a
69B	b
70A	a
70B	b
71	b
72	b
73	a
74A	a
74B	b
75A	a
75B	b
76	b
77	a
78	a
79	a
80	b
81	a
82	a
83	b
84	a
85	a
86	a
87	a
88	a
89	a
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96	a
97	a
98	b
99	a
100	a
101	b

21

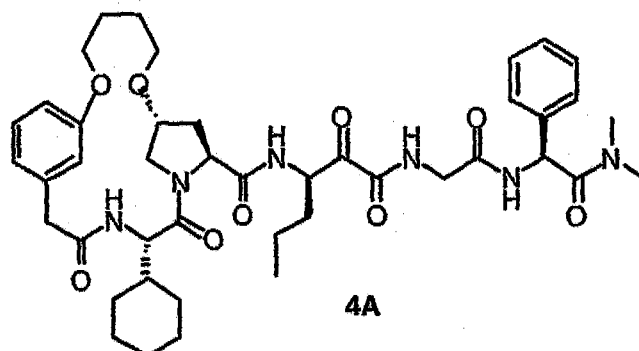
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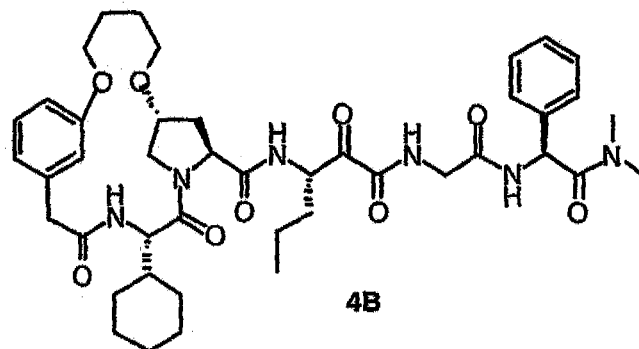
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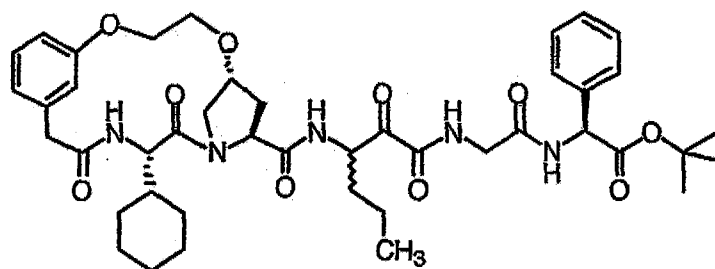
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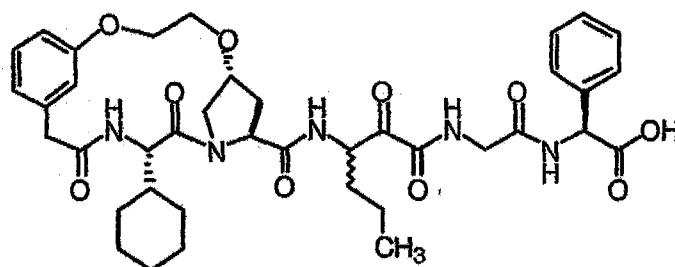
4B

23

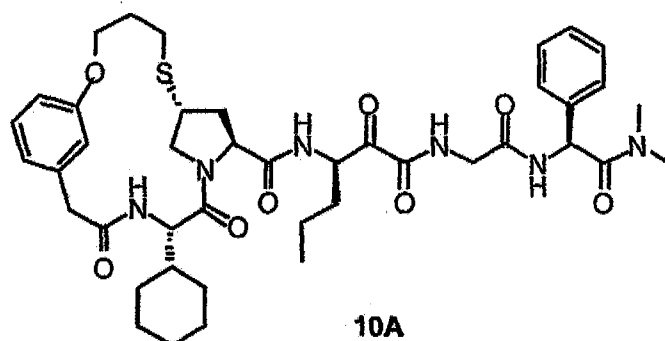
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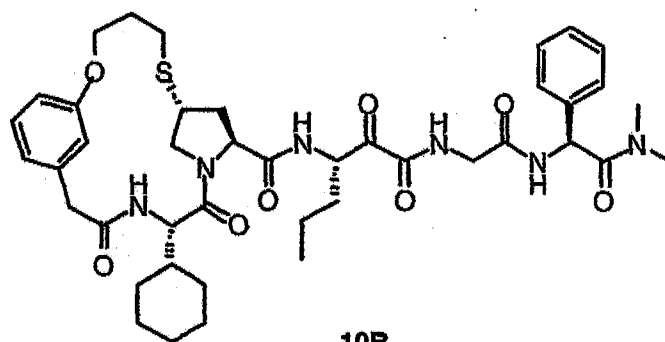
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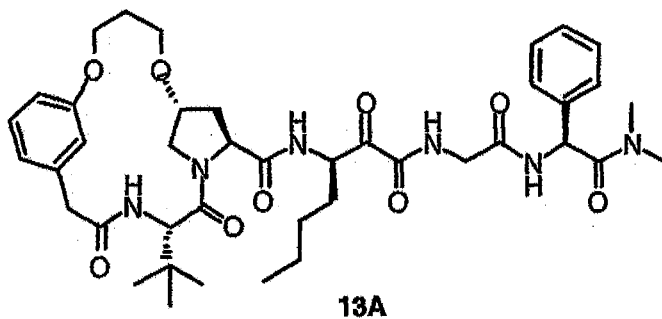
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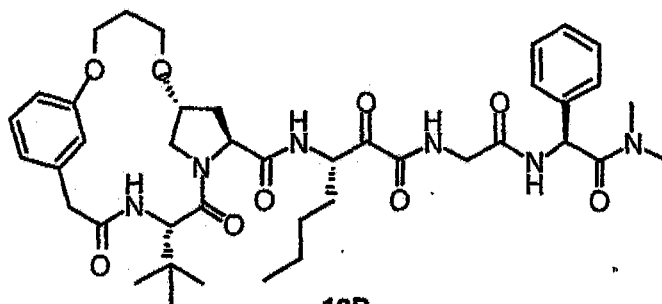
10B

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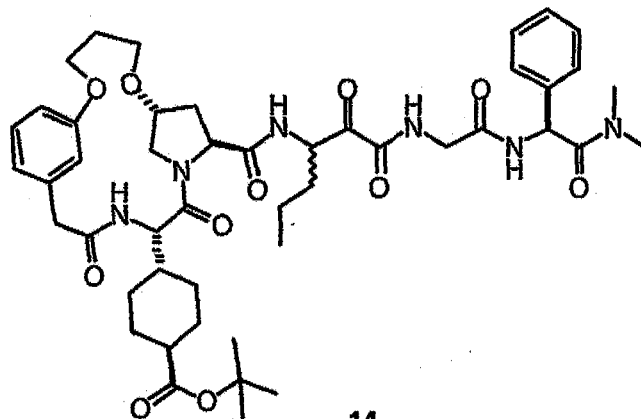
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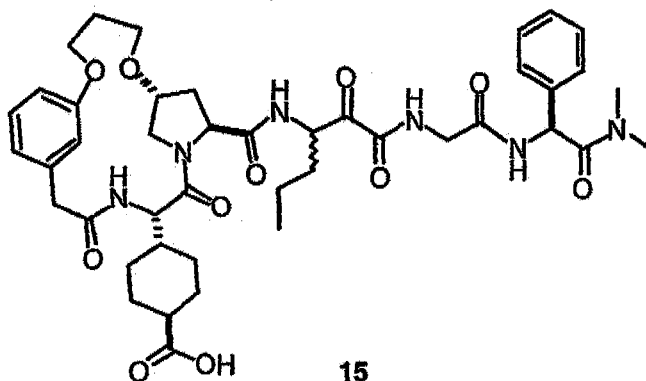
13A



13B



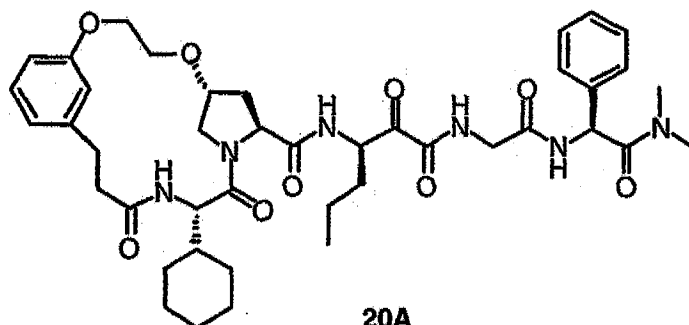
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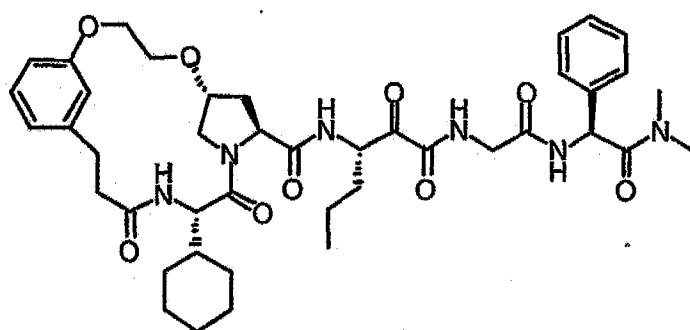
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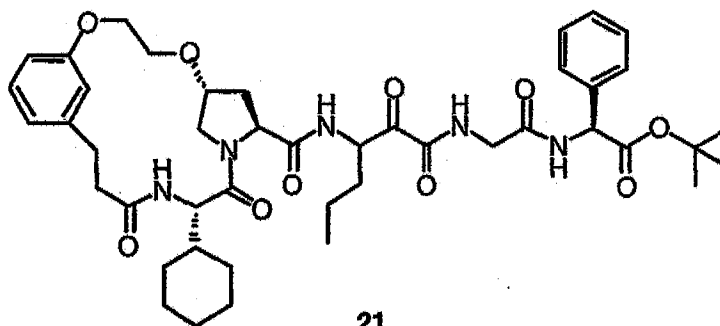
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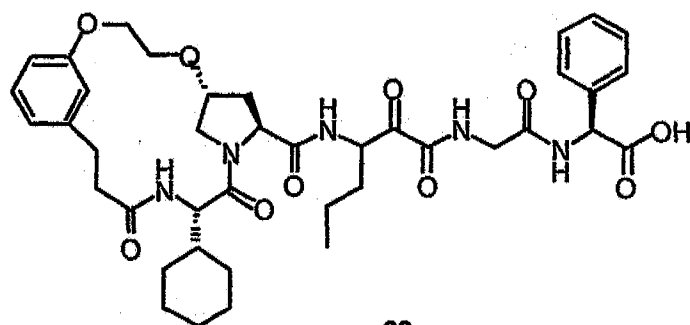
20A



20B



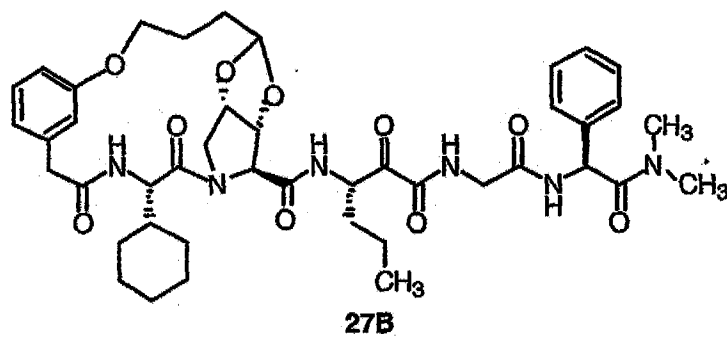
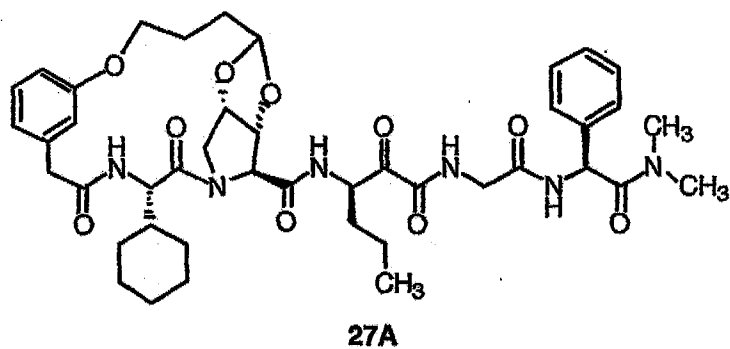
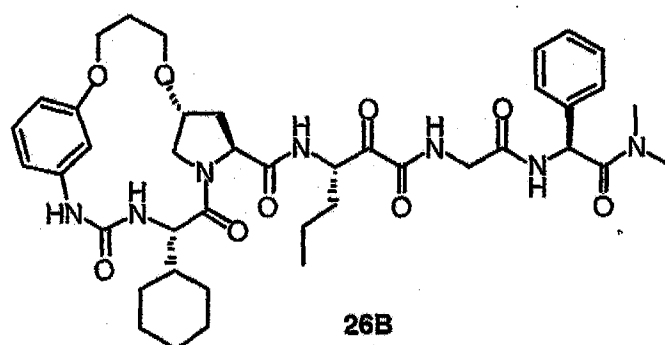
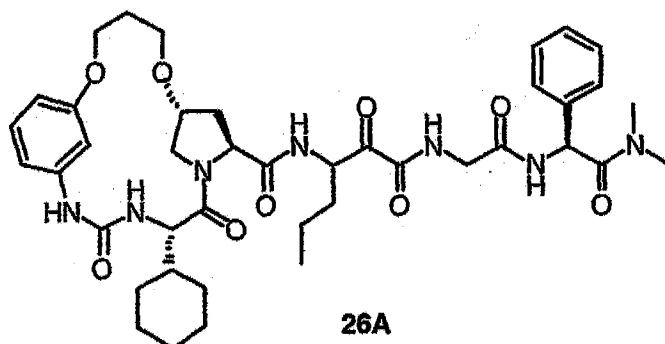
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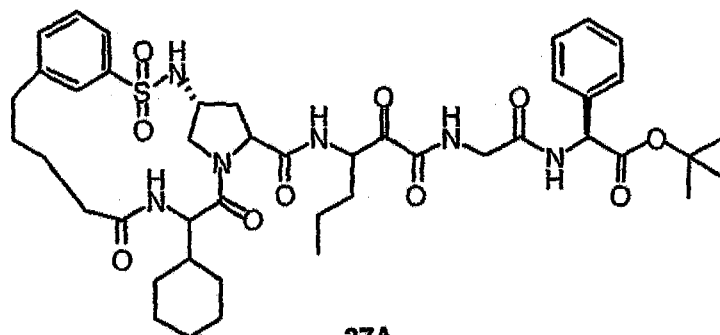
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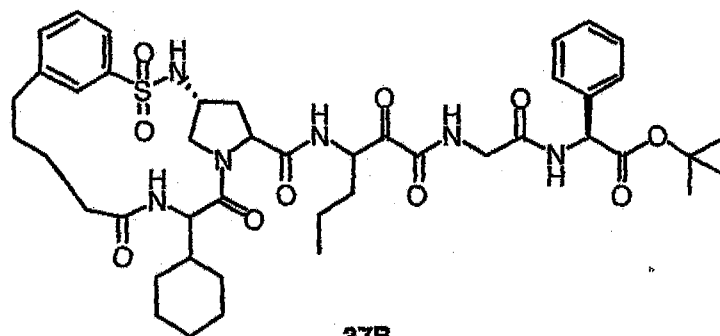


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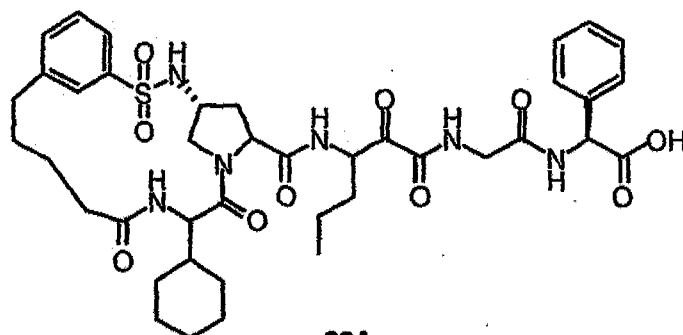
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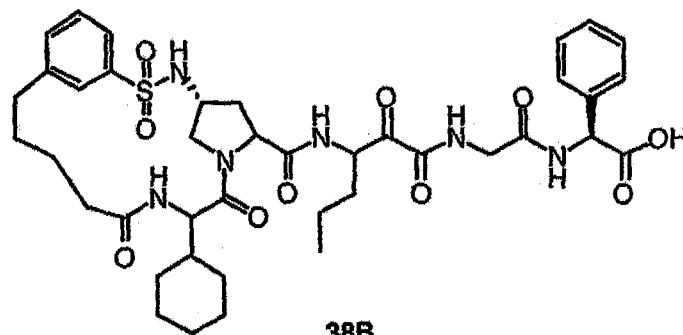
37A



37B



38A

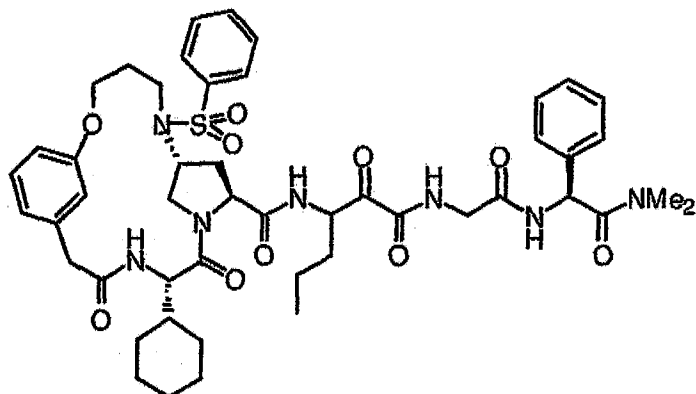


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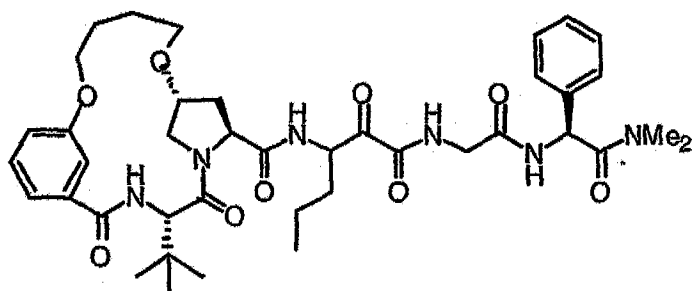
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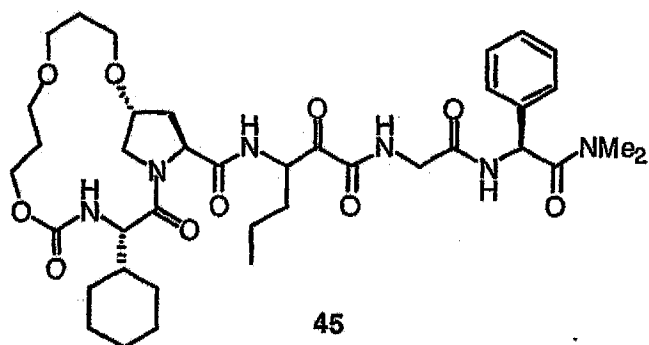
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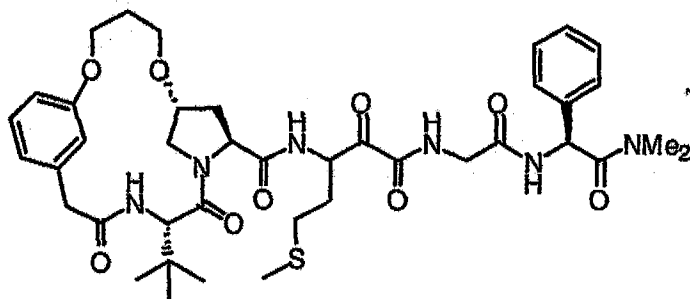
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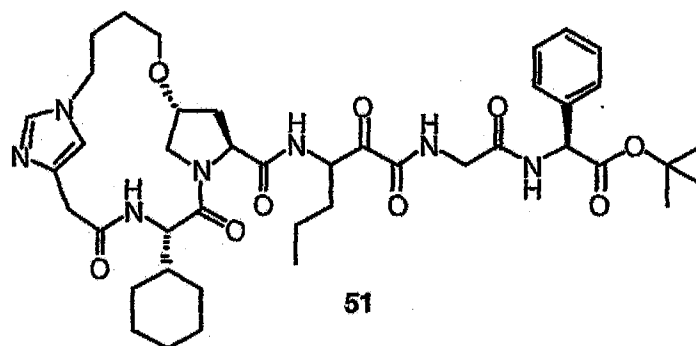
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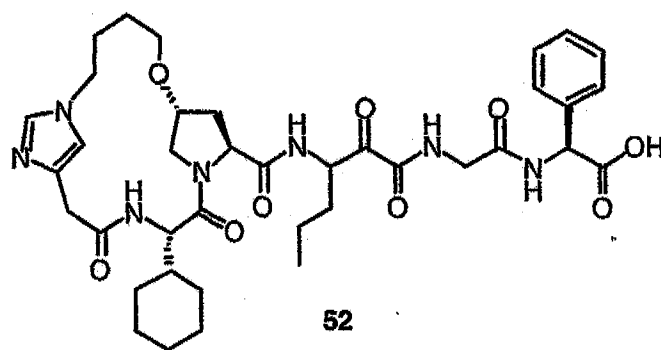
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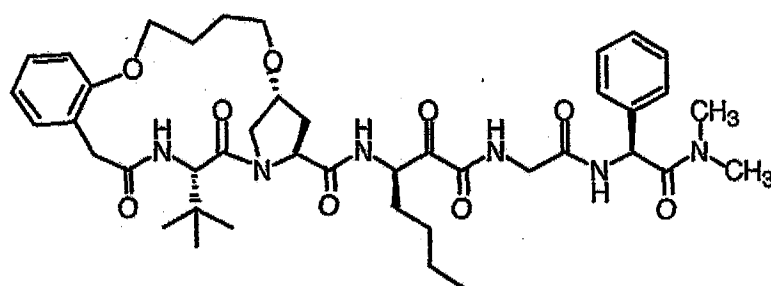


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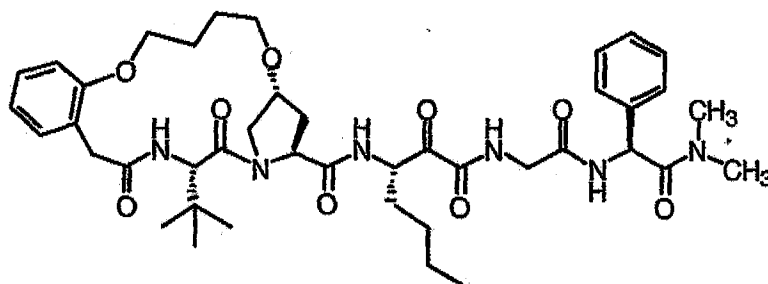


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53A

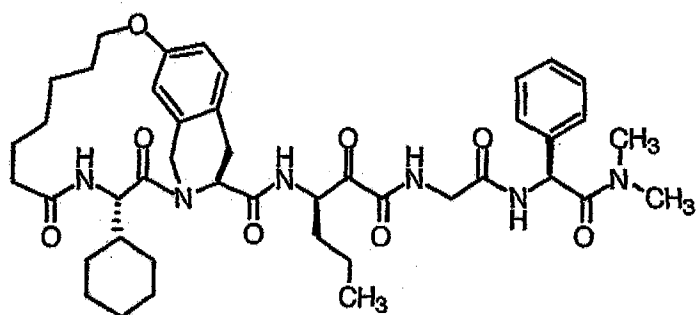


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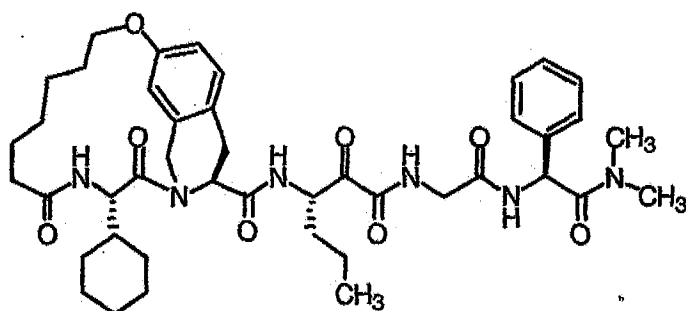
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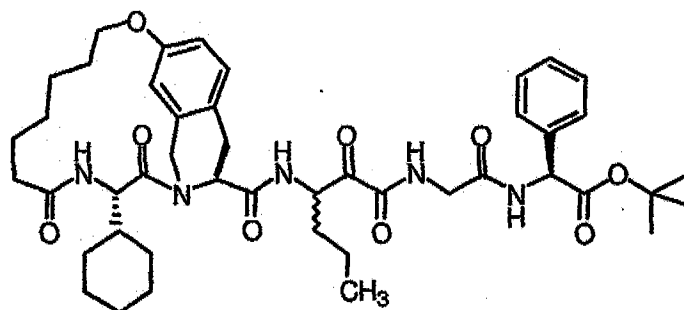
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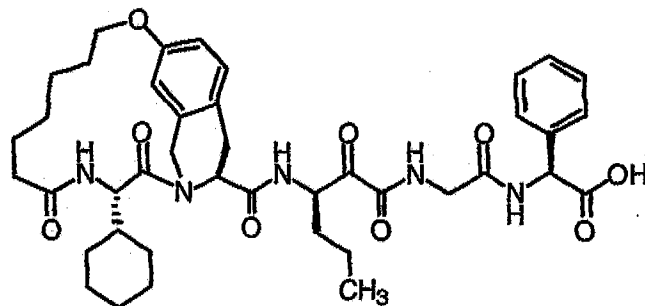


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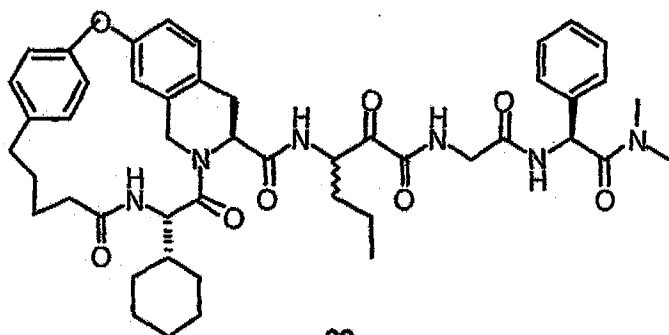
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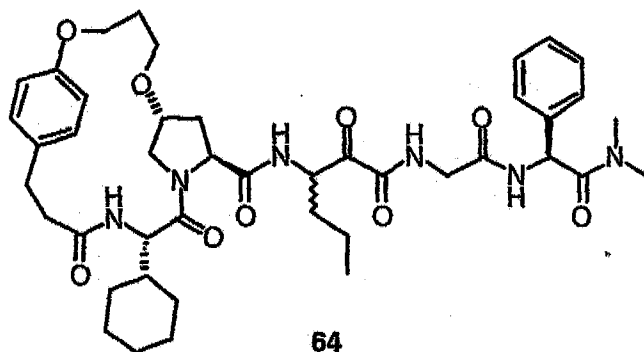
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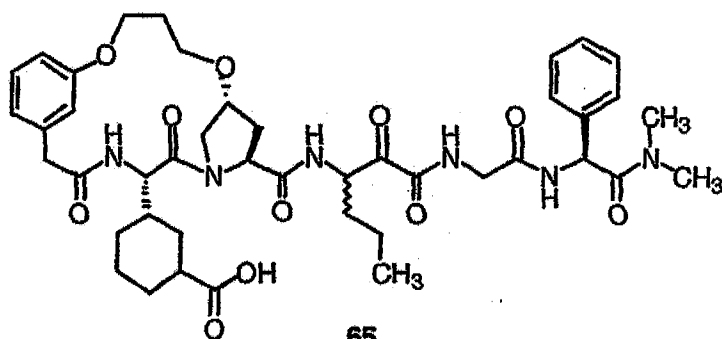
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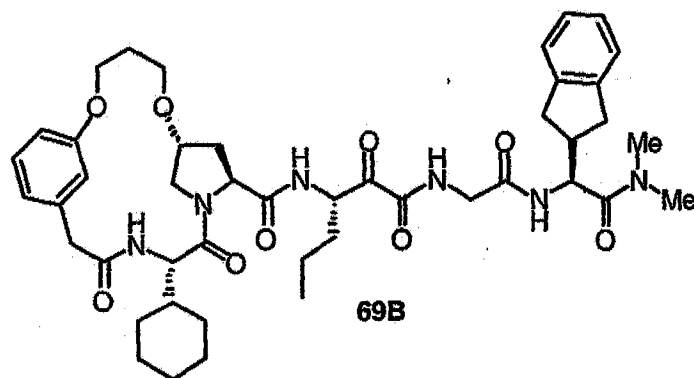
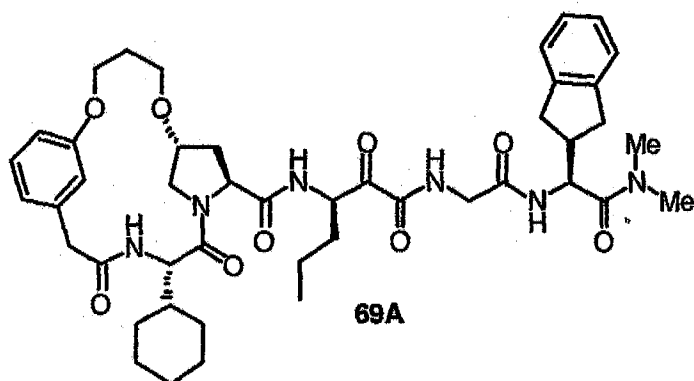
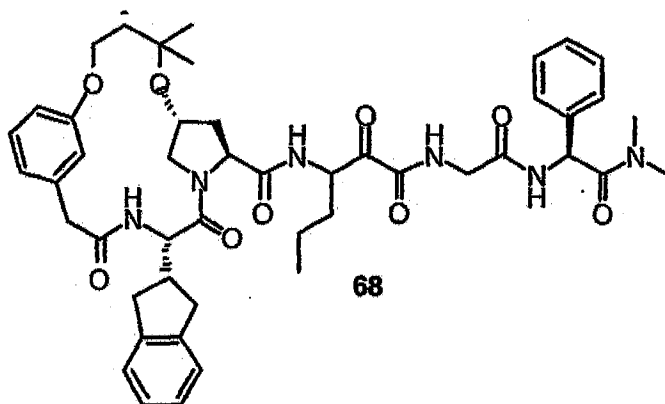


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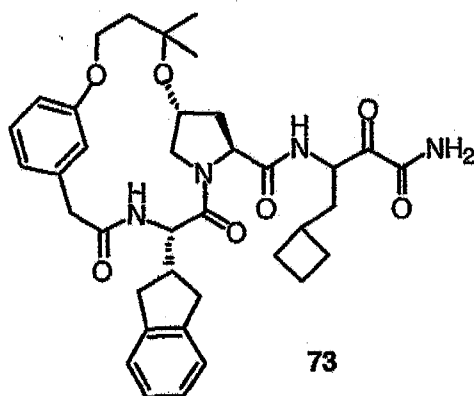
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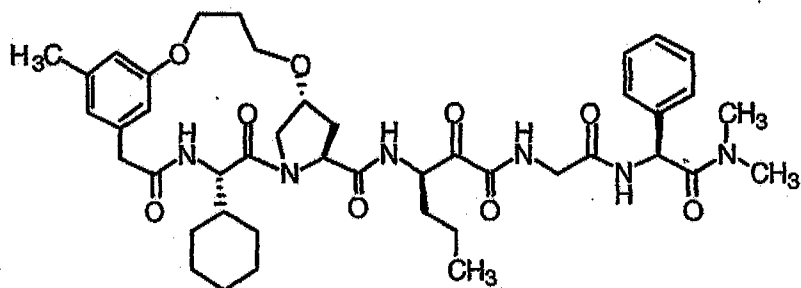
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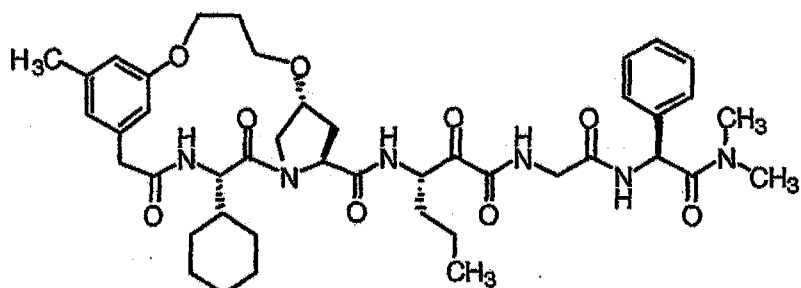
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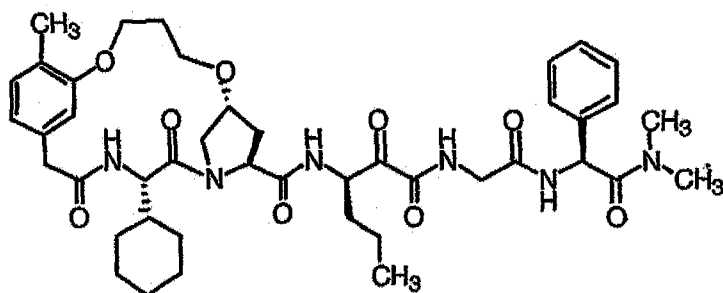
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74A



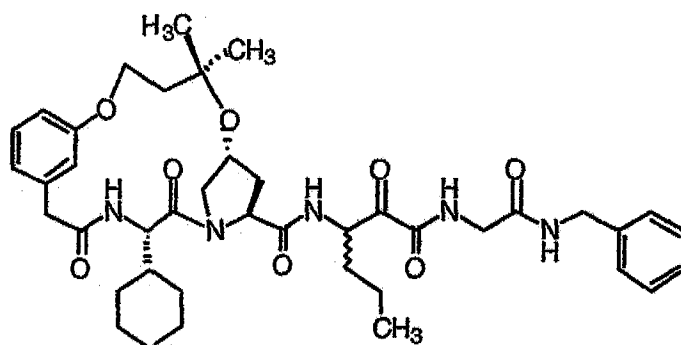
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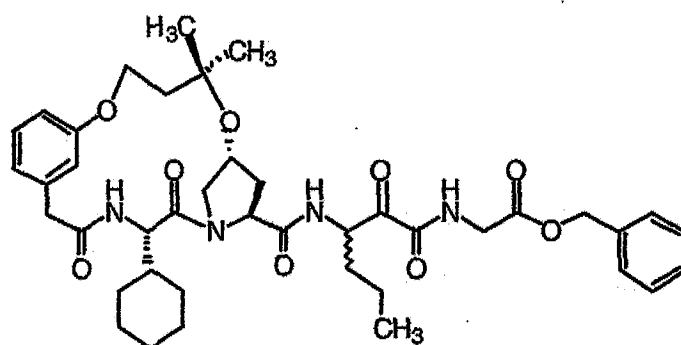
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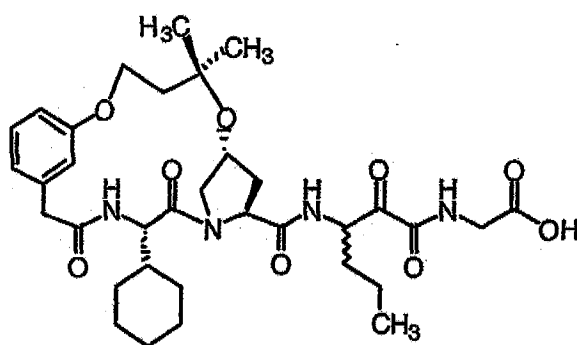
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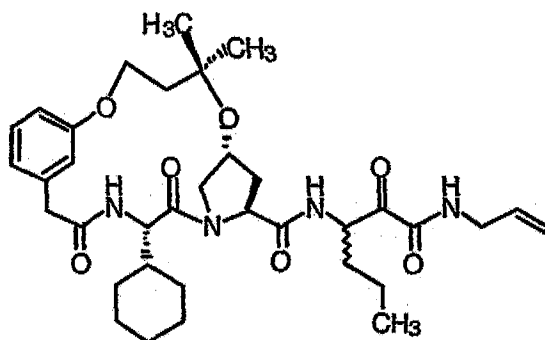
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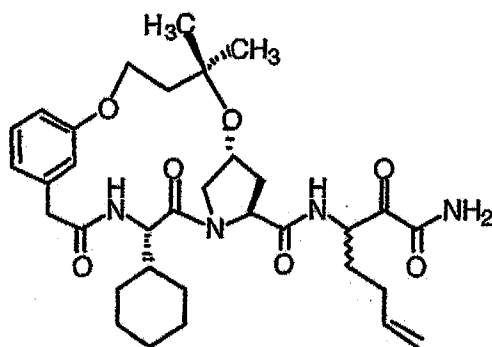
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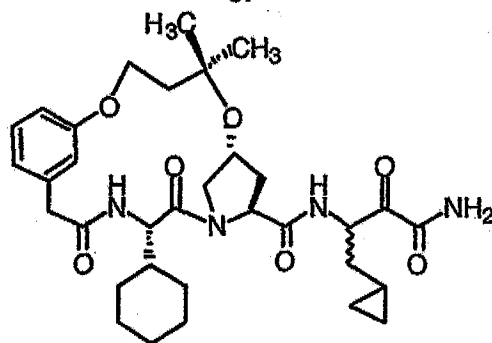
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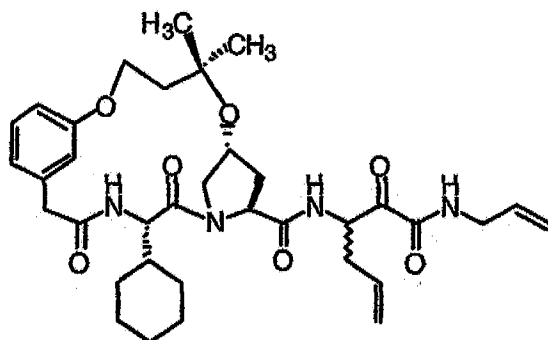
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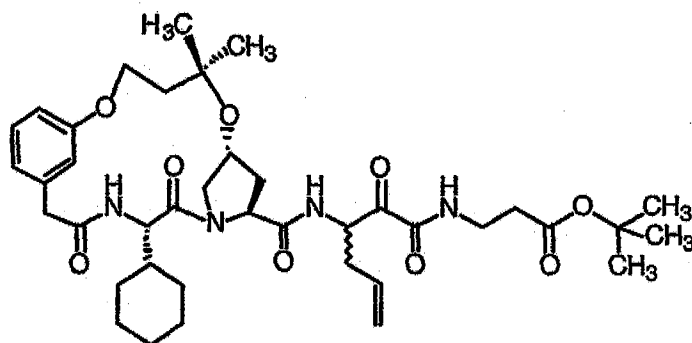
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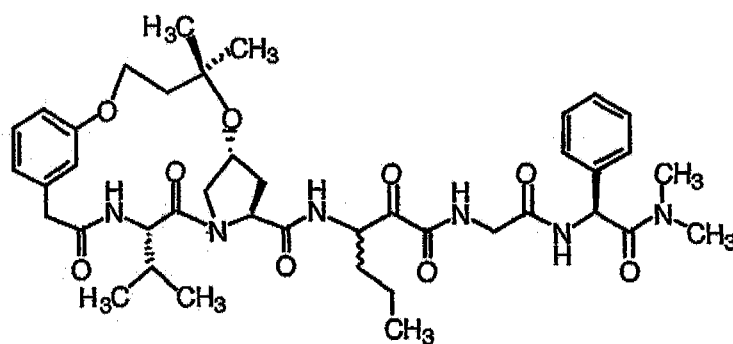
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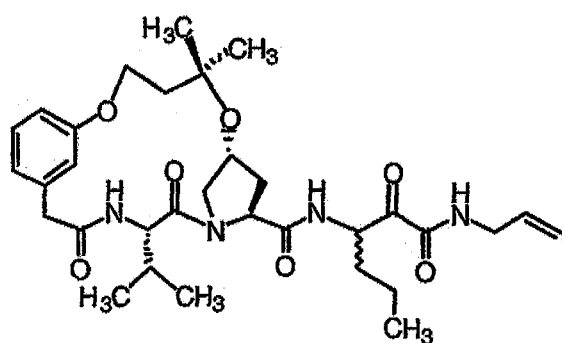
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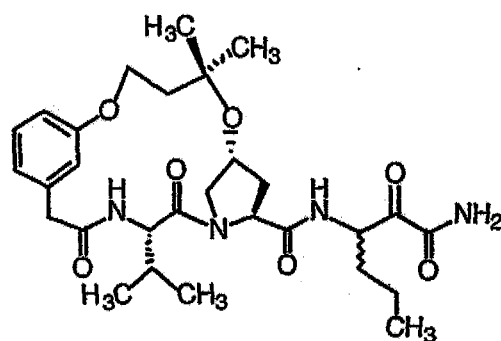
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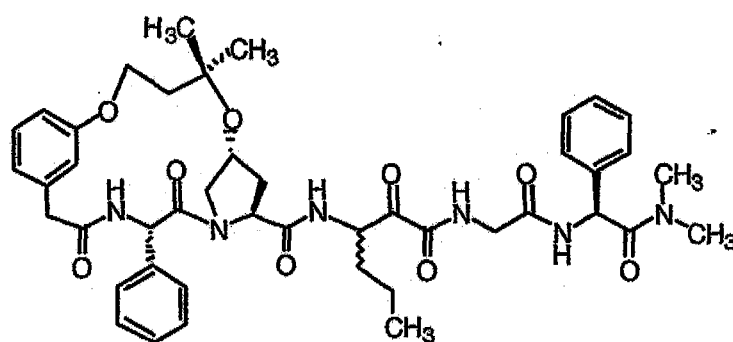
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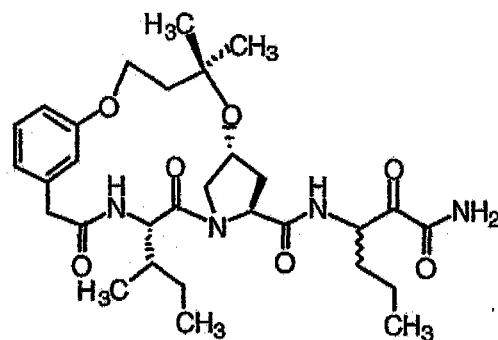
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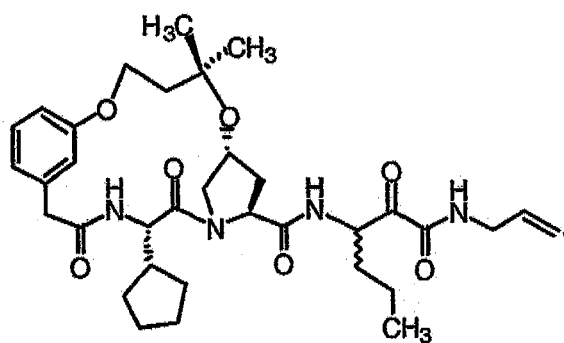
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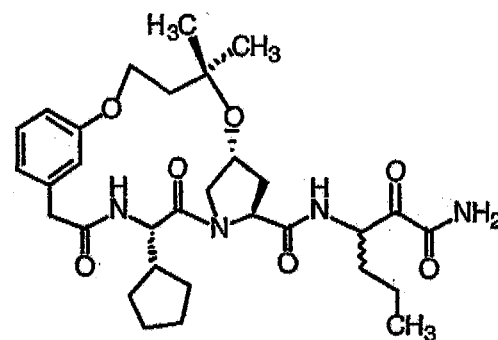


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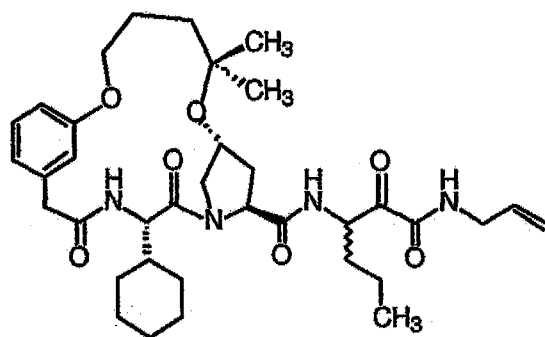


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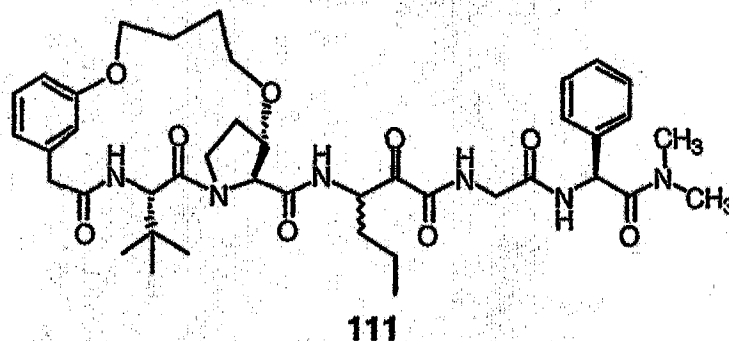


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5 Depending upon the structure, the compounds of the invention may form pharmaceutically acceptable salts with organic or inorganic acids, or organic or inorganic bases. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and
10 carboxylic acids well known to those skilled in the art. For formation of salts with bases, suitable bases are, for example, NaOH, KOH, NH_4OH , tetraalkylammonium hydroxide, and the like.

In another embodiment, this invention provides pharmaceutical compositions comprising the above-described inventive macrocycles as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders.

20 In yet another embodiment, the present invention discloses methods for-
preparing pharmaceutical compositions comprising the inventive macrocycle
compounds as an active ingredient. In the pharmaceutical compositions and
methods of the present invention, the active ingredients will typically be
administered in admixture with suitable carrier materials suitably selected with
25 respect to the intended form of administration, i.e. oral tablets, capsules (either
solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels,
elixirs, dispersible granules, syrups, suspensions, and the like, and consistent

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the

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carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include

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hydroxytetrahydroisoquinoline-3-carboxylic acid ("TIC"), suitable substitution of any of both the natural and unnatural amino acids will result in the formation of the desired macrocycles based on such substitution.

Abbreviations which are used in the descriptions of the schemes,

5 preparations and the examples that follow are:

THF: Tetrahydrofuran

DMF: *N,N*-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

10 HOObt: 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one

EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

NMM: *N*-Methylmorpholine

ADDP: 1,1'-(Azodicarbonyl)dipiperidine

DEAD: Diethylazodicarboxylate

15 MeOH: Methanol

EtOH: Ethanol

Et₂O: Diethyl ether

Bn: Benzyl

Boc: *tert*-Butyloxycarbonyl

20 Cbz: Benzyloxycarbonyl

Cp: Cyclopentylidenyl

Ts: *p*-toluenesulfonyl

Me: Methyl

PyBrOP: Tris(pyrolidino)bromophosphonium hexafluorophosphate

25 DMSO: Dimethyl sulfoxide

TFA: Trifluoroacetic acid

HOBt: Hydroxybenzotriazole

Hünigs base: Diisopropylethyl amine

BOP: Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

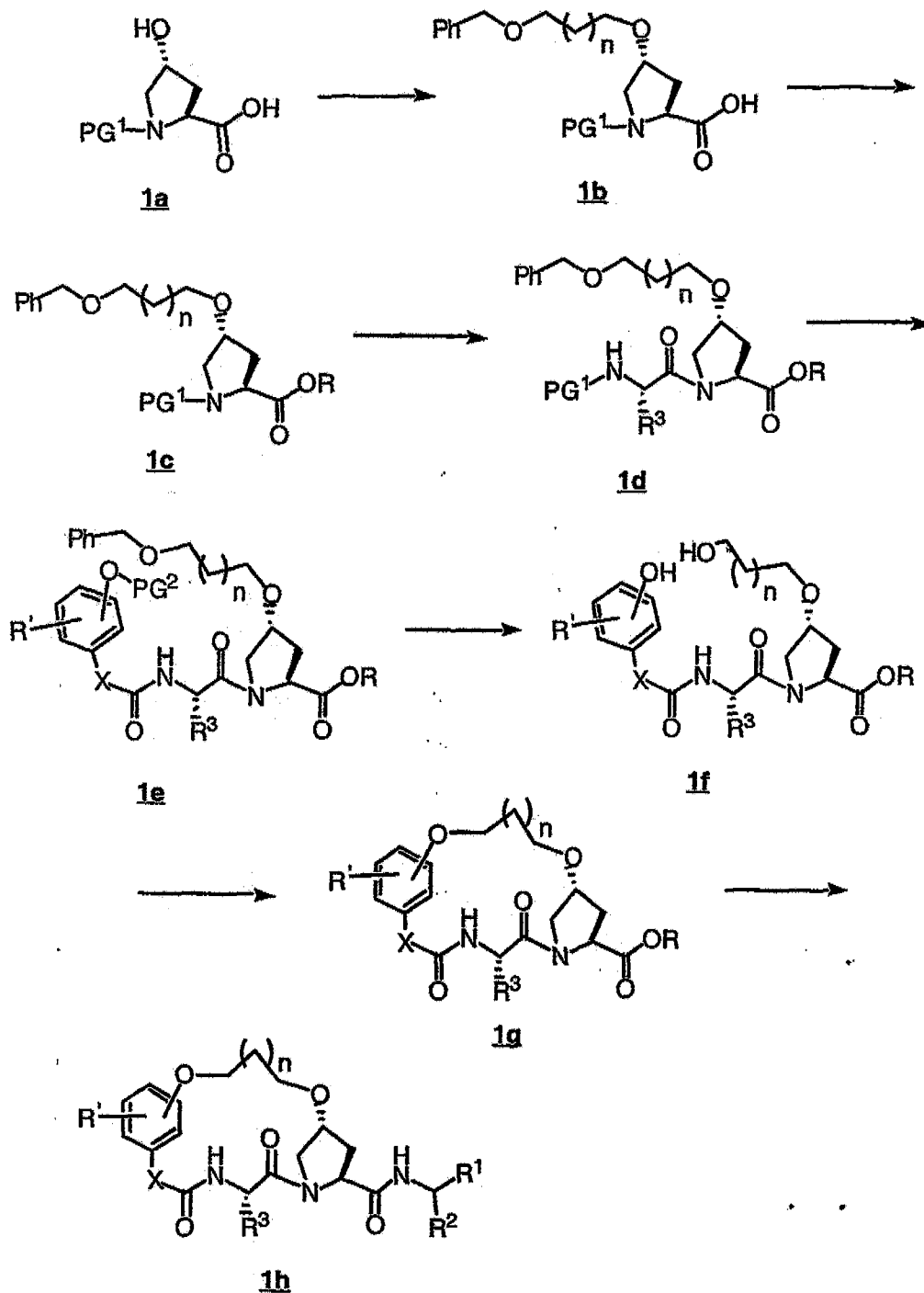
30 LDA: Lithium diisopropyl amide

Ph₃P: Triphenyl phosphine

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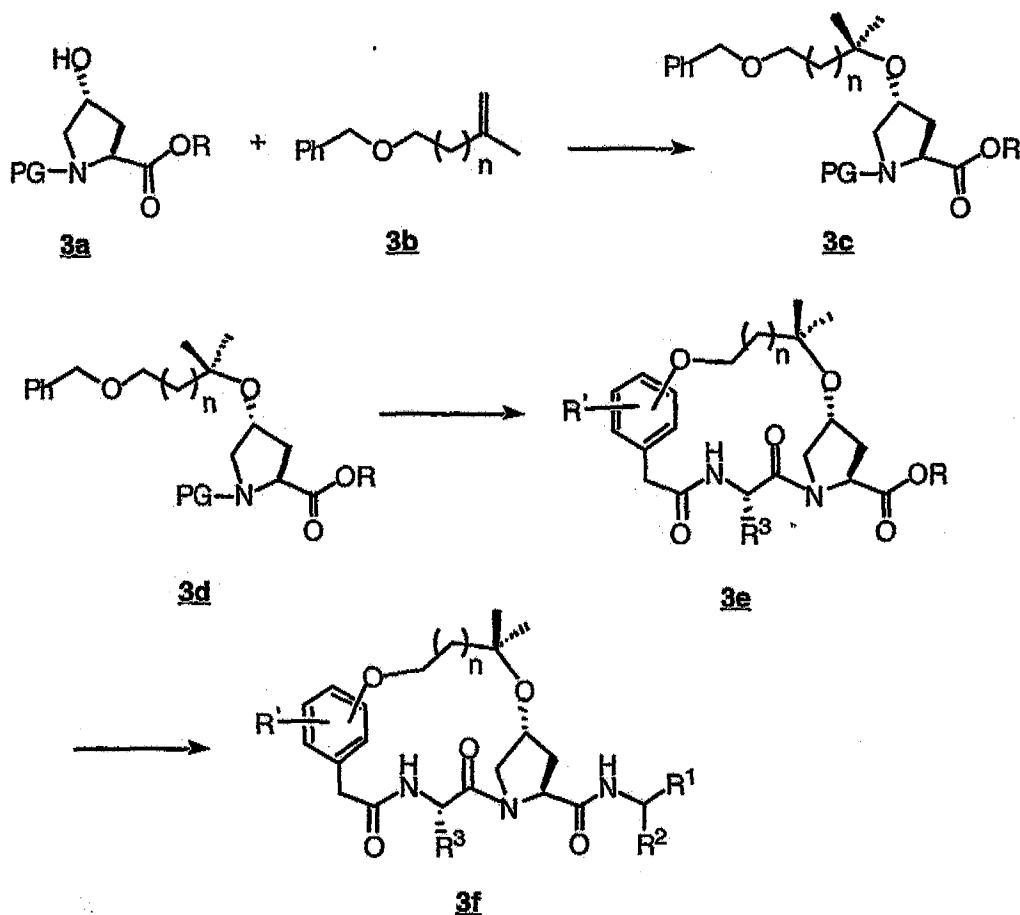
Scheme 1



The preparation of the compound of Formula **2e**, wherein R¹, R², R³, R and R' are defined above, is outlined in **Scheme 2**. The protected 3,4-dehydroproline **2a** is diastereoselectively dihydroxylated to afford *cis*-diol **2b**. The acetal formation between **2b** and an aldehyde can be accomplished in the

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Scheme 3

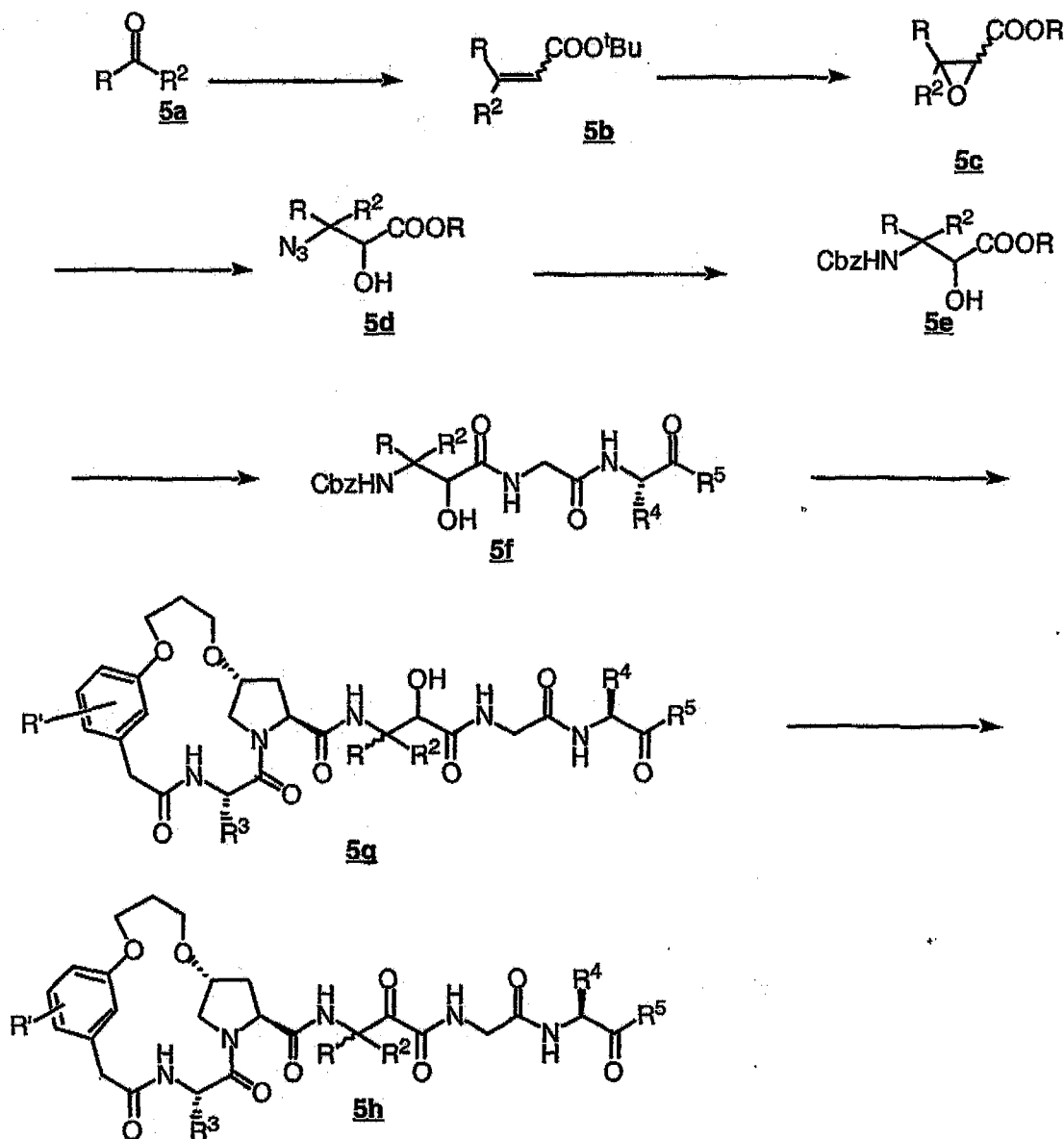


- 5 The preparation of the compound of Formula **4f**, wherein R^1 , R^2 , R^3 , R , and n are defined above, is outlined in **Scheme 4**. The coupling between amino ester **4a** and a Boc-protected amino acid was realized in the presence of NMM, HOObt, and EDCI-HCl. After removal of the Boc group from **4b**, the dipeptide is coupled to a terminal alkene carboxylic acid to give **4c**. The double bond was
- 10 then converted to an alcohol through hydroboration. The macrocyclization of the phenol alcohol is accomplished under Mitsunobu conditions by using triphenylphosphine and ADDP. After the resulting ester **4e** is hydrolyzed to an acid with lithium hydroxide, the acid is coupled to an amine intermediate to afford **4f**.

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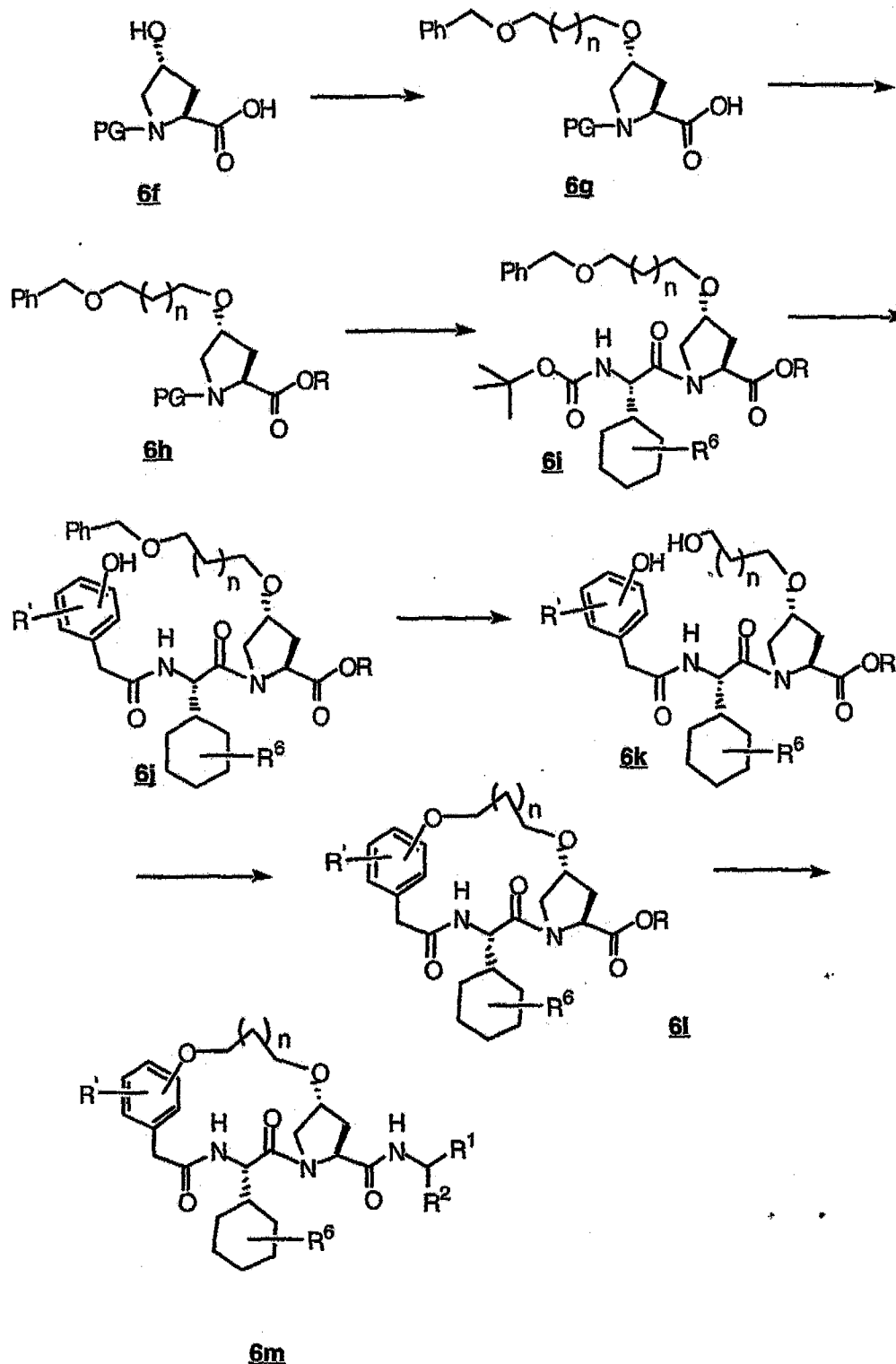
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Scheme 5:



- 5 The compound of formula **6m** is synthesized as outlined in **Scheme 6** wherein R^1 , R^2 , R' and n are defined in **Scheme 1** and R^6 being alkyl, aryl, ester, carboxylic acid and carboxyamides. The compound of type **6b** is synthesized from **6a** by a Wittig olefination using Ph_3PCH_3I and BuLi. The compound **6b** is further aminohydroxylated to synthesize compound of the type **6c**, which was
- 10 reduced using Rh/C, and H_2 to afford compound of type **6d**. The compound **6d** was oxidized to compound of type **6e** using $RuCl_3$ and H_5IO_6 . The compound **6e**

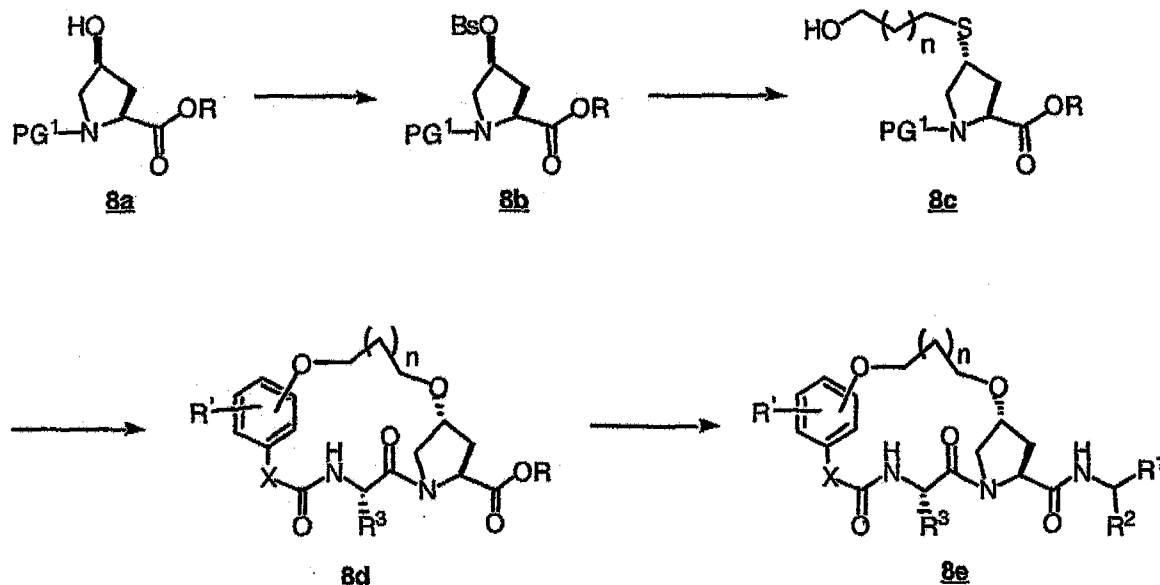
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The compounds of type **7d** are synthesized using the arene ruthenium chemistry wherein the substituents R^1 , R^2 , R^3 , R^4 are defined in **Scheme 1**, and $n=0$ to 3. The synthesis of the compound of formula **7b** was obtained from

5 compound of type **7a** by an EDCI, HOBT, Hünig's base coupling. The treatment of

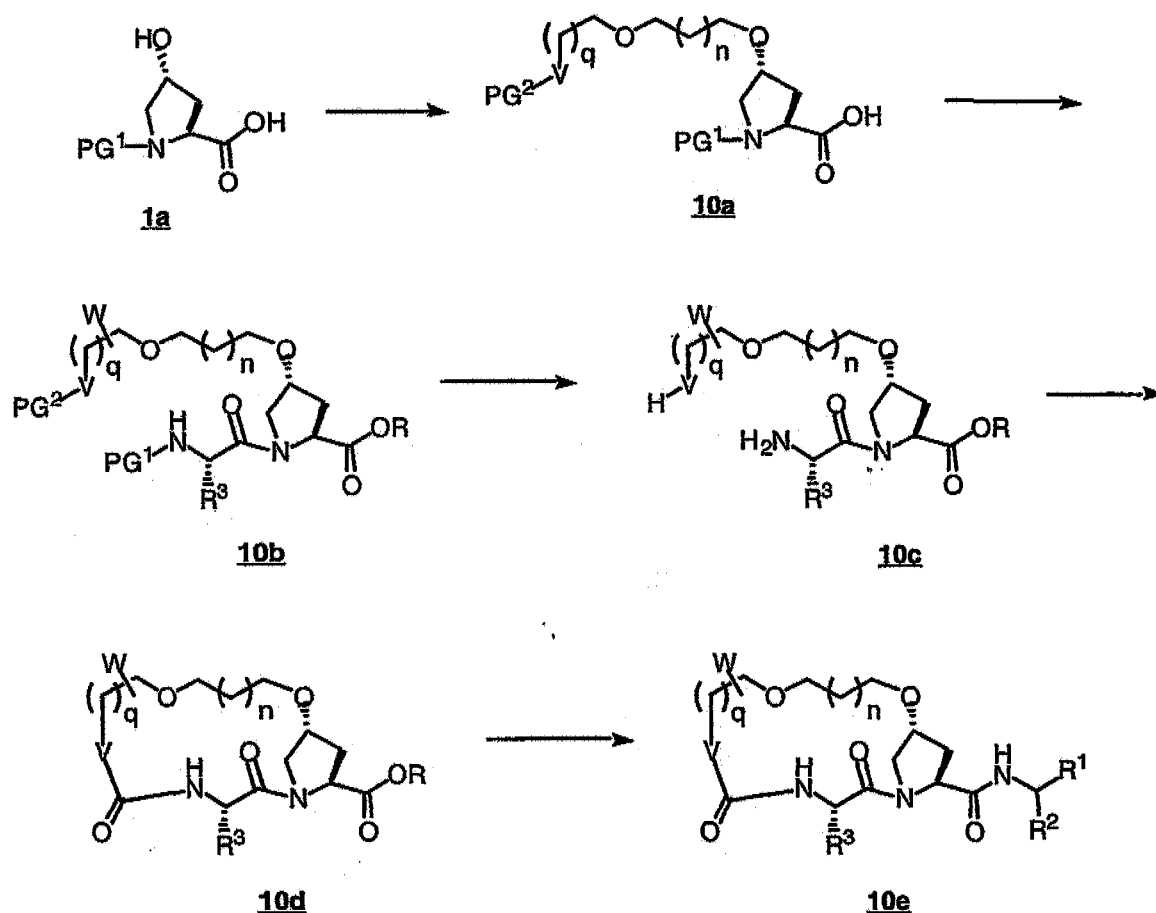
Scheme 8



- 5 The preparation of the compound of formula **9d**, wherein R^1 , R^2 , R^3 are defined above, R' is alkyl, heteroalkyl (OR'' , SR''' , $NR''R'''$ wherein R'' and R''' are alkyl groups), halo substituent at *ortho*, *meta*, or *para*-position to oxygen atom; R is alkyl, aryl, or alkylaryl groups; n is from zero to five; X is $(CH_2)_m$ where m is one to five, oxygen atom, NY where Y is hydrogen atom, alkyl, aryl group; and LG is
- 10 leaving group (e.g., OTs, Br) is outlined in **Scheme 9**. The protected 4-hydroxyproline derivative **1a** is converted to **9a** via formation of **1d** (which is described in **Scheme 1**). Removal of the benzyl ether followed by conversion to an appropriate leaving group and unravelling the N protecting group provided **9b**. Conversion to the macrocyclic ester **9c** was carried out by treatment with sodium carbonate/sodium iodide in refluxing acetone. Subsequent processing to the
- 15 desired target **9d** was accomplished as outlined in **Scheme 1**.

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Scheme 10

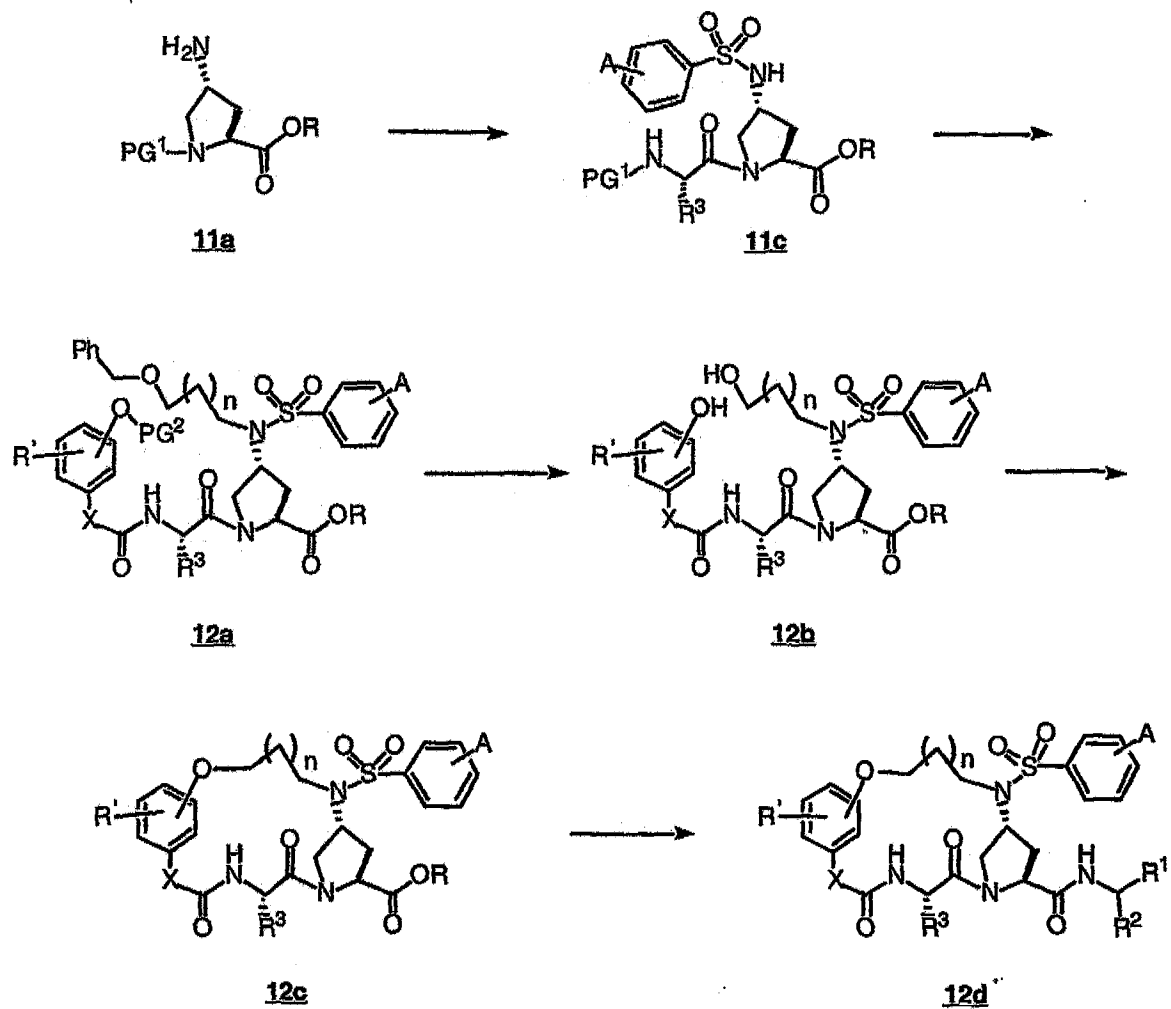
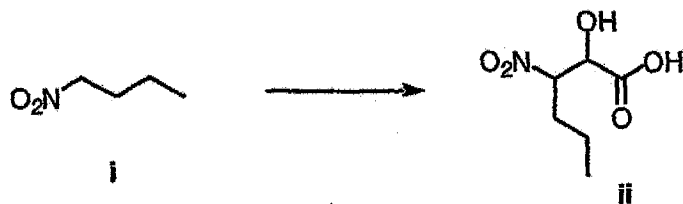


- 5 The preparation of the compound of formula **11g**, wherein R^1 , R^2 , R^3 are defined above, R is alkyl, aryl, or alkylaryl groups; X is $(CH_2)_m$, $(CH_2)_mO$, $(CH_2)_mNY$ where m is one to five, and Y is hydrogen atom, alkyl, aryl group; A is hydrogen atom or appropriately positioned halogen atom; PG^1 is appropriate protecting groups ($PG^1 = t\text{-boc}$, cbz , etc) is outlined in **Scheme 11**. The protected 4-
- 10 aminoproline derivative **11a** is converted to **11b** by treatment with suitable benzenesulfonyl chloride and a base. Removal of protecting group and coupling with a protected aminoacid derivative gave **11c**. This was converted to **11d** using similar deprotection, coupling strategy. Palladium(0) catalyzed cyclization afforded **11e** as a mixture of isomers which was hydrogenated to provide

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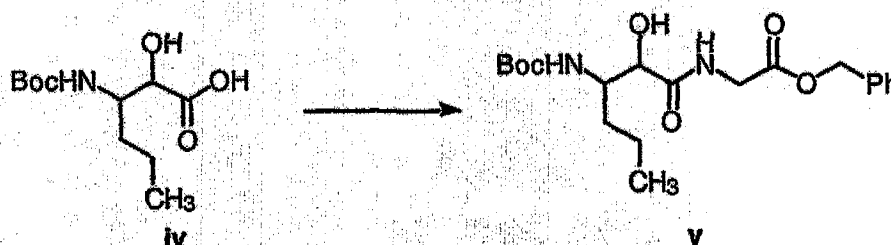
Scheme 12

5 **Preparation of Intermediates:****Intermediate A:****Step 1:**

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The resulting solution was stirred for 10 minutes, followed by addition of di-*t*-butyldicarbonate (0.110 g, 14.0 mmol) and stirred at 0°C for 15 minutes. The solution was then warmed to room temperature, stirred for 45 minutes and kept at refrigerator overnight and concentrated to dryness to give a crude material. To the solution of this crude material in EtOAc (100 mL) and ice, was added KHSO₄ (3.36 g) and H₂O (32 mL) and stirred for 4-6 minutes. The organic layer was then separated and the aqueous layer was extracted twice with EtOAc and the combined organic layer was washed with water, brine, dried over Na₂SO₄, filtered and concentrated to dryness to give the product as a clear gum (3.0 g, 89% yield).

Step 4:

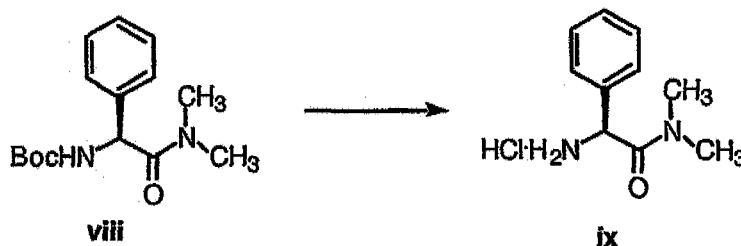


To a stirred solution of starting material (3.00 g, 12.0 mmol) in DMF (15 mL) and CH₂Cl₂ (15 mL) at -20°C was added HOObt (1.97 g, 12.0 mmol), *N*-methyl morpholine (4.0 mL, 36.0 mmol) and EDCI (2.79 g, 14.5 mmol) and stirred for 10 minutes, followed by addition of HCl-H₂N-Gly-OBn (2.56 g, 13.0 mmol). The resulting solution was stirred at -20°C for 2 hrs, then kept at refrigerator overnight and concentrated to dryness, followed by dilution with EtOAc (150 mL). The EtOAc solution was then washed twice with saturated NaHCO₃, H₂O, 5%-H₃PO₄, brine, dried over Na₂SO₄, filtered and concentrated to dryness to give the product (4.5 g, 94%). LRMS *m/z* MH⁺= 395.1.

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concentrated in vacuo to afford crude product **viii** (4.86 g) as a white solid, which was used without further purification.

Step 7:

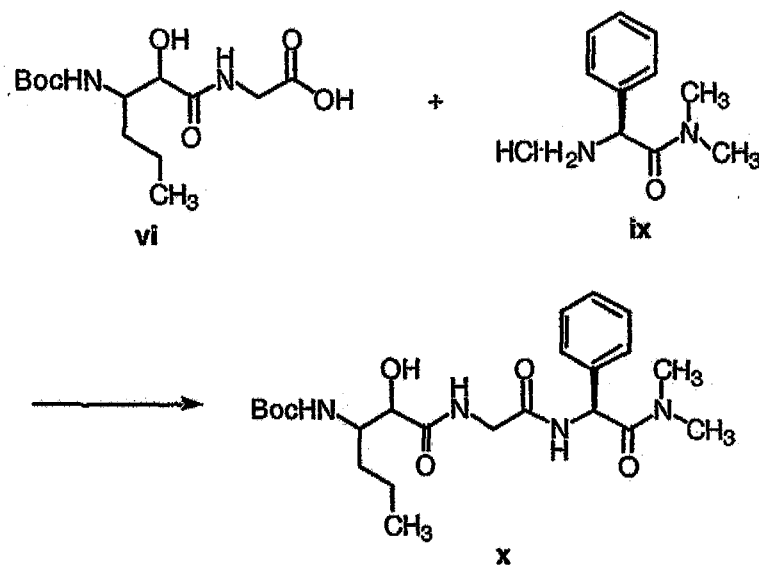


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The *N*-Boc-phenylglycine dimethylamide **viii** (4.70 g, crude) was dissolved in 4 N HCl (60 mL, 240 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 4 h, the solution was concentrated in vacuo to yield a white solid which was used in the next reaction without further purification. LRMS m/z $MH^+ = 179.0$.

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Step 8:



The desired compound **x** was prepared according to the coupling procedures described in Step 4. LRMS m/z $MH^+ = 465.1$.

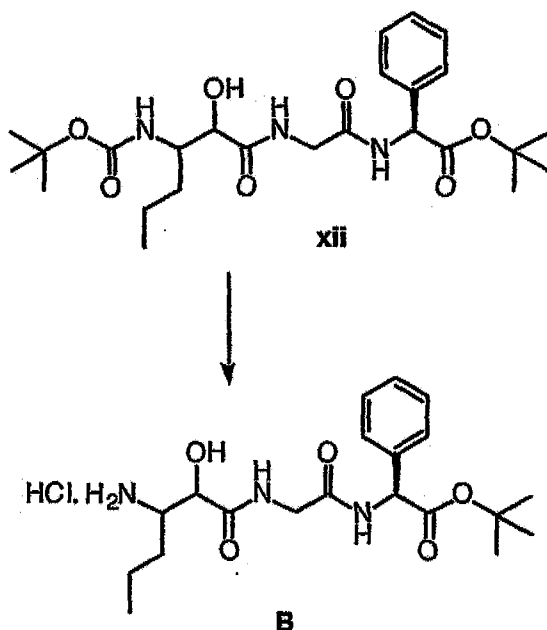
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The crude material was sufficiently pure for further studies. A portion of the product was purified by flash chromatography using 97/3 dichloromethane/MeOH.

HRMS (FAB) Calcd for $C_{25}H_{40}N_3O_7$: 494.2866 ($M+H$)⁺. Found: 494.2863.

Step 2

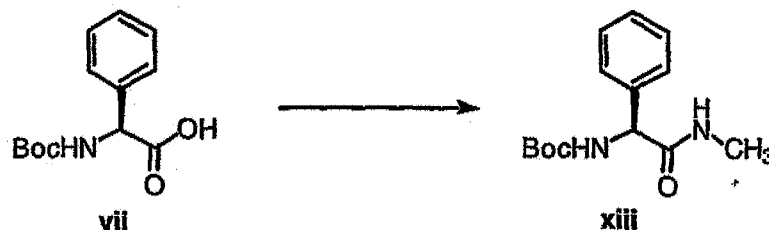


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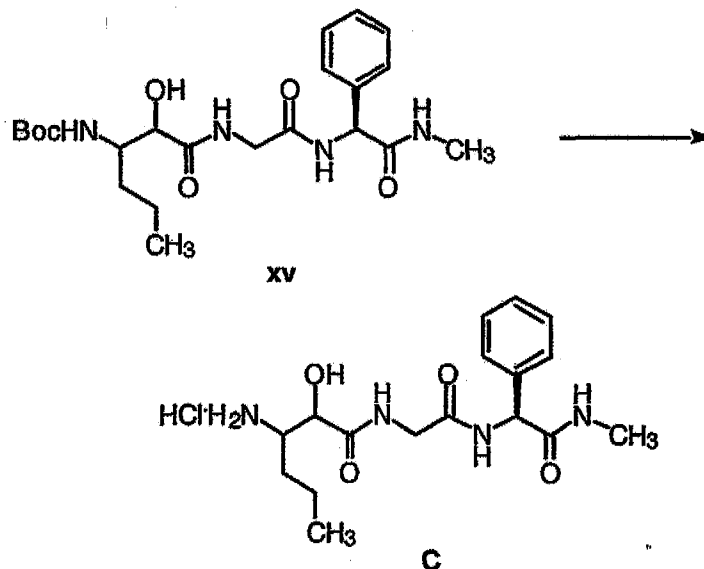
The desired product **B** was obtained by the procedure described for Intermediate **A**, Step 7. The crude material was used without further purification.

Intermediate C:

10 Step 1:



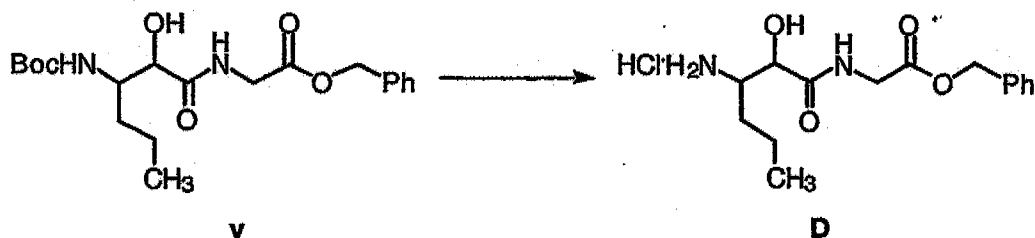
The desired compound **xiii** was prepared similar to the coupling procedures described in Step 6 for intermediate **A** except for substituting methylamine for dimethylamine.

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00086Step 4:

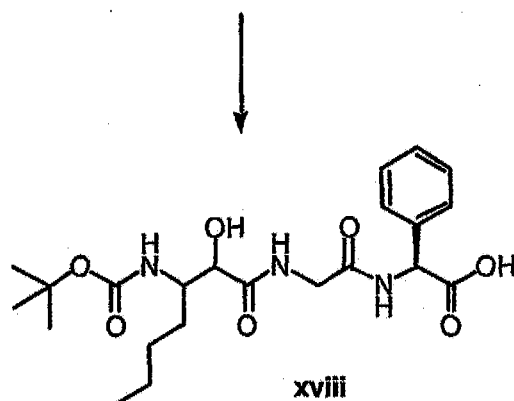
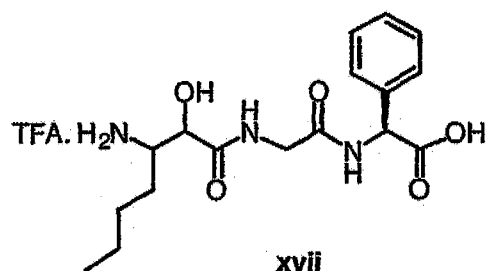
5 The desired intermediate **C** was prepared according to the procedures described in Step 7 for intermediate **A**. LRMS m/z $MH^+ = 351.1$. It was used without further purification.

Intermediate D:

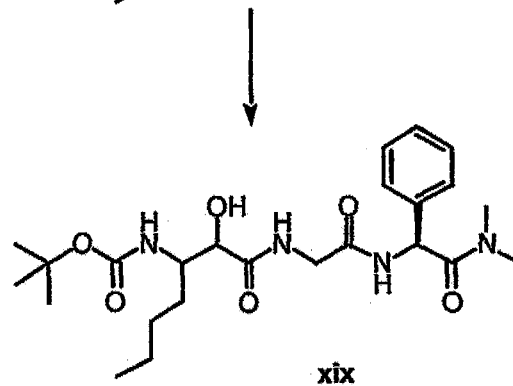
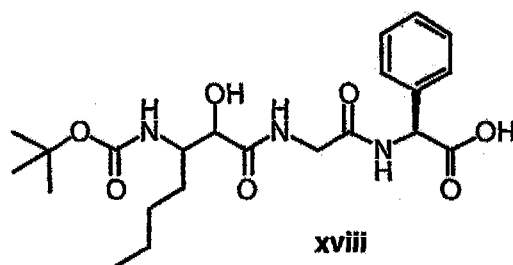
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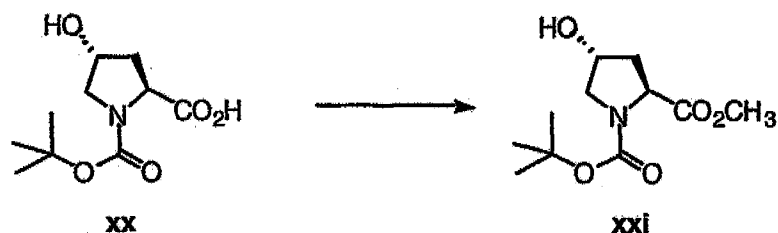


15 The desired intermediate **D** was prepared from compound **v** according to the procedures described in Step 7 for intermediate **A**. It was used without further purification.

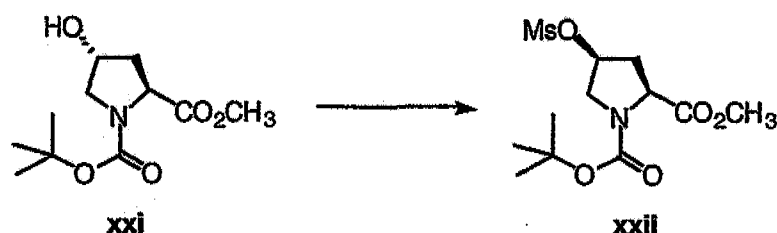
55
00057Step 2

The desired compound **xviii** was obtained by the method described for Intermediate A, Step 3. Sodium carbonate was used as the base instead of NaOH. The crude material **xviii** was carried further without purification.

Step 3

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00056**Intermediate F****Step 1**

- 5 To a cold (0°C) solution of **xx** (20.0 g, 86.5 mmol) in benzene (300 mL) and MeOH (50 mL) was added trimethylsilyl diazomethane (2M in hexanes, 56 mL, 112 mmol) dropwise till the solution remained yellow. The reaction mixture was concentrated to provide 21 g of **xxi** (99% yield) which was pure enough to be carried further. HRMS (FAB) Calcd for C₁₁H₂₀NO₅: 246.1341 (M+H)⁺. Found:
- 10 246.1347.

Step 2

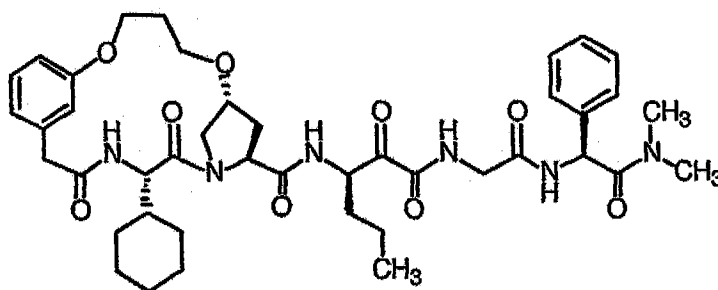
- 15 To a cold (~5°C) mechanically stirred mixture of triphenylphosphine (31.97 g, 121.9 mmol) and methanesulfonic acid (7.66 mL, 118.1 mmol) in toluene was added DEAD (26.47 g, 152 mmol) slowly while maintaining the reaction temperature below 35°C. After the addition was complete, the reaction mixture was cooled to 20°C and a solution of **xxi** (23.71 g, 96.8 mmol) in toluene was
- 20 added followed by triethylamine (5.39 mL, 38.7 mmol). The mixture was heated to 70-75°C for 6 hrs and cooled to 5-10°C for 1 hr. All the solid material were filtered off and the filtrate was washed with 5% KH₂PO₄ solution and brine. The organic layer was dried (Na₂SO₄), and concentrated. Flash column chromatography of the residue using 95/5 dichloromethane/EtOAc provided 26 g

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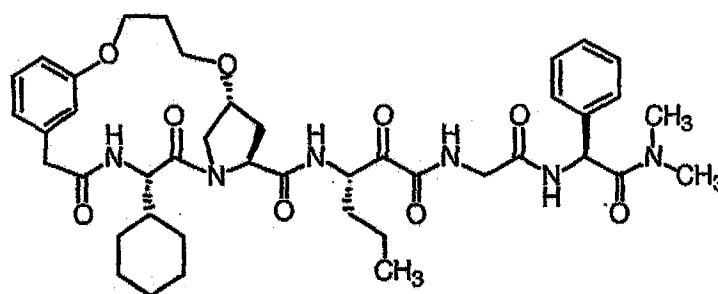
Examples

Example 1: Preparation of compounds of Formulas 1A and 1B:

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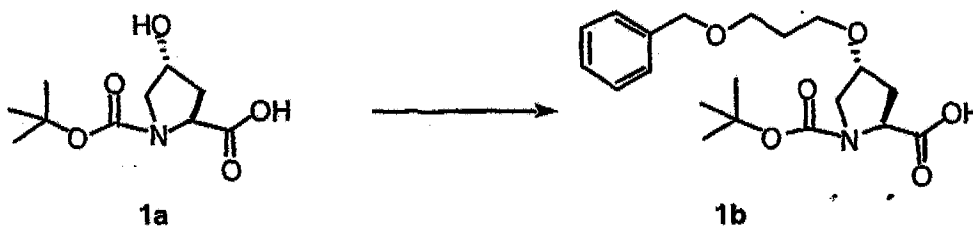


1A



1B

Step A:



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To a solution of Boc-Hyp-OH (7.0 g, 30.3 mmol) and benzyl 3-bromopropyl ether (7.8 g, 34.0 mmol) in anhydrous DMF (400 mL) at room temperature was added sodium hydride (3.5 g, 60% dispersion in mineral oil, 87.5 mmol) and sodium iodide (0.5 g, 3.33 mmols) with stirring. The resulting suspension was vigorously stirred at room temperature overnight (18 h). The reaction was

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solution was concentrated in vacuo and the residue was kept under vacuum overnight to yield a white solid which was used in the next coupling reaction without further purification.

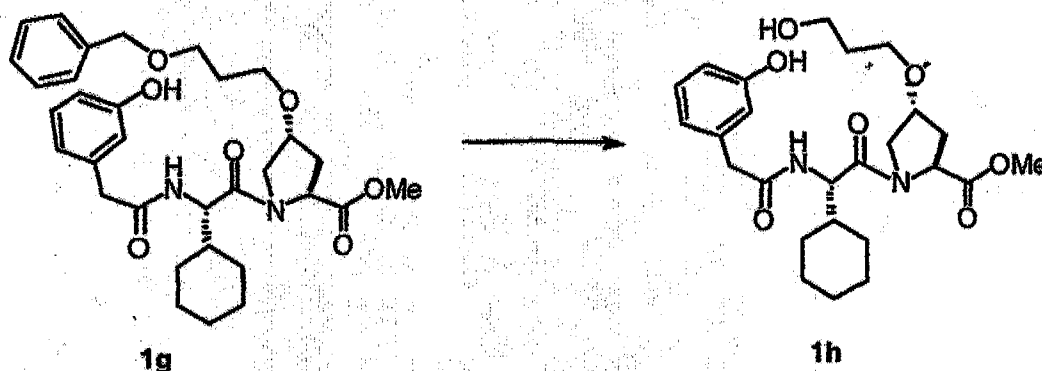
Step D:



To a solution of the amine ester **1d** (from Step 1B), *N*-Boc-cyclohexylglycine (4.10 g, 14.9 mmol), HOOBt (2.60 g, 15.9 mmol) and EDCI (3.41 g, 17.8 mmol) in anhydrous DMF (150 mL) and CH₂Cl₂ at -20°C, was added NMM (6.50 mL, 59.1 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1h. EtOAc (450 mL), brine (100 mL) and 5% H₃PO₄ (100 mL) were added. The separated organic solution was washed with 5% H₃PO₄ (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (10 to 20 % EtOAc-CH₂Cl₂) afforded **1e** (6.60 g, 84% 2 steps) as a white solid. ¹H NMR (400 MHz, d₆-DMSO) δ 7.36-7.25 (m, 5 H), 6.87 (d, *J* = 8.9 Hz, 1 H), 4.46-4.40 (m, 2 H), 4.25 (t, *J* = 8.3 Hz, 1 H), 4.11 (s, 1 H), 4.05-4.04 (m, 1 H), 4.03-3.94 (m, 1 H), 3.60 (s, 3 H), 3.50-3.41 (m, 4 H), 2.25-2.20 (m, 1 H), 1.95-1.88 (m, 1 H), 1.77-1.55 (m, 9 H), 1.35 (s, 9 H), 1.19-0.90 (m, 4 H); ¹³C NMR (100 MHz, d₆-DMSO) δ 172.0, 170.7, 155.6, 138.8, 128.2, 127.4, 127.3, 78.0, 77.1, 71.9, 66.6, 65.1, 57.4, 56.3, 51.8, 34.5, 29.6, 28.6, 28.2, 25.9, 25.6, 25.5.

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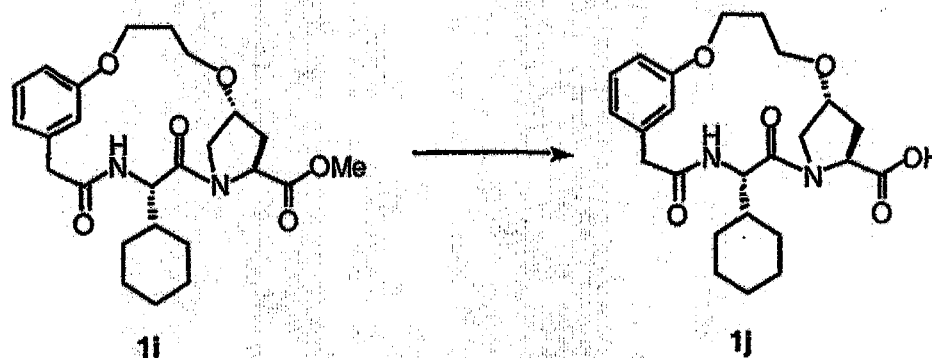
To a solution of the amine **1f** (from Step 1D), 3-hydroxy phenylacetic acid (1.90 g, 12.5 mmol), HOOBt (2.10 g, 12.9 mmol) and EDCI (2.85 g, 14.9 mmol) in anhydrous DMF (250 mL) and CH₂Cl₂ (100 mL) at -20°C, was added NMM (4.20 mL, 38.2 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1h. EtOAc (500 mL), brine (100 mL) and 5% H₃PO₄ (100 mL) were added. The separated organic solution was washed with 5% H₃PO₄ (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography (10 to 20 % EtOAc-CH₂Cl₂) afforded **1g** (6.30 g, 11.1 mmol, 90 % (2 steps)) as a white solid. ¹H NMR (400 MHz, d₆-DMSO) δ 9.26 (s, 1 H), 8.19 (d, *J* = 8.5 Hz, 1 H), 7.36-7.25 (m, 5 H), 7.05-7.01 (m, 1 H), 6.66-6.64 (m, 1 H), 6.60-6.57 (m, 1 H), 4.46-4.39 (m, 2 H), 4.34 (t, *J* = 8.3 Hz, 1 H), 4.29-4.25 (m, 1 H), 4.09-4.08 (m, 1 H), 3.91 (d, *J* = 11.0 Hz, 1 H), 3.66-3.58 (m, 1 H), 3.61 (s, 3 H), 3.50-3.39 (m, 5 H), 3.30 (d, *J* = 13.7 Hz, 1 H), 2.24-2.18 (m, 1 H), 1.95-1.89 (m, 1 H), 1.74-1.57 (m, 8 H), 1.18-0.89 (m, 5 H); ¹³C NMR (100 MHz, d₆-DMSO) δ 172.0, 170.3, 170.0, 157.1, 138.6, 137.6, 128.9, 128.2, 127.4, 127.3, 119.6, 116.1, 113.2, 76.9, 71.8, 66.6, 65.2, 57.4, 54.7, 51.9, 51.8, 41.8, 34.4, 29.6, 28.5, 28.0, 25.5, 25.5; HRMS *m/z* 567.3073 [calcd for C₃₂H₄₂N₂O₇, 567.3070].

Step G:

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2 % MeOH in CH₂Cl₂) to afford a mixture of the macrocycle **1i** and triphenylphosphine oxide. ¹H NMR (400 MHz, d₆-DMSO) δ 8.47 (d, *J* = 9.7 Hz, 1 H), 7.17-7.13 (m, 1 H), 6.79 (s, 1 H), 6.73 (d, *J* = 1.8 Hz, 1 H), 6.71 (d, *J* = 1.8 Hz, 1 H), 4.50-4.45 (m, 1 H), 4.24 (dd, *J* = 10.3, 7.6 Hz, 1 H), 4.17-4.06 (m, 4 H), 3.68 (d, *J* = 15.1 Hz, 1 H), 3.63 (s, 3 H), 3.60-3.51 (m, 2 H), 3.37 (d, *J* = 15.1 Hz, 1 H), 3.35-3.27 (m, 1 H), 2.51-2.43 (m, 1 H), 1.85-1.47 (m, 9 H), 1.22-1.12 (m, 3 H), 0.97-0.88 (m, 2 H); ¹³C NMR (100 MHz, d₆-DMSO) δ 172.0, 170.0, 169.8, 158.4, 138.1, 129.1, 121.8, 115.4, 112.2, 77.0, 64.9, 63.6, 57.0, 54.3, 53.4, 51.8, 41.3, 33.2, 28.9, 28.5, 28.2, 26.0, 25.2; HRMS *m/z* 459.2495 [calcd for C₂₅H₃₄N₂O₆, 459.2495].

Step I:



An aqueous lithium hydroxide solution (0.45 g in 30 mL H₂O) was added to a 0°C solution of the methyl ester **1i** in THF (30 mL) and methanol (30 mL). The mixture was stirred in an ice bath and warmed to room temperature along with it in 4 h. The progress of the reaction was monitored by TLC. After the volatiles were removed in vacuo, EtOAc (150 mL) and water (30 mL) were added and the two layers separated. The aqueous solution was extracted again with CH₂Cl₂ (150 mL), after which it was acidified to pH = 1. EtOAc (200 mL) was then added and the aqueous solution was saturated with solid sodium chloride. After separation of the layers, the aqueous layer was extracted with EtOAc (2 X 150 mL). Organic solutions were combined, dried with magnesium sulfate, filtered and concentrated in vacuo to afford **1j** (1.45 g, 3.26 mmol, 35 %, 2 steps) as a pale

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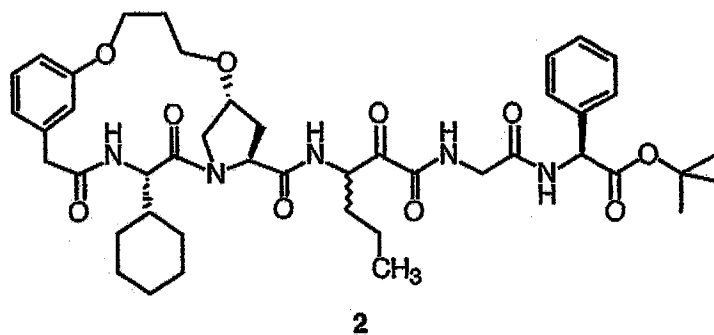
mL), brine (50 mL) and 5% H_3PO_4 (50 mL) were added. The separated organic solution was washed, successively, with 5% H_3PO_4 (80 mL), saturated aqueous sodium bicarbonate solution (2 X 80 mL), water (80 mL), and brine (80 mL), dried with magnesium sulfate, filtered and concentrated in vacuo. Flash

- 5 chromatography (4 to 7.5 % $\text{MeOH-CH}_2\text{Cl}_2$) afforded **1k** as a mixture of four diastereomers (0.59 g, 0.75 mmol, 56%) as a white solid. ^1H NMR (400 MHz, d_6 -DMSO) δ 8.54-8.35 (m, 2 H), 7.95-6.98 (m, 8 H), 6.79-6.77 (m, 1 H), 6.72-6.70 (m, 2 H), 5.96-5.73 (m, 2 H), 4.53-4.45 (m, 1 H), 4.35-3.61 (m, 11 H), 3.54-3.41 (m, 1 H), 3.40-3.22 (m, 1 H), 2.93-2.92 (m, 3 H), 2.84 (s, 3 H), 2.42-2.17 (m, 1 H), 1.87-
10 1.55 (m, 10 H), 1.49-1.06 (m, 7 H), 0.98-0.75 (m, 5 H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 172.1, 171.9, 171.8, 170.8, 170.7, 170.4, 170.4, 170.3, 170.0, 169.8, 169.7, 169.6, 169.2, 169.2, 167.9, 167.8, 167.8, 158.4, 158.3, 138.2, 138.15, 138.11, 138.07, 137.6, 137.50, 137.48, 129.1, 128.5, 128.3, 127.8, 127.7, 121.7, 121.6, 115.4, 115.3, 112.09, 112.07, 112.0, 111.9, 76.9, 76.8, 73.3, 72.1, 71.9,
15 64.9, 64.8, 63.2, 58.7, 58.5, 57.9, 57.8, 54.6, 54.5, 54.48, 53.8, 53.78, 53.7, 53.66, 53.0, 52.9, 51.0, 50.8, 50.7, 41.6, 41.5, 41.4, 41.3, 36.6, 35.3, 33.9, 33.86, 33.5, 32.9, 32.1, 29.9, 29.0, 28.9, 28.5, 28.4, 28.3, 26.0, 25.9, 25.3, 25.25, 25.2, 18.6, 18.56, 18.5, 13.8, 13.7; HRMS m/z 791.4339 [calcd for $\text{C}_{42}\text{H}_{58}\text{N}_6\text{O}_9$, 791.4344, error = 1 ppm].

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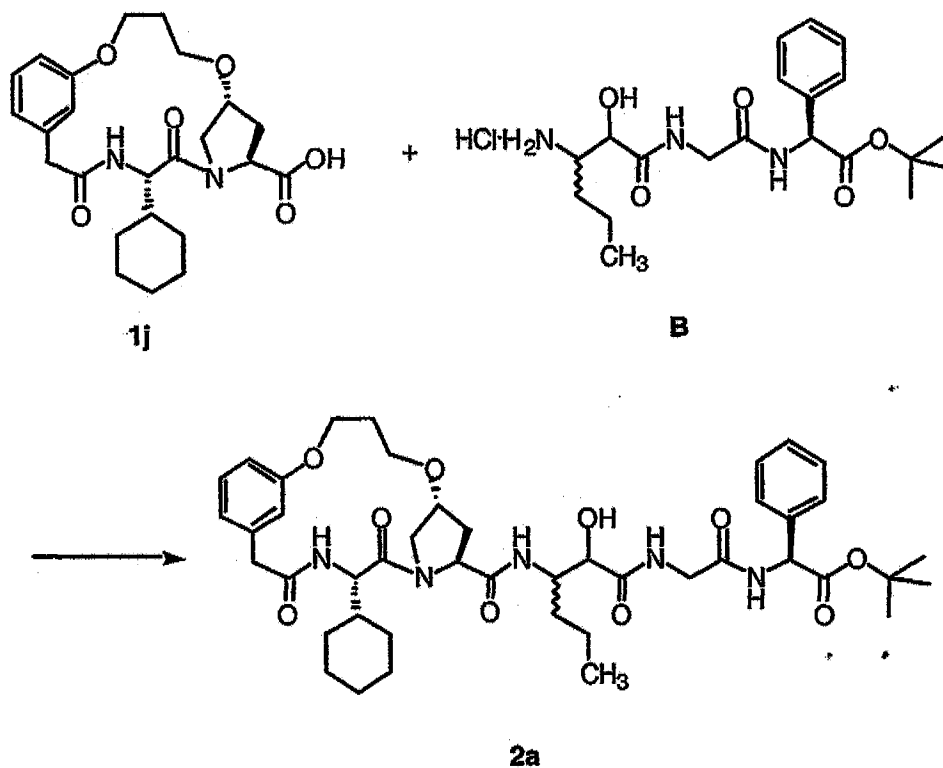
to 4 % MeOH-CH₂Cl₂) afforded two diastereomers **1A** (250 mg, 0.32 mmol) and **1B** (217 mg, 0.28 mmol, 82% combined yield) as white solids.

Example 2: Preparation of Compound 2:



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Step A:



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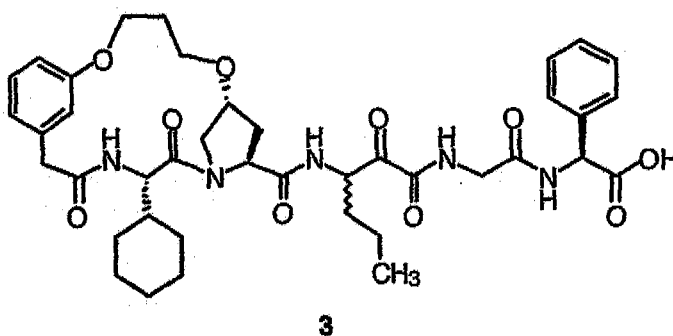
The desired compound **2a** was prepared according to the method of Example 1, Step J, except for substituting the amine **B** for the amine **A**. The hydroxy amide was obtained as a mixture of inseparable diastereomers in the form of a white solid in 60 % yield.

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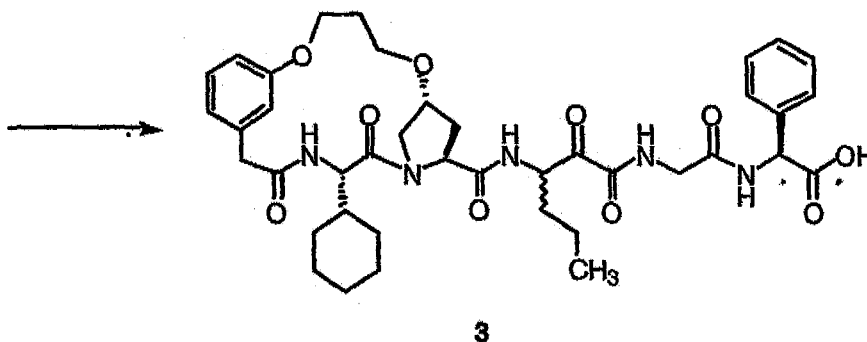
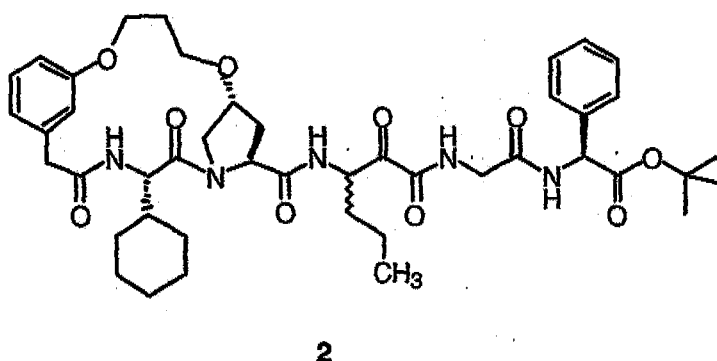
28.4, 28.3, 27.5, 26.0, 26.0, 25.4, 25.3, 25.2, 18.7, 18.6, 18.5, 13.9, 13.8; HRMS m/z 820.4493 [calcd for $C_{44}H_{61}N_5O_{10}$, 820.4497].

Example 3: Preparation of the Compound of Formula 3 below:



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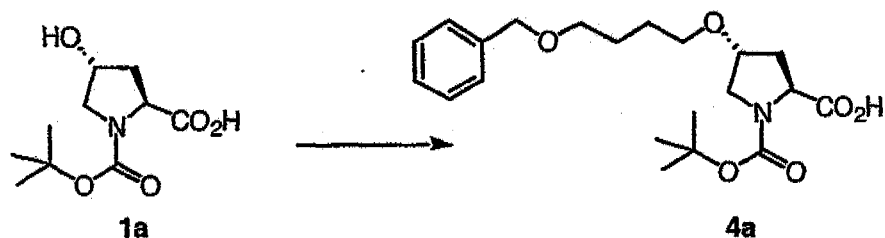
Step A:



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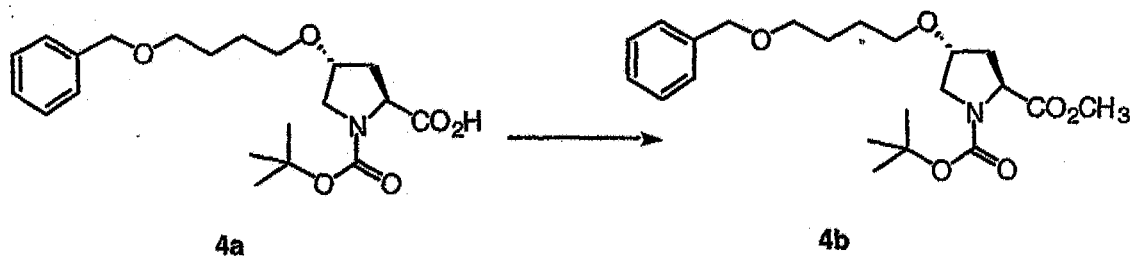
A solution of the *t*-Butyl ester 2 (26 mg, 0.032 mmol) in trifluoroacetic acid (2 mL) and CH_2Cl_2 (2 mL) was stirred at room temperature for 3 h. After the volatiles were removed in vacuo, the residue was dissolved in 50% MeOH-

103

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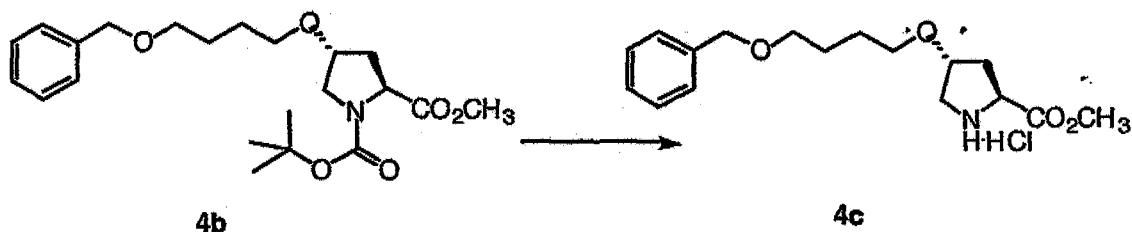
The desired product **4a** was obtained by the method described for Example 1, Step A. The crude material was carried to the next step as it was.

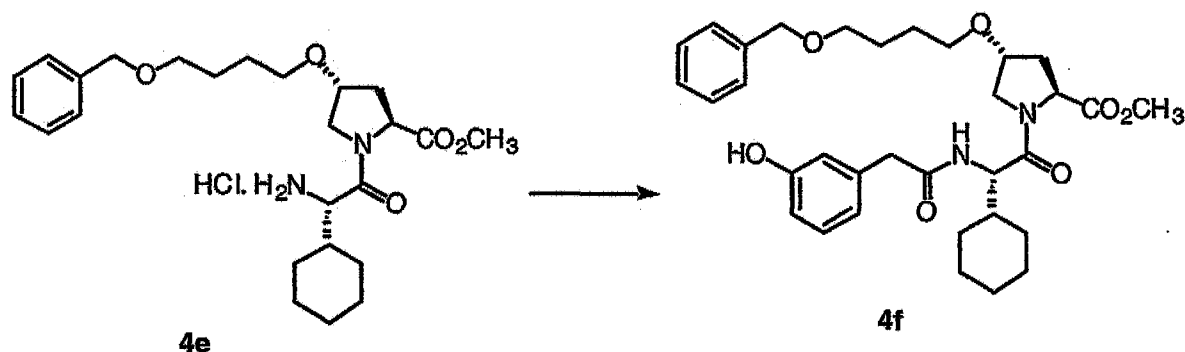
Step B:



The desired product **4b** was obtained by the method described for Example 1, Step B. The material was purified by flash column chromatography using 80/20 to 75/25 hexanes/ethyl acetate to provide **4b** in 50% yield as a colorless oil.

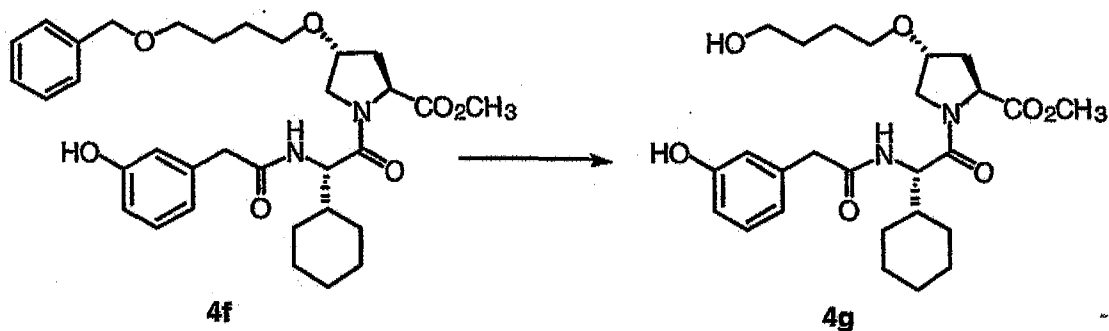
Step C:



Step F:

The desired product **4f** was obtained by the method described in Example 1, Step F. The material was purified by flash column chromatography using 80/20 to 60/40 dichloromethane/ethyl acetate to provide **4f** in 85% yield. HRMS (FAB)

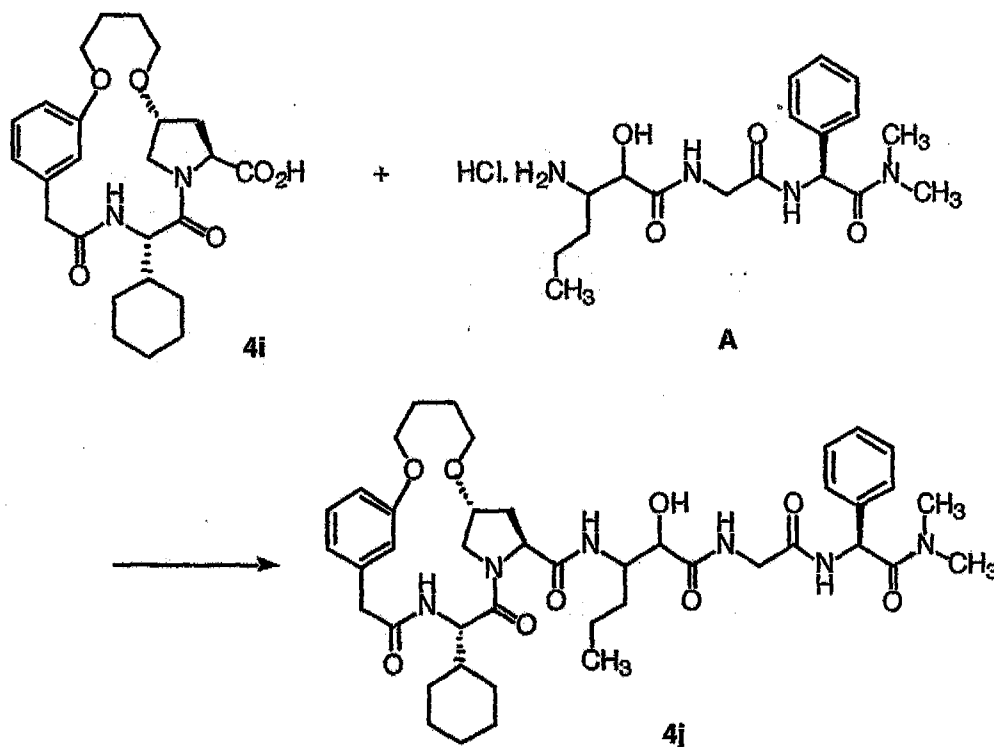
Calcd for $\text{C}_{33}\text{H}_{45}\text{N}_2\text{O}_7$: 581.3227 ($\text{M}+\text{H}$)⁺. Found: 581.3222.

Step G:

The desired product **4g** was obtained by the method described in Example 1, Step G. The crude material was carried to the next step as was. HRMS (FAB) Calcd for $\text{C}_{26}\text{H}_{39}\text{N}_2\text{O}_7$: 491.2757 ($\text{M}+\text{H}$)⁺. Found: 491.2761.

(m, 1H), 3.62-3.68 (m, 2H), 3.91-3.99 (m, 3H), 4.04-4.08 (m, 2H), 4.46 (t, 1H), 6.67-6.72 (m, 3H), 7.13 (app. t, 1H), 8.36 (d, 1H), 12.40 (br. s, 1H); ^{13}C NMR (DMSO- d_6) δ 25.26, 25.31, 25.97, 26.62, 28.42, 33.28, 39.75, 41.49, 53.50, 54.28, 57.45, 67.57, 67.98, 77.25, 111.07, 115.23, 121.48, 129.11, 137.99, 158.33, 170.07, 172.92; HRMS (FAB) Calcd for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_6$: 459.2495 ($\text{M}+\text{H}$) $^+$. Found: 459.2494.

Step J:



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The expected product **4j** was synthesized as described earlier for the Example 1 Step J. The material after work-up was of sufficient purity to be carried forward to the next step. HRMS (FAB) Calcd for $\text{C}_{43}\text{H}_{61}\text{N}_6\text{O}_9$: 805.4500 ($\text{M}+\text{H}$) $^+$. Found: 805.4492.

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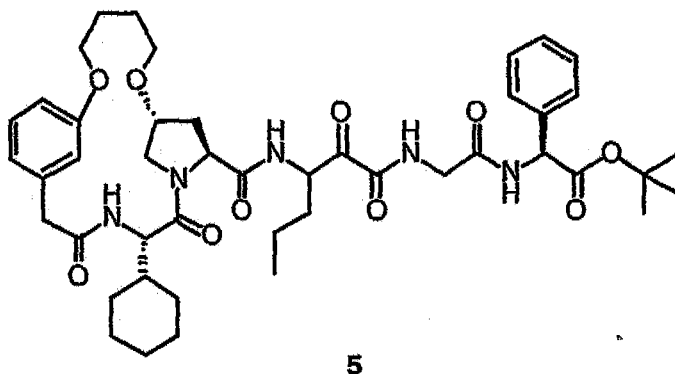
109

HRMS (FAB) Calcd for $C_{43}H_{59}N_6O_9$: 803.4344 ($M+H$)⁺. Found: 803.4339

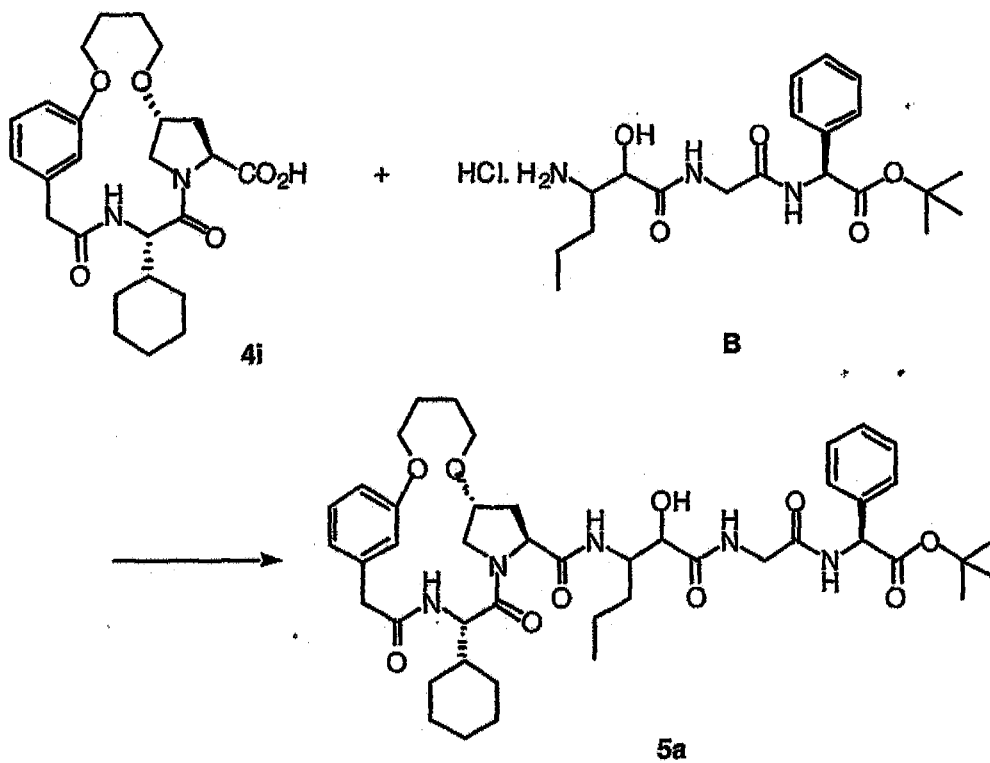
(4A), 803.4347 (4B).

Example 5: Preparation of Compound 5:

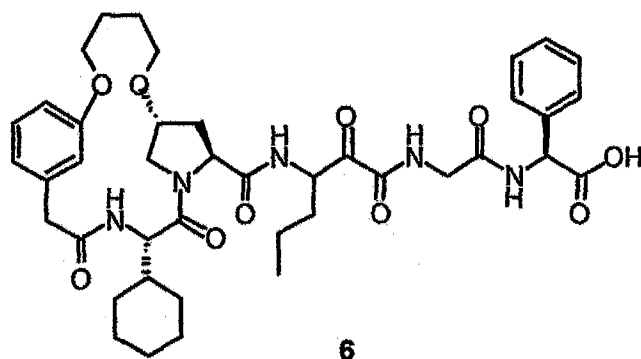
5

**Step A:**

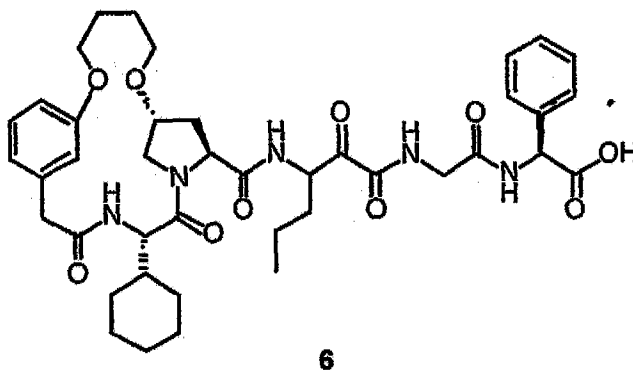
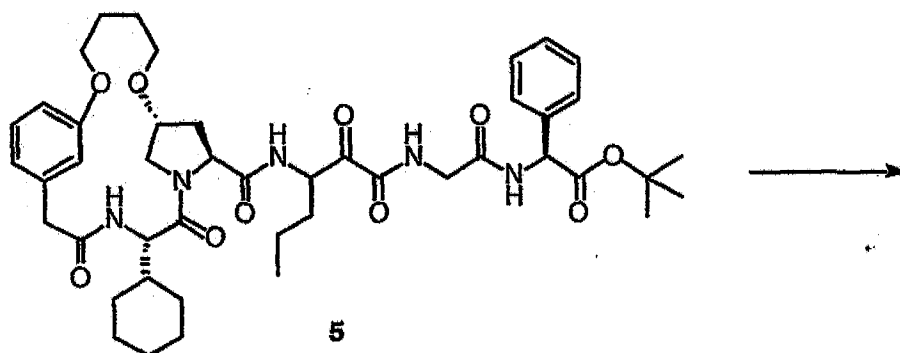
10



111

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00070**Example 6: Preparation of Compound 6:**

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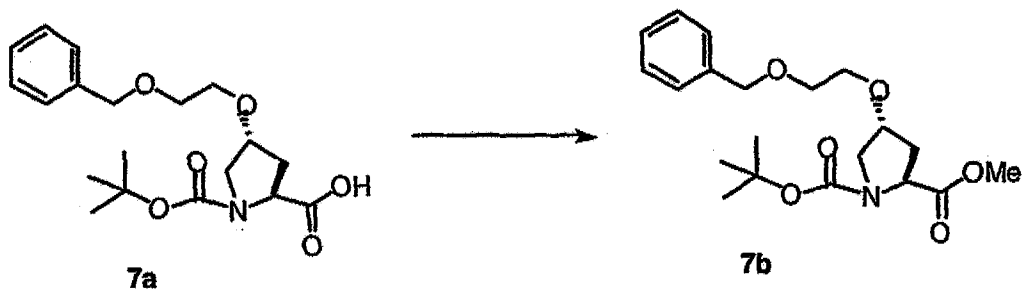
Step A:

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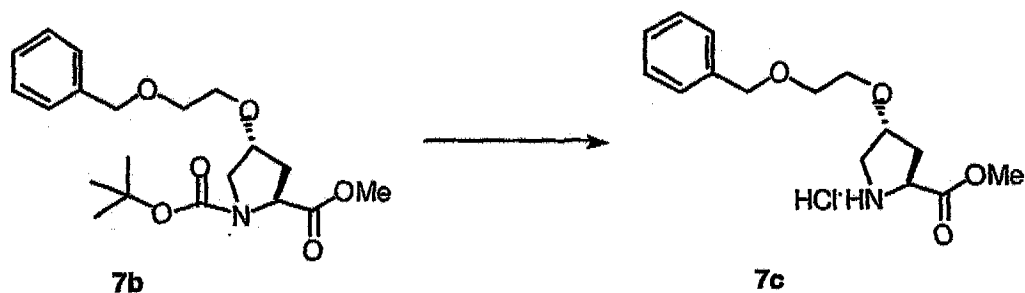
113

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Step B:

5 The desired compound **7b** was prepared from **7a** according to the procedure of Example 1, Step B.

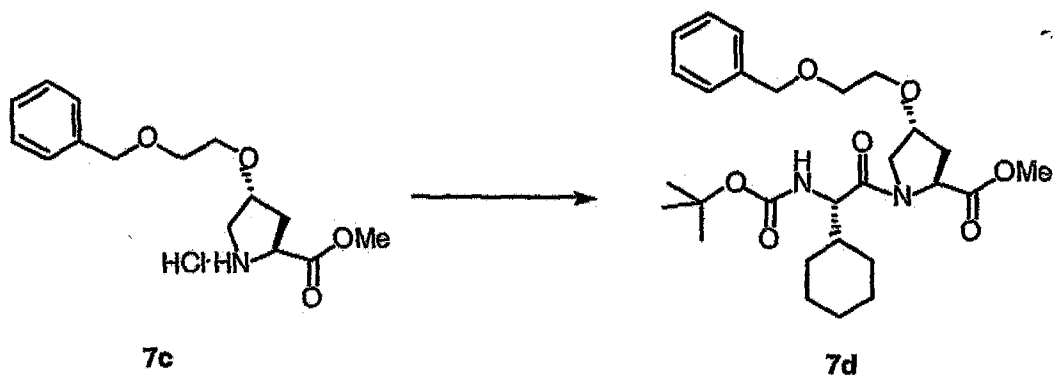
Step C:

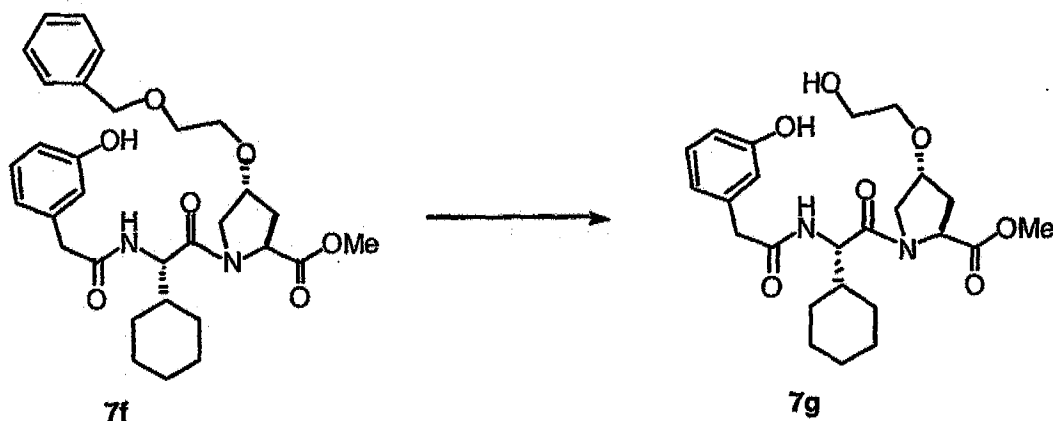
10

The desired compound **7c** was prepared from **7b** according to the procedure of Example 1, Step C. The product was used in Step D without further purification.

Step D:

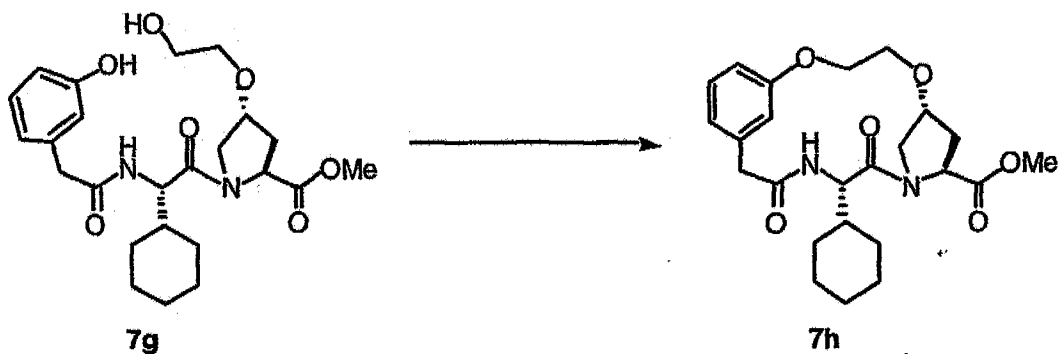
15



Step G:

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The desired compound **7g** was prepared from **7f** according to the procedure of Example 1, Step F.

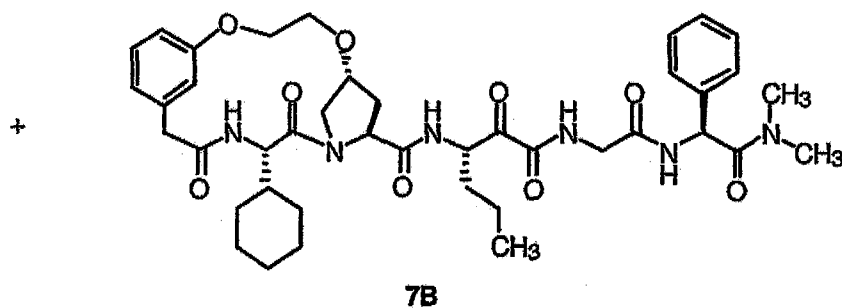
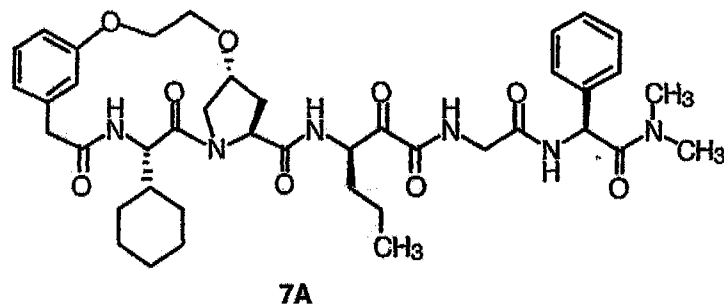
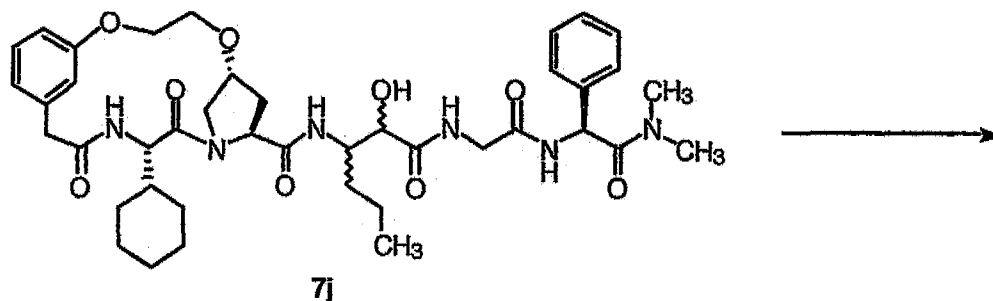
Step H:

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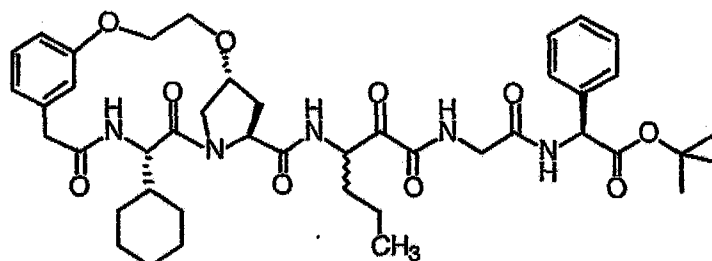
A solution of the phenol alcohol **7g** (830 mg, 1.79 mmol) and ADDP (1.36 g, 5.39 mmol) in anhydrous CH_2Cl_2 (200 mL) was bubbled with Argon through a frit glass bubbler for 20 min. To this solution at 0°C was added triphenylphosphine (1.41 g, 5.38 mmol). After stirring at 0°C for 20 min, the solution was warmed to room temperature and stirred overnight (20 h) under nitrogen. After removal of solvent in vacuo, the residue was purified by flash chromatography (1 to 3 % MeOH in CH_2Cl_2) to afford a mixture of the desired product **7h** and triphenylphosphine oxide, which was used in Step I without further purification.

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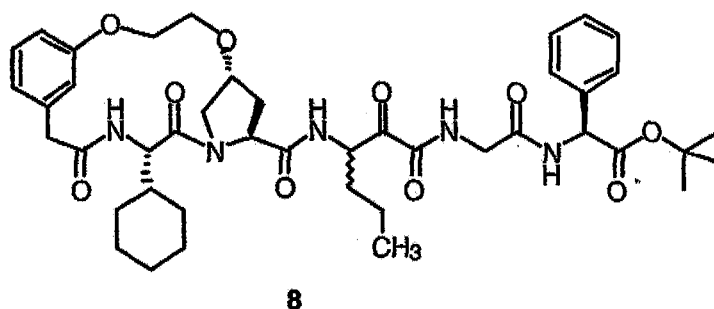
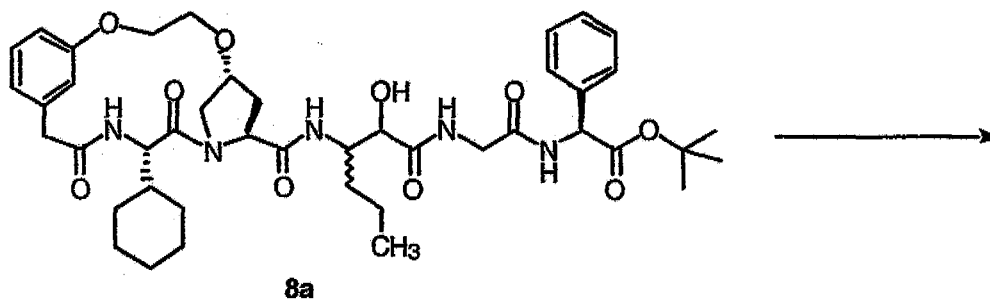
117

71
00073Step K:

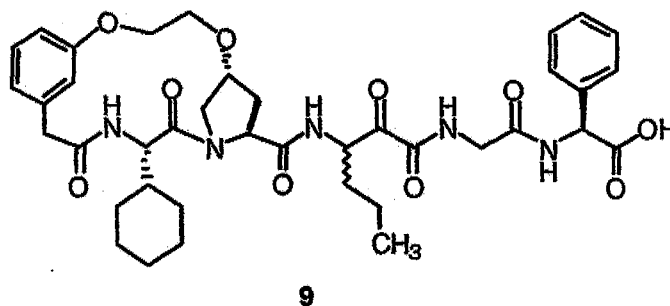
- 5 The desired compound 7A and 7B were prepared from 7j according to the procedure of Example 1, Step K.

Example 8: Preparation of Compound of Formula 8:

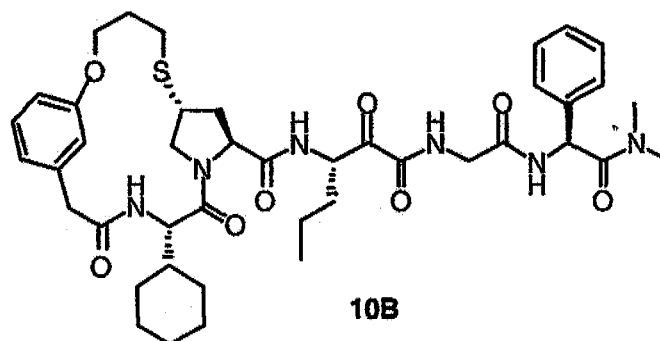
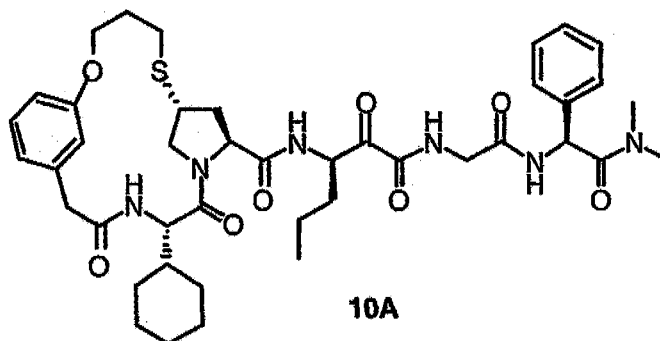
119

72
~~00074~~Step B:

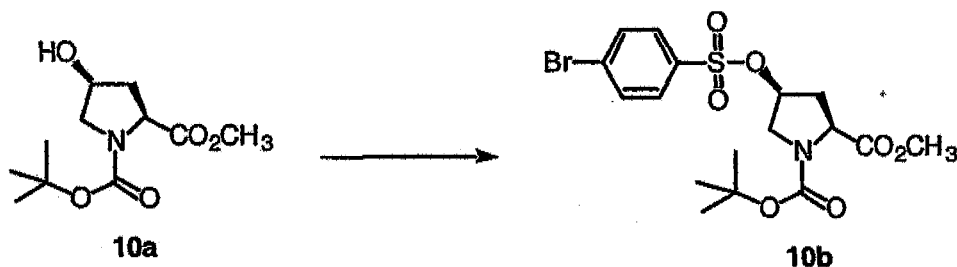
- 5 The desired compound 8 was prepared in 72 % yield from 8a according to the method of Example 1, Step K.

Example 9: Preparation of Compound of Formula 9:

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Example 10: preparation of Compounds of Formula 10A and 10B:**Step A:**

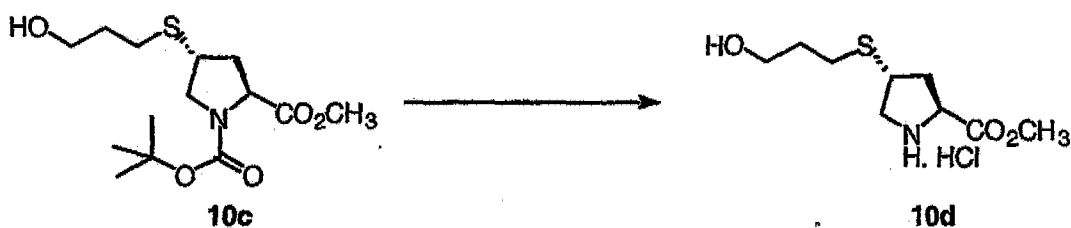
5



To a 0°C solution of 10a (10 g, 41 mmol) in dichloromethane (60 mL) was added triethylamine (28.68 mL, 204 mmol) slowly. 4-bromobenzenesulfonyl chloride (20.91 g, 82 mmol) and DMAP (few crystals) were then added and the temperature was maintained at 0°C for 30 min. The reaction mixture was left standing in the refrigerator (~5°C) overnight followed by slow warming to ambient temperature over two hours. At this time TLC analysis revealed complete consumption of the starting material. The reaction mixture was diluted with

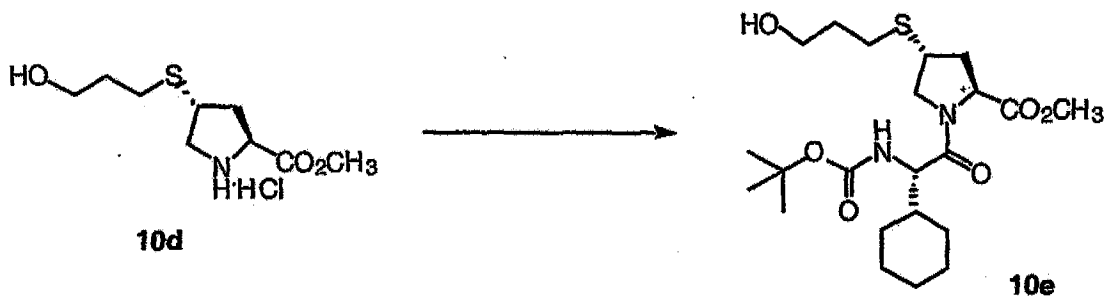
2.34 (m, 2H), 2.69 (t, 2H), 3.23-3.49 (m, 2H), 3.73-3.78 (m, 5H), 3.86-3.95 (m, 1H), 4.33-4.37 and 4.42-4.46 (2dd, 1H); ^{13}C NMR (mixture of rotamers, CDCl_3) δ 28.21, 28.30, 32.15, 32.23, 36.65, 37.27, 40.45, 40.89, 52.16, 52.35, 52.50, 52.84, 58.32, 58.55, 61.22, 61.41, 80.35, 153.49, 153.99, 173.05, 173.23; HRMS (FAB) Calcd for $\text{C}_{14}\text{H}_{26}\text{NO}_5\text{S}$: 320.1532 ($\text{M}+\text{H}$) $^+$. Found: 320.1528.

Step C:



The desired compound **10d** was prepared by the protocol described for Example 1, Step C. Reaction conditions were 0°C , 1hr. The material was carried to the next step as it was.

Step D:



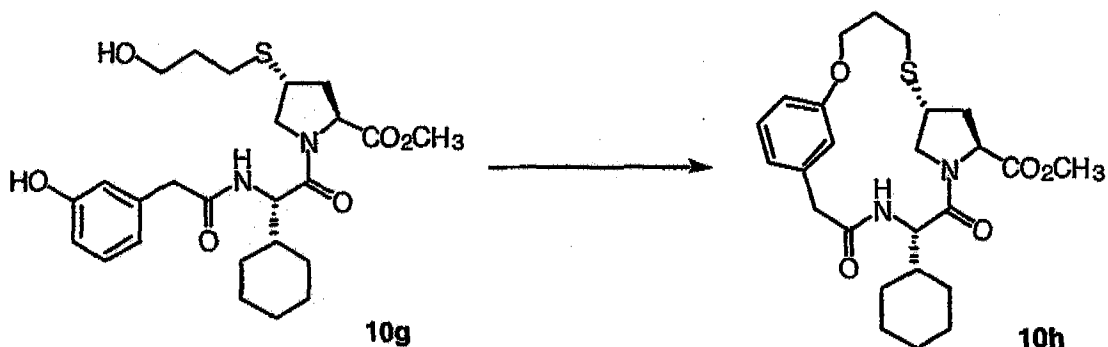
The desired compound **10e** was prepared by the method described for Example 1, Step D. The coupling reaction was carried out at -8°C for 2 days. After workup the product **10e** was sufficiently pure by TLC and was obtained in 80% yield; HRMS (FAB) Calcd for $\text{C}_{22}\text{H}_{39}\text{N}_2\text{O}_6\text{S}$: 459.2529 ($\text{M}+\text{H}$) $^+$. Found: 459.2523.

75

171.87, 171.96; HRMS (FAB) Calcd for $C_{25}H_{37}N_2O_6S$: 493.2372 ($M+H$)⁺.

Found: 493.2364.

Step G:

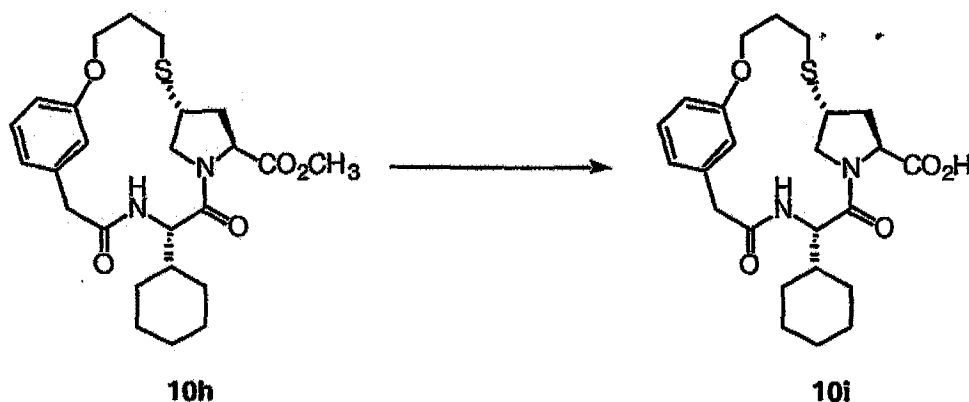


The desired compound **10h** was prepared by the protocol described for Example 1, Step G. The crude product was suspended in 80/20 ethyl acetate/hexane, and the solid material was filtered off. The filtrate was concentrated and purified by flash column chromatography using 80/20

hexane/acetone to yield 22% of **10h** as a solid. ¹H NMR ($CDCl_3$) δ 0.98-1.30 (m), 1.64-1.90 (m), 2.06-2.14 (m, 1H), 2.16-2.21 (dd, 2H), 2.62-2.70 (m, 2H), 3.38-3.46 (m, 2H), 3.60-3.66 (m, 3H), 3.71 (s, 3H), 3.88-3.94 (dd, 1H), 4.07-4.15 (m, 1H), 4.22-4.29 (m, 1H), 4.48 (t, 1H), 4.60 (t, 1H), 5.97 (br t, 1H), 6.76-6.81 (m, 2H), 6.99 (br s, 1H), 7.20 (dd, 1H); HRMS (FAB) Calcd for $C_{25}H_{35}N_2O_5S$: 475.2267

($M+H$)⁺. Found: 475.2260.

Step H:



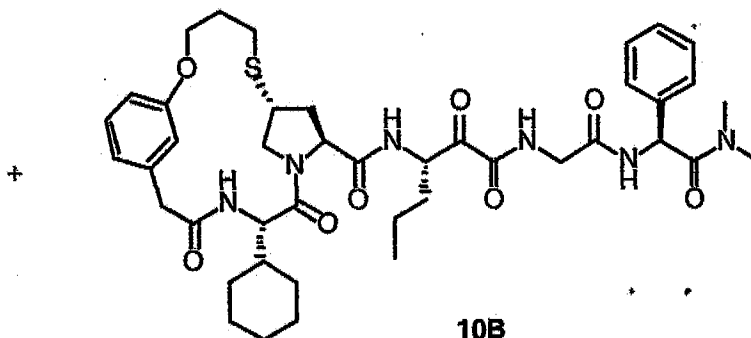
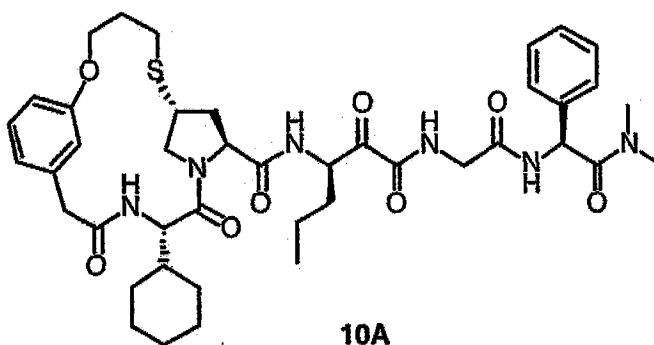
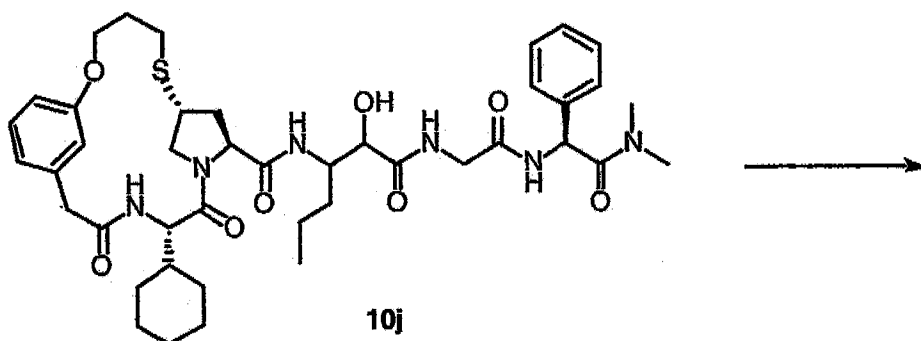
127

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76

workup was sufficiently pure by TLC for further manipulations; HRMS (FAB)

Calcd for $C_{42}H_{59}N_6O_8S$: 807.4115 ($M+H$)⁺. Found: 807.4103.

Step J:

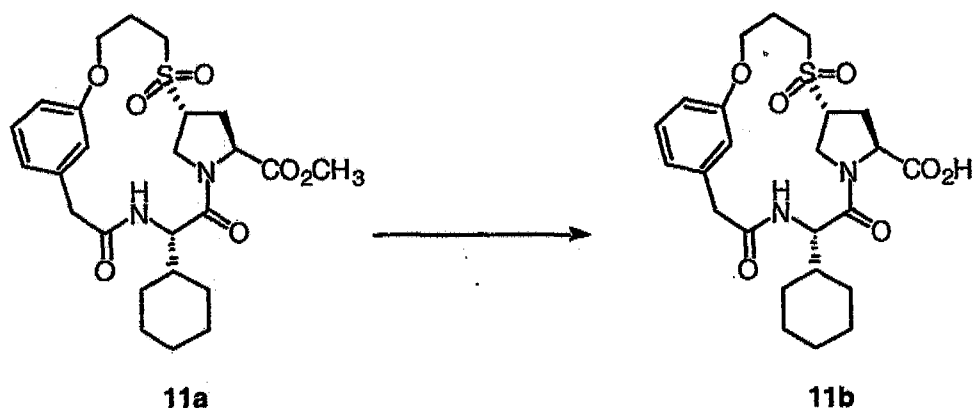


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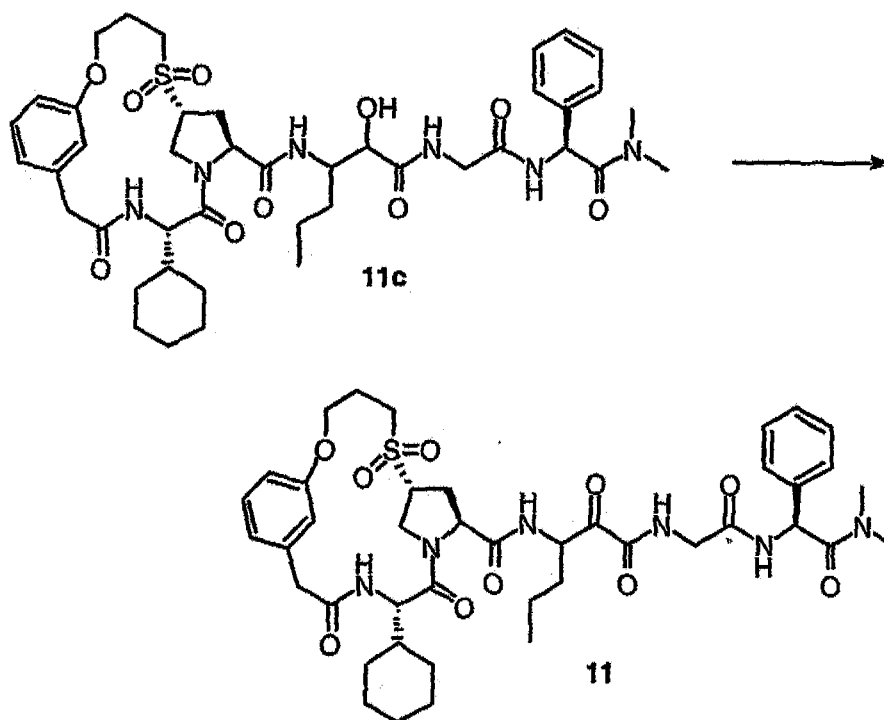
To a solution of **10j** (180 mg, 0.22 mmol) in dichloromethane was added sequentially DMSO (0.313 mL, 4.4 mmol), DCC (908 mg, 4.4 mmol), and dichloroacetic acid (36.4 μ L, 0.44 mmol). The reaction mixture was stirred overnight at ambient temperature. It was quenched by addition of aqueous 5% citric acid solution (5mL) and MeOH (1mL) and stirred for 30 min. The solid

To a cold (0°C) solution of **10h** (200 mg, 0.42 mmol) in dichloromethane (10 mL) was added MCPBA (60%, 364 mg, 1.26 mmol). The reaction mixture was slowly warmed to ambient temperature over 16 hrs. The reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate and sodium bisulfite solution. The organic layer was dried (Na₂SO₄), and concentrated. Purification by flash column chromatography using 98/2 dichloromethane/methanol provided **11a** (138 mg, 65% yield). HRMS (FAB) Calcd for C₂₅H₃₅N₂O₇S: 507.2165 (M+H)⁺. Found: 507.2158.

Step B:



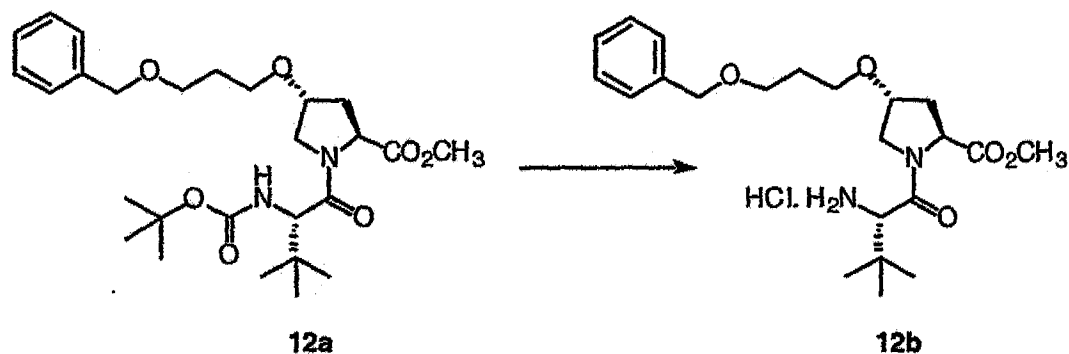
The expected product **11b** was synthesized as described for Example 1, Step I in 90% yield as a white solid; HRMS (FAB) Calcd for C₂₄H₃₃N₂O₇S: 493.2008 (M+H)⁺. Found: 493.2012.

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78Step D:

- 5 The desired product **11** was obtained by the oxidation protocol described earlier for Example 1, Step K. Purification by flash column chromatography using 98/2 dichloromethane/methanol afforded **11** in 4% yield (2 steps). HRMS (FAB) Calcd for $C_{42}H_{57}N_6O_{10}S$: 837.3857 ($M+H$)⁺. Found: 837.3865.

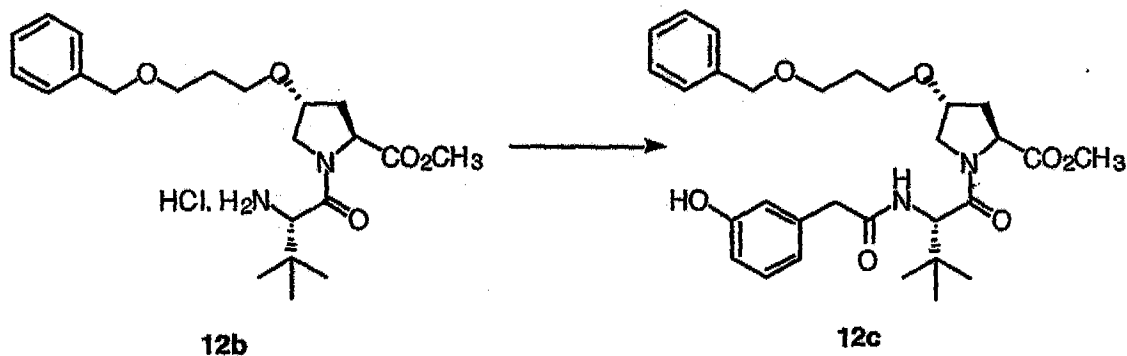
138.45, 155.62, 165.06, 171.13, 172.54; HRMS (FAB) Calcd for $C_{27}H_{43}N_2O_7$: 507.3070 (M+H)⁺. Found: 507.3077.

Step B:



The desired compound **12b** was prepared by the protocol described for Example 1, Step E. The material was carried forward to the next step.

Step C:

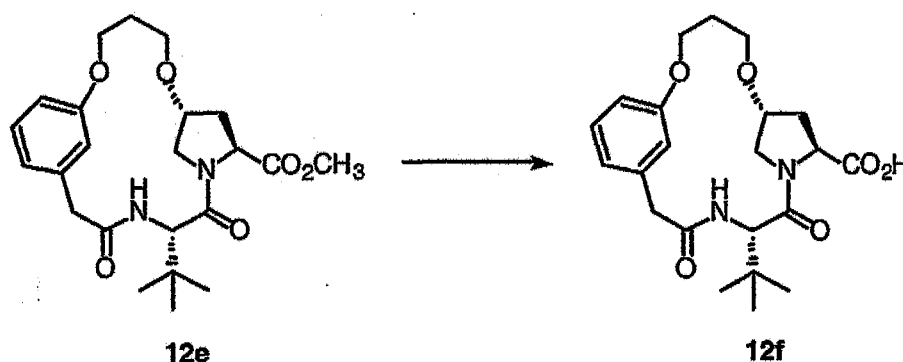


The desired product **12c** was obtained by the procedure described for Example 1, Step F. The material was purified by flash column chromatography using 99/1 dichloromethane/methanol to yield **12c** in 91%. ¹³C NMR (CDCl₃) δ 26.24, 29.93, 34.95, 35.96, 43.48, 52.18, 53.09, 57.06, 58.06, 66.10, 66.92, 72.93, 77.43, 114.59, 116.14, 120.87, 127.58, 127.64, 127.74, 128.37, 130.02,

process once again, the filtrate was concentrated and applied on the column as a dichloromethane solution. The column was eluted with 75/25 hexane/acetone to yield 29% of **12e**. HRMS (FAB) Calcd for $C_{23}H_{33}N_2O_6$: 433.2339 ($M+H$)⁺.

Found: 433.2339.

5 Step F:



The advanced intermediate **12f** was synthesized as described for Example
10 1, Step I, in quantitative yield; ¹H NMR (DMSO-d₆) δ 0.96 (s, 9H), 1.66-1.70 (m, 1H), 1.75-1.82 (m, 2H), 2.43 (dd, 1H), 3.32-3.36 (m, 2H), 3.48-3.52 (m, 1H), 3.55 (dd, 1H), 3.84 (app. d, 1H), 3.99 (app. d, 1H), 4.06-4.10 (m, 3H), 4.16 (dd, 1H), 4.69 (d, 1H), 6.70-6.72 (m, 3H), 7.15 (app. t, 1H), 8.42 (d, 1H), 12.43 (br. s, 1H); ¹³C NMR (DMSO-d₆) δ 26.25, 28.54, 33.31, 34.97, 41.22, 53.96, 56.11, 56.97,
15 63.36, 64.96, 76.84, 111.94, 115.25, 121.73, 129.13, 138.36, 158.27, 169.85, 170.15, 173.04; HRMS (FAB) Calcd for $C_{22}H_{31}N_2O_6$: 419.2182 ($M+H$)⁺.
Found: 419.2180.

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81

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the pamphlet!

WO 01-77113

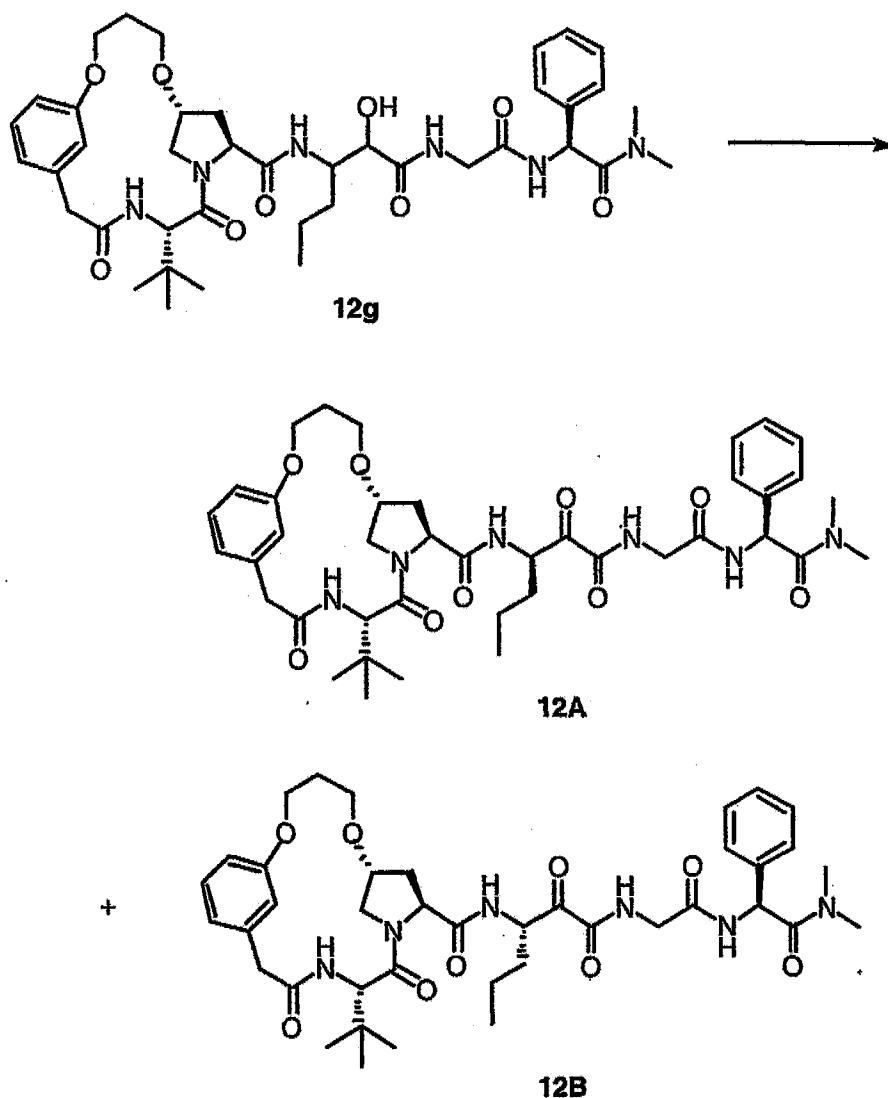
2/3

Date: 18 oct 2001

Destination: Agent

Address:

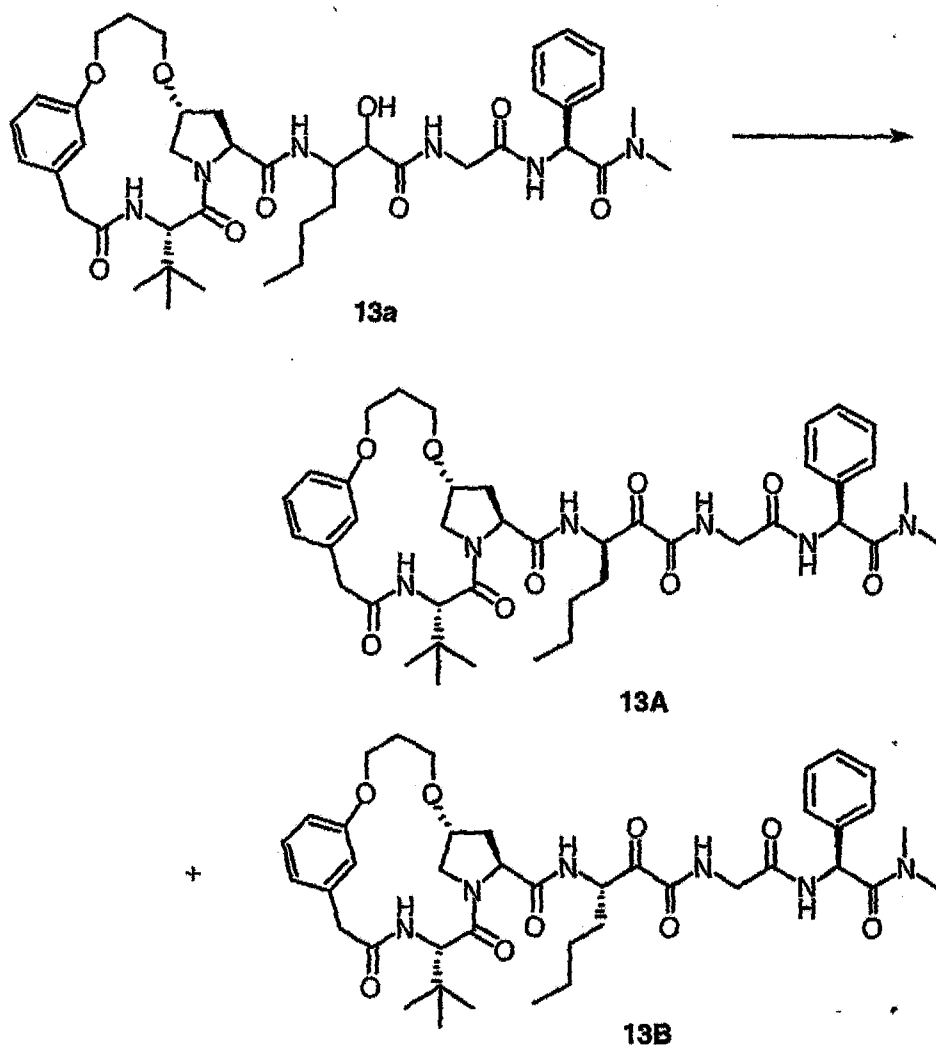
137

Step H:

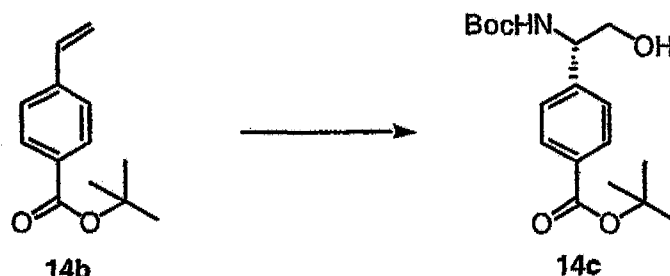
- 5 The desired products **12A** and **12B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 98/2 to 96/4 of dichloromethane/methanol afforded separate isomers **12A** and **12B**, and some mixture. Combined yield = 57% (for 2 steps). HRMS (FAB) Calcd for $C_{40}H_{55}N_6O_9$: 763.4031 ($M+H$)⁺. Found:
- 10 763.4040 (**12A**), 763.4047 (**12B**).

The expected product **13a** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step. HRMS (FAB) Calcd for C₄₁H₅₉N₆O₉: 779.4344 (M+H)⁺. Found: 779.4350.

5 Step B:



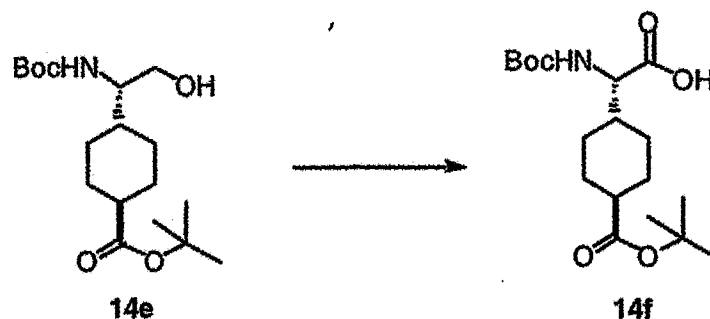
10 The desired products **13A** and **13B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 100/0 to 96/4 dichloromethane/methanol afforded separate isomers **13A** and **13B**, and some mixture. Combined yield = 50% (for 2 steps).

Step B:

- 5 A solution of tert-butyl carbamate (5.96 g, 50.9 mmol) in 1-PrOH (68 mL) was treated with aq. NaOH (128 mL, 0.41 M) and tert-butyl hypochlorite (5.5g, 50.9 mmol). The reaction mixture was cooled to 0° C and (DHQ)2Phal (780 mg, 1.00 mmol) in 1-PrOH (64 mL) was added. A solution of tert-butyl-4-vinylbenzoate **14b** in 1-PrOH (119 mL) was added followed by K₂OsO₄•H₂O (248 mg, 0.7
- 10 mmol) and the reaction mixture was stirred at 0° C for 4-5 h. The reaction turns green and all the starting material disappears with a new product formed. The reaction mixture was concentrated in vacuo and the residue was diluted with H₂O (300 mL) and extracted with EtOAc (3x100 mL). The combined organic layer was extracted with aq. HCl (200 mL), brine(100 mL) dried (Na₂SO₄) filtered conc. in
- 15 vacuo and purified by chromatography (SiO₂, EtOAc/Hexanes 1:2) to yield **14c** as a colorless solid (4.6 g, 82%). ¹H NMR (CD₃OD, δ) 7.90 (d, 2 H, J=6.0 Hz), 7.40 (d, 2 H, J=6.3 Hz), 7.22 (bd, 1 H, J=5.7 Hz), 4.69 (bs, 1 H), 3.71-3.62 (m, 2 H) 1.58 (s, 9 H), 1.39 (s, 9 Hz); ¹³C NMR (CD₃OD, 75 MHz) 169.7, 160.5, 149.8, 134.5, 132.9, 130.4, 84.7, 82.9, 68.7, 60.7, 31.25, 30.9 MS (FAB) 675.2 ([2M+1]⁺, 15), 338 ([M+1]⁺, 15), 282 (65), 225 (50), 165 (100); HRMS calcd for C₁₈H₂₈NO₅ (M+1): 338.1887; found 338.1967.
- 20

85

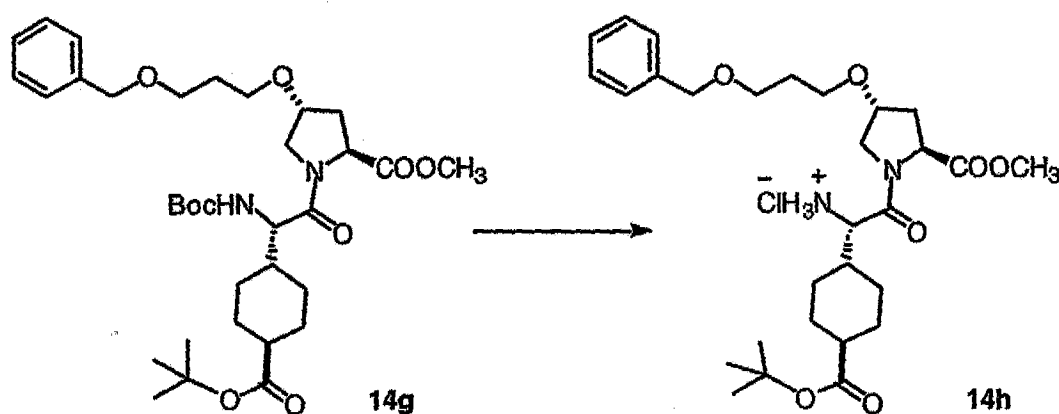
A solution of amino alcohol **14d** (3.3 g, 11.08 mmol) in dry THF (200 mL) was cooled to -78 °C (dry ice/acetone, internal temperature -68°C) was treated with LDA (44 mL, 2M soln in heptanes, 88 mmol, 8.0 equiv.). The reaction mixture was stirred at -78° C for 2 h and quenched with CH₃OH (20 mL). The reaction mixture was treated with aq. HCl (150 mL, 1 M) and extracted with ether (3x100 mL). The combined ether layer was extracted with brine (50 mL) dried (MgSO₄), concentrated in vacuo and purified by crystallization from boiling hexanes. The solid separating out from the mother liquor was predominantly *cis* stereo isomer, where concentration of the mother liquor gave the pure *trans* isomer. The above sequence was repeated twice more to obtain 2.7 g of the trans compound and 600 mg of *cis/trans* mixture. ¹³C NMR (CDCl₃, 75 MHz) 175.3, 156.6, 79.8, 63.6, 57.0, 44.1, 38.3, 37.7, 28.9, 28.6, 28.4, 28.1, 26.6, 26.1. MS (electron spray) 344 (M⁺, 50), 288 (50) 232 (90), 188 (100).

Step F:

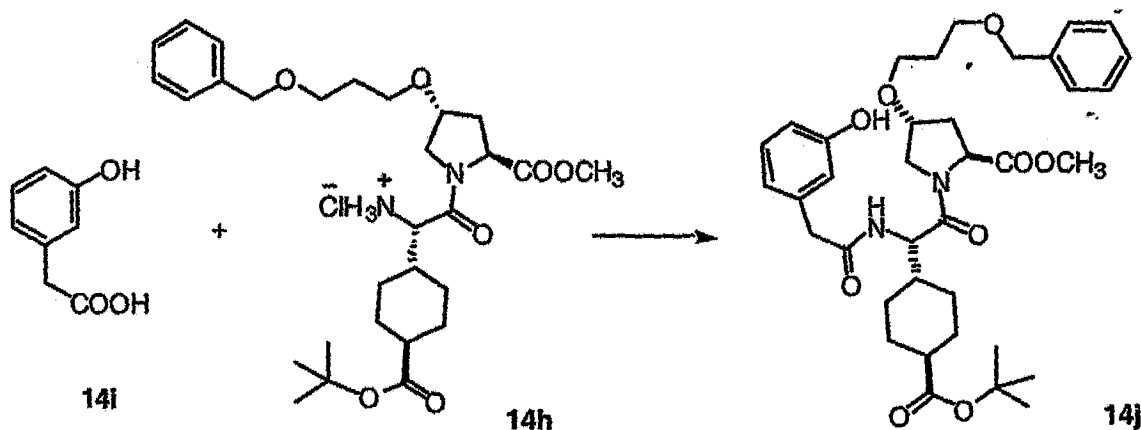
A solution of alcohol **14e** (2.6 g, 7.6 mmol) in CH₃CN (150 mL) and CCl₄ (150 mL) was treated with H₂O (22 mL), cooled to 0°C, treated with periodic acid (7.05 g, 30.92 mmol, 4.0 equiv.) and RuCl₃•3H₂O (60 mg, 0.3 mmol, 4 mol%). The reaction mixture was stirred at rt. for 3h, and concentrated in vacuo. The residue was diluted with water (150 mL) and extracted with EtOAc (3x100 mL). The combined organic layer was extracted with H₂O (100 mL) and with aq. NaOH (1M, 3x100 mL). The combined aq. layers were acidified with HCl (6M, pH ~1) and extracted with EtOAc (3x100 mL). The ethyl acetate layers were pooled, extracted with brine (100 mL) dried (Na₂SO₄) filtered concentrated in vacuo to yield acid **14f** (1.8 g, 66%) used for further couplings without further purification. MS (FAB)

145

127.5, 127.4, 127.3, 79.8, 79.7, 79.0, 77.5, 72.5, 66.7, 65.4, 58.1, 56.6, 52.1, 51.3, 43.9, 40.4, 39.4, 38.6, 34.6, 29.8, 28.4, 27.9, 27.3, 26.1, 25.4, 24.5; MS (FAB) 633 ([M+1]⁺, 11), 533 (55), 477 (24), 428 (5), 294 (100), 234 (12) 156 (40), 128 (39); CHN Calcd. for C₃₄H₅₂NO₉ C 64.53% H 8.28% N 4.43%; Found C 64.41% H 8.00% N 4.19%.

Step H:

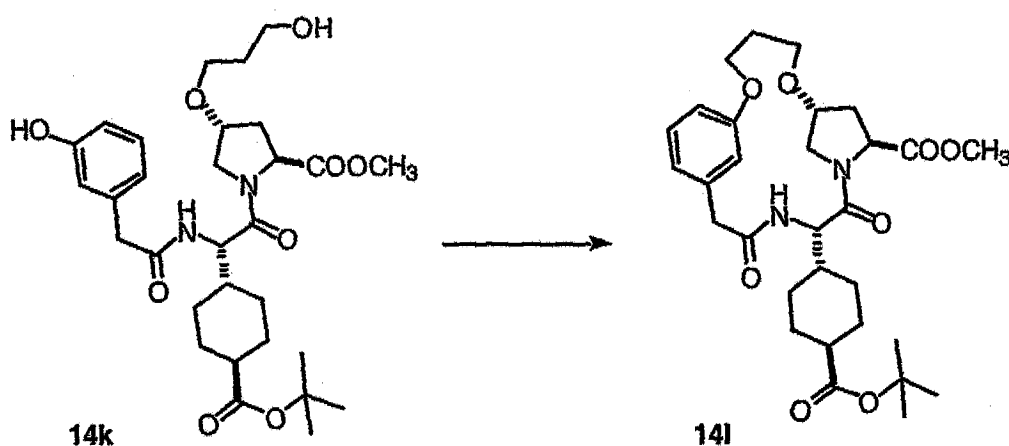
A solution of Boc-trans-4-tertbutylcarboxycyclohexyl glycine **14g** (1.8 g) in HCl (4M soln in dioxane, 60 mL) was stirred at rt. for 4-5 h. The reaction was followed by TLC (EtOAc/Hex 3:7) for the disappearance of starting material and the appearance of base line product. The reaction mixture was concentrated in vacuo and the residue was dried in the pump overnight. The solid **14h** was used for couplings without further purification.

Step I:

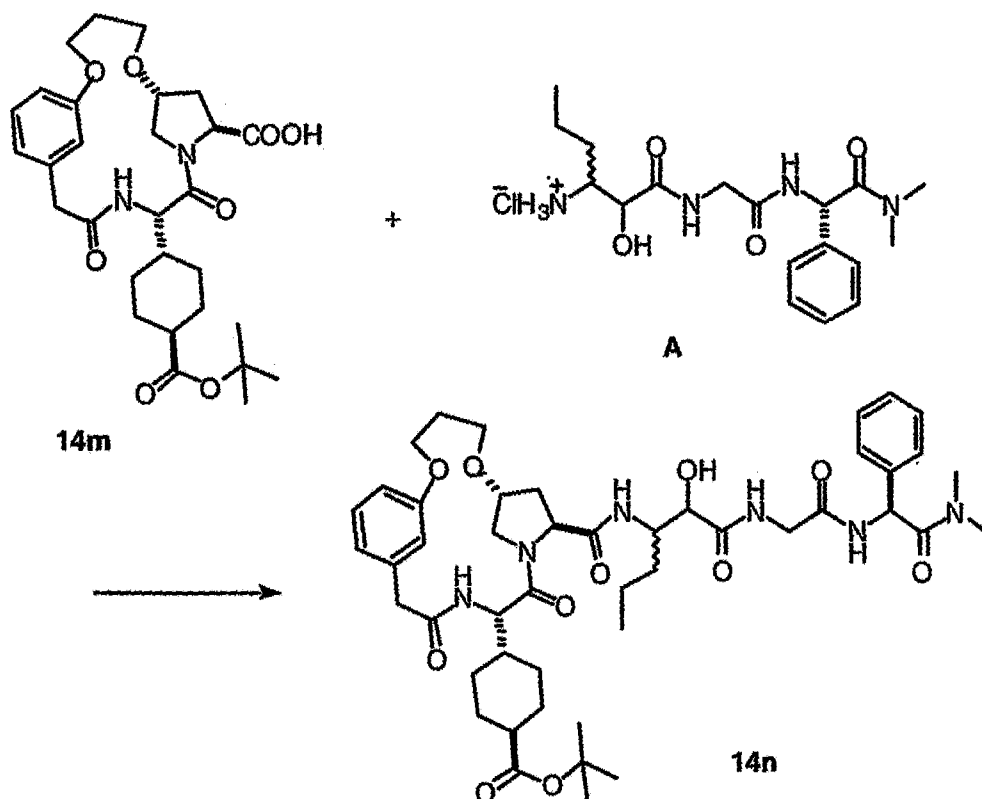
115.7, 113.6, 100.0, 94.8, 79.9, 79.8, 77.5, 65.1, 58.5, 58.2, 55.6, 55.5, 54.3, 52.2, 51.5, 43.9, 42.1, 39.4, 35.0, 32.4, 28.6, 28.4, 27.5, 27.2, 27.1, 26.1, 25.2, 25.0; MS (FAB): 577 ($[M+1]^+$, 70), 521 (10), 443 (10), 387 (10), 374 (10), 318 (15), 290 (100), 248 (30); HRMS calcd. for $C_{30}H_{45}N_2O_9$ ($M+H$) $^+$: 577.3125;

5 Found 577.3133.

Step K:

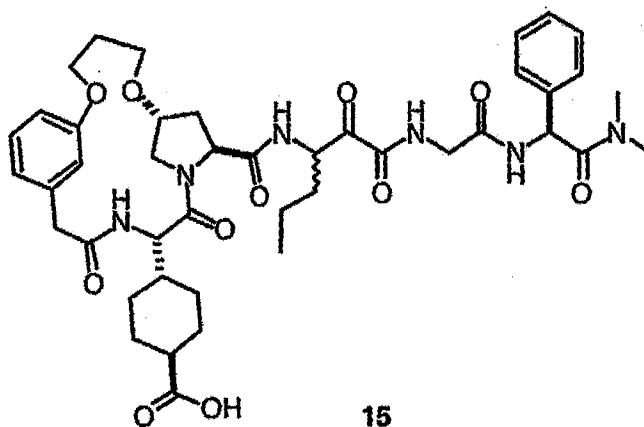


- 10 A solution of alcohol 14k (600 mg, 1.05 mmol) and ADDP (787 mg, 3.12 mmol, 3.0 equiv.) in CH_2Cl_2 (30 mL) was treated with Ph_3P (818 mg, 3.12 mmol, 3.0 equiv.) under a positive pressure of dry N_2 at 0 °C. The reaction mixture was stirred at rt. for 24 h, concentrated in vacuo and the residue was purified by chromatography (SiO_2 , acetone/Hexanes 2:3) to yield a colorless solid 14l (120
- 15 mg, 22%) of cyclic product; R_f 0.73 (acetone/Hexanes 1:1); ^1H NMR (CD_3OD , δ) 7.13 (t, 1 H $J=7.8$ Hz), 6.76 (s, 1 H), 6.71 (t, 2 H, $J=8.1$ Hz), 4.58 (d, 1 H, $J=9.9$ Hz), 4.37 (dd, 1 H, $J=7.8, 2.7$ Hz), 4.23-4.11 (m, 4 H), 3.74-3.61 (m, 2 H), 3.66 (s, 3 H), 3.59-3.40 (m, 2 H), 2.54-2.41 (m, 1 H), 2.19-2.10 (m, 1 H), 1.98-1.42 (m, 10 H), 1.43 (s, 9 H); ^{13}C NMR (CD_3OD , δ) 175.6, 172.4, 172.1, 170.8, 159.0, 137.0,
- 20 129.1, 121.7, 115.7, 112.2, 94.8, 79.8, 77.4, 65.2, 64.0, 57.6, 55.2, 53.8, 51.3, 44.0, 41.5, 39.1, 33.3, 28.7, 28.1, 26.9; MS (electron spray) 559 ($[M+1]^+$, 100) 327 (10), 189 (20); HRMS calcd. for $C_{30}H_{43}N_2O_8$ ($M+1$) $^+$: 559.3019; Found:

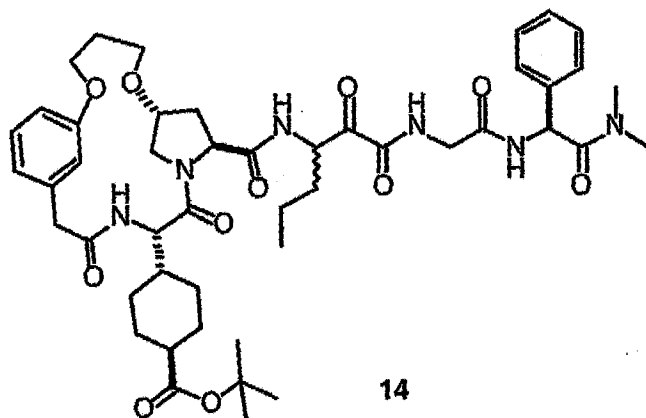
Step M:

- 5 A solution of carboxylic acid **14m** (110 mg, 0.21 mmol) in DMF (3.0 mL) and CH₂Cl₂ (5.0 mL) was treated with Hünigs base (109 mg, 0.84 mmol, 4.0 equiv. 155.0 μ L) and HOObt (52 mg, 0.315 mmol, 1.5 equiv.). The reaction mixture was cooled to 0 °C and treated with EDCI (61 mg, 0.31 mmol, 1.5 equiv.). The reaction mixture was stirred at 0 °C and treated with amine hydrochloride **A** after 30 min. The reaction mixture was stirred at rt. for 24 h and concentrated in vacuo to remove DMF and CH₂Cl₂. The residue was diluted with aq. HCl (100 mL) and extracted with CH₂Cl₂ (3x75 mL). The combined organic layers were extracted with aq. NaOH (1M, 3x50 mL), brine (100 mL) and concentrated in vacuo. The residue **14n** (79 mg) was oxidized without further purification.
- 10

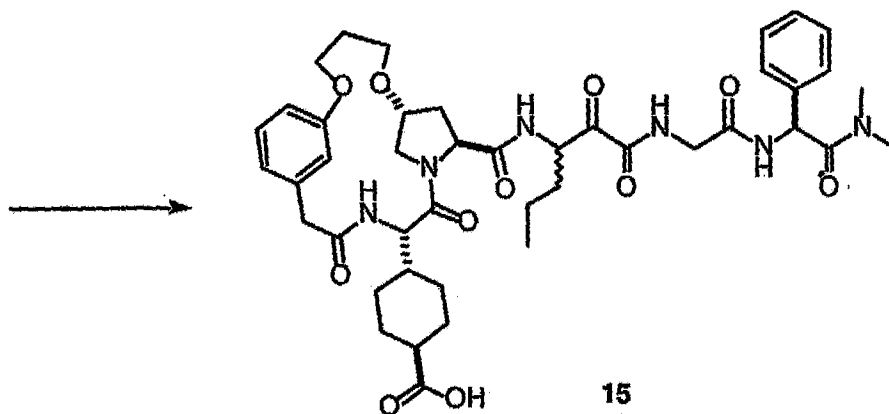
151

Example 15: Preparation of Compound 15:

15

5 Step A:

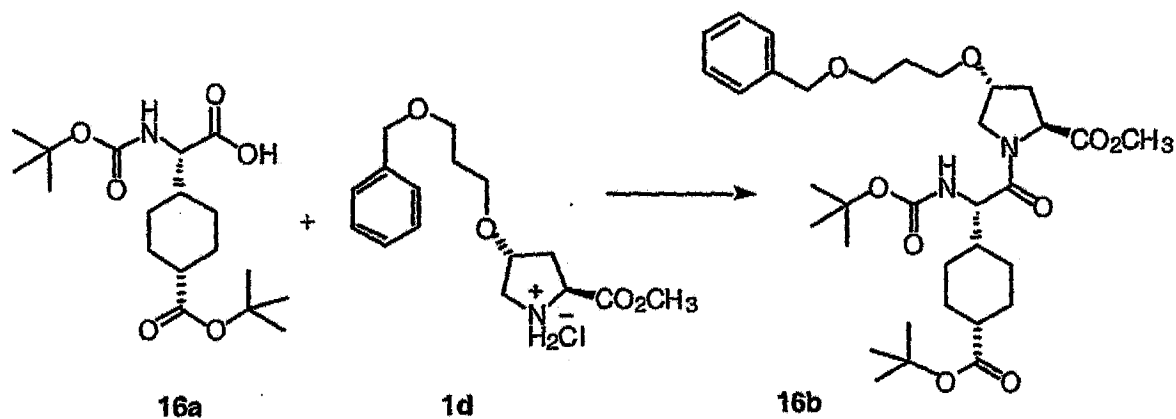
14



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258(20), 246 (100), 202 (70), 200 (20); HRMS calcd. for $C_{18}H_{32}NO_6$ ($M+1$)⁺: 358.2230; Found: 358. 2237.

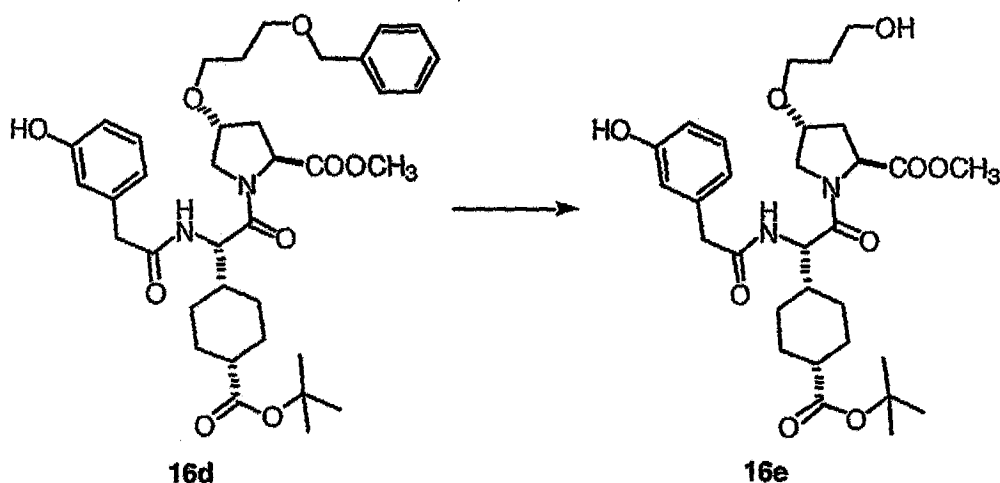
Step B:



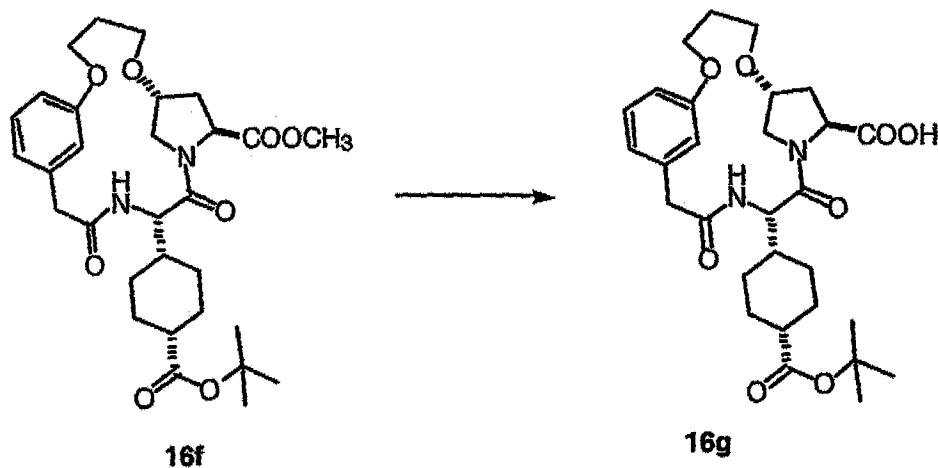
The desired compound **16b** was prepared from **16a** in 41% yield according to the procedure of Example 14, Step G; $[\alpha]_D -52.7$ (c 0.3 $CHCl_3$, 25); ^1H NMR ($CDCl_3$, δ) 7.35-7.21 (m, 5 H), 6.63 (d, 1 H, $J=9.3$ Hz), 4.46 (d, 2 H, $J=4.3$ Hz), 4.41 (t, 1 H, $J=9.3$ Hz), 4.38-4.07 (m, 3 H), 3.68 (s, 3 H), 3.66-3.43 (m, 5 H), 2.45 (p, 1 H, $J=4.2$ Hz), 2.32 (dd, 1 H, $J=7.8, 5.7$ Hz), 2.02-1.90 (m, 3 H), 1.90-1.56 (m, 3 H), 1.56-1.24 (m, 24 H); ^{13}C NMR (CD_3OD , δ) 174.7, 172.4, 172.0, 156.4, 138.4, 128.0, 127.5, 127.4, 79.8, 79.0, 77.5, 72.5, 66.6, 65.3, 58.0, 55.3, 52.1, 51.3, 40.4, 38.6, 34.7, 29.7, 27.4, 27.03, 26.1, 24.5. MS (FAB) 633.2 [($M+1$)⁺, 100]; HRMS calcd for $C_{34}H_{53}N_2O_9$ ($M+1$)⁺: 633.3751; Found 633.3759.

6 H), 2.54-2.42 (m, 1 H), 2.28-2.39 (m, 1 H), 2.1-1.9 (m, 3 H), 1.86-1.64 (4 H), 1.50-1.38 (m, 14 H); ^{13}C NMR (CDCl_3 , δ) 175.0, 172.4, 171.5, 171.1, 157.1, 138.5, 136.0, 130.1, 128.5, 127.9, 127.7, 121.0, 116.0, 114.8, 80.5, 77.6, 73.0, 66.9, 66.2, 58.2, 54.3, 52.5, 52.3, 43.4, 39.4, 39.9, 34.9, 30.0, 28.2, 26.8, 26.6, 26.0, 24.0; MS (FAB) 689 $[(\text{M}+\text{Na})^+]$, 35), 667 $[(\text{M}+\text{H})^+]$, 23), 633 (5), 294 (100), 204 (39), 156 (63).

Step E:



The desired compound **16e** was prepared from **16d** according to the procedure of Example 14, Step J. The product was used without further purification.

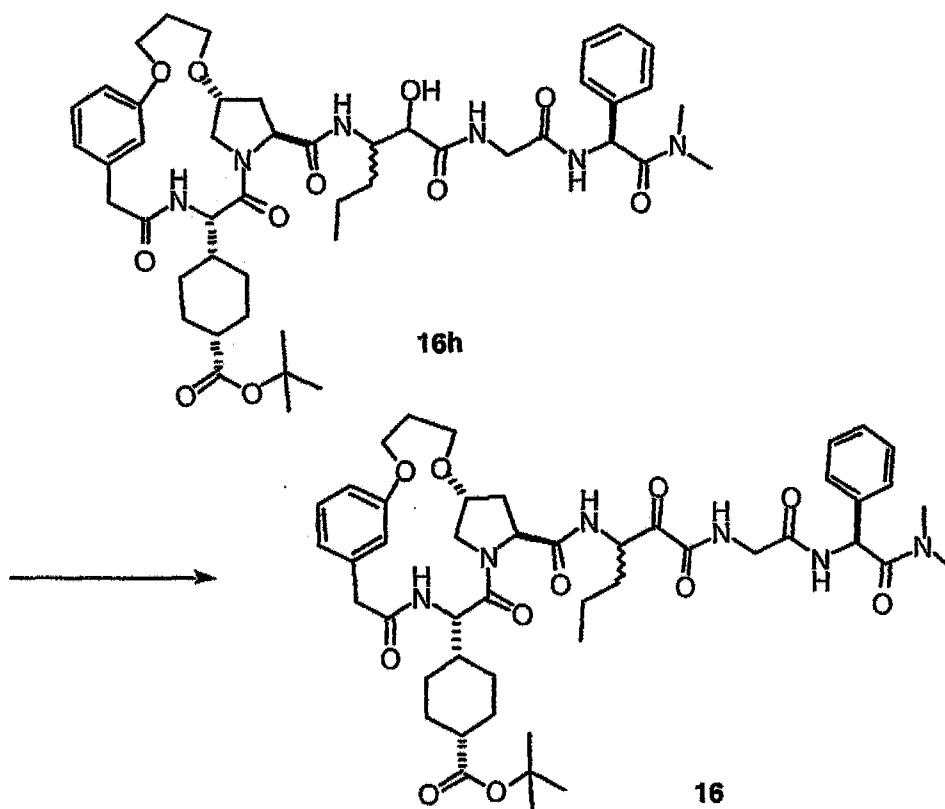
Step G:

5

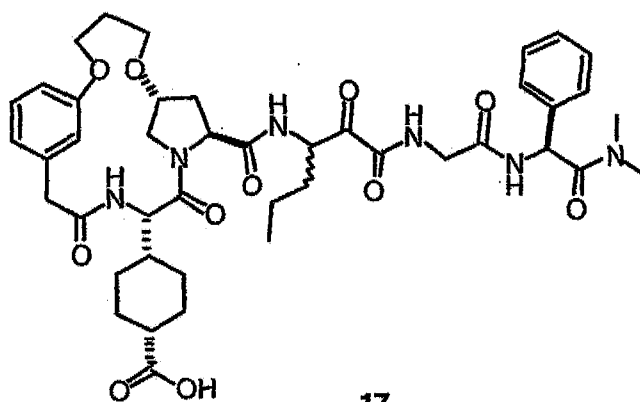
The desired compound **16g** was prepared from **16f** according to the procedure of Example 14, Step H. The product was used without further purification.

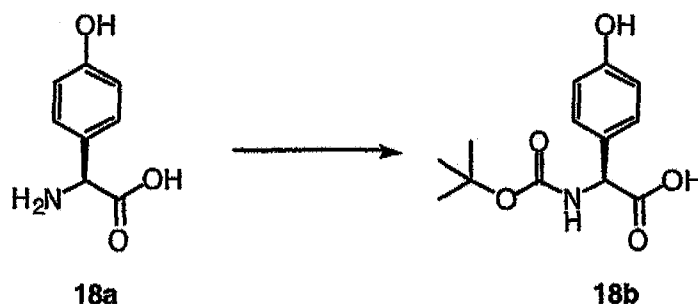
97
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93

159

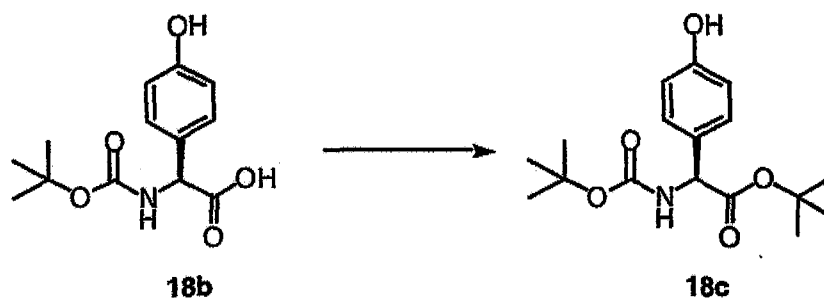
Step I

The desired compound **16** was prepared as a colorless solid from **16h** in 40% yield according to the procedure of Example 14, Step N. MS (electron spray) 889 [(M+1)⁺, 85], 637 (20), 530 (75), 265 (100); HRMS calcd. for C₄₇H₆₅N₆O₁₁: 889.4711; Found 889.4699.

Example 17: Preparation of Compound 17:

Step A:

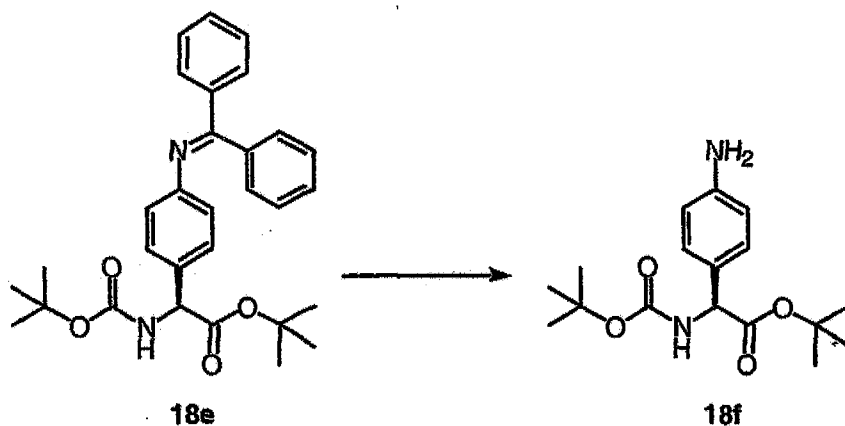
To a cold (0°C) slurry of **18a** (15.0 g, 90 mmol) in dioxane (100 mL), water (100 mL), and saturated sodium bicarbonate (100 mL) was added a solution of tert-butoxycarbonyl anhydride (7.2 g, 33 mmol) in dioxane (100 mL). The reaction mixture was slowly warmed to ambient temperature over 6 hr. The reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with diethylether (2 x 150 mL). The ether layer was discarded. The aqueous layer was acidified slowly with solid citric acid (pH ~ 4) and extracted with ethyl acetate (3 x 150 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford **18b** (14.6 g, 61% yield) as a white foam.

Step B:

To a 80°C solution of **18b** (14.6 g, 54.68 mmol) in toluene (230 mL) was added DMF-di-tert-butyl acetal (53 mL, 218.72 mmol) dropwise over 2 hrs. The reaction mixture was maintained at the same temperature for 1 hr after the addition was complete. It was then cooled to ambient temperature and

To an oven dried flask was added THF (75 mL, previously deoxygenated by bubbling argon), palladium acetate (74 mg, 0.33 mmol), R-(+)-BINAP (311 mg, 0.495 mmol), and cesium carbonate (5.38 g, 16.5 mmol) under argon atmosphere. To this mixture was added **18d** (5.0 g, 11 mmol) followed by diphenylketimine (2.77 mL, 16.5 mmol). The flask was flushed with argon and heated to reflux for 12 hrs (overnight). Cooled the reaction mixture to ambient temperature and diluted with ether (500 mL). The organic layer is washed with saturated ammonium chloride solution (2 x 300 mL), dried (Na₂SO₄) and concentrated. Purification by flash chromatography using 100/0 to 90/10 dichloromethane/ethyl acetate provided the required product **18e** (3.58 g) in 67% yield.

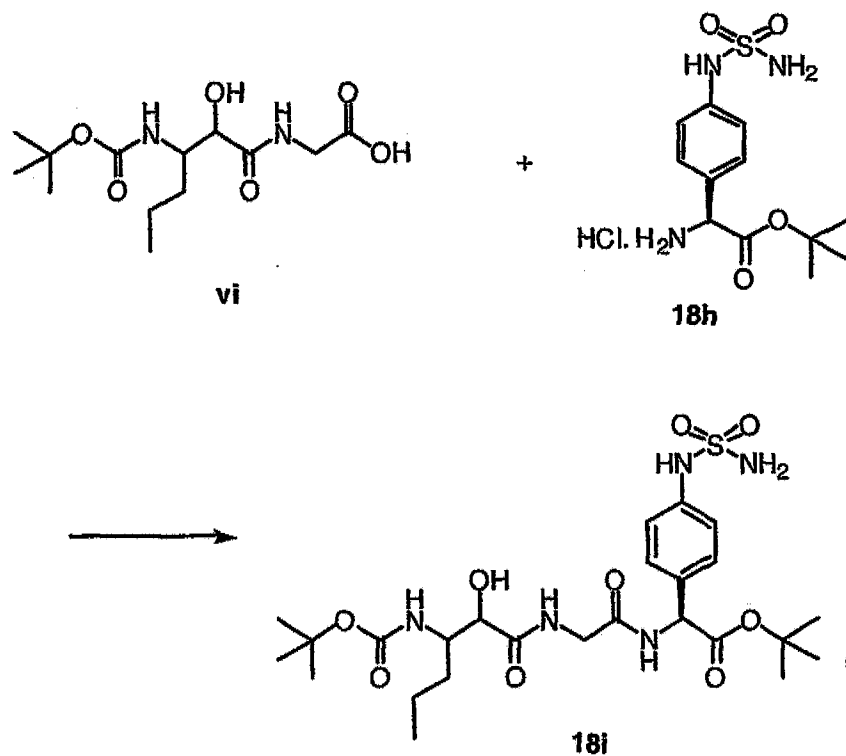
Step E:



To a solution of **18e** (3.0 g, 6.17 mmol) in methanol (62 mL) was added sodium acetate (1.218 g, 14.8 mmol), and hydroxylamine hydrochloride (0.774 g, 11.11 mmol). The reaction mixture was stirred at ambient temperature for 3 hrs. The reaction mixture was concentrated, diluted with dichloromethane and washed with 0.1 N NaOH solution. The organic layer was dried (Na₂SO₄) and concentrated. Purification by flash column chromatography using 95/5 to 92/8 dichloromethane/ethyl acetate afforded **18f** (1.31 g) in 66% yield.

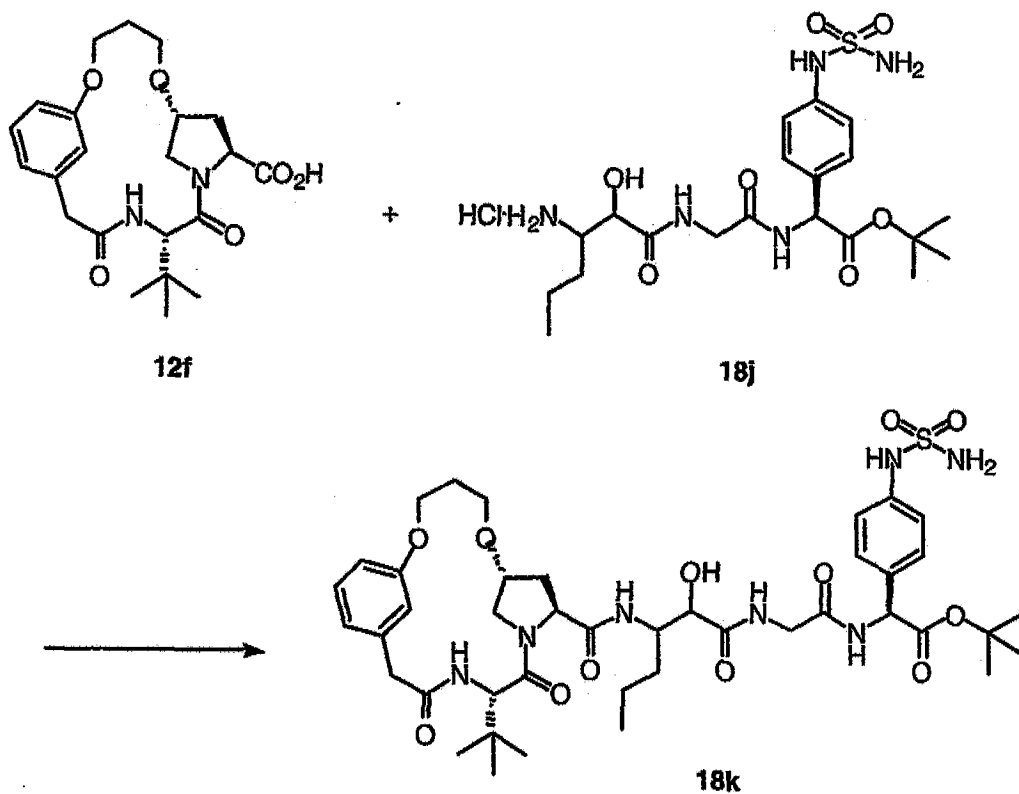
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96

165

Step H:

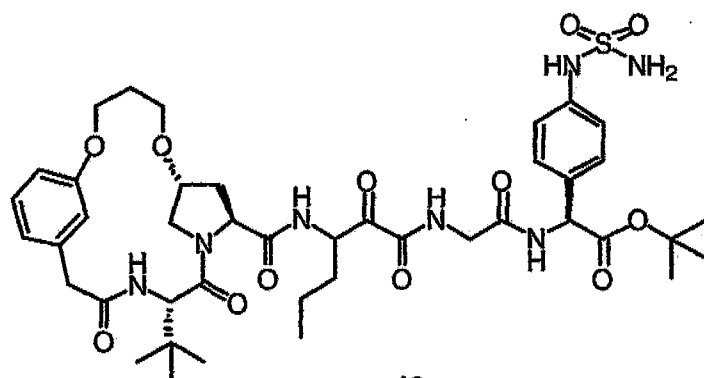
- 5 The expected product 18i was synthesized as described earlier for the Example 1, Step D. The crude material was purified by flash chromatography using 98/2 to 90/10 dichloromethane/methanol to afford 18i in 34% yield.

167

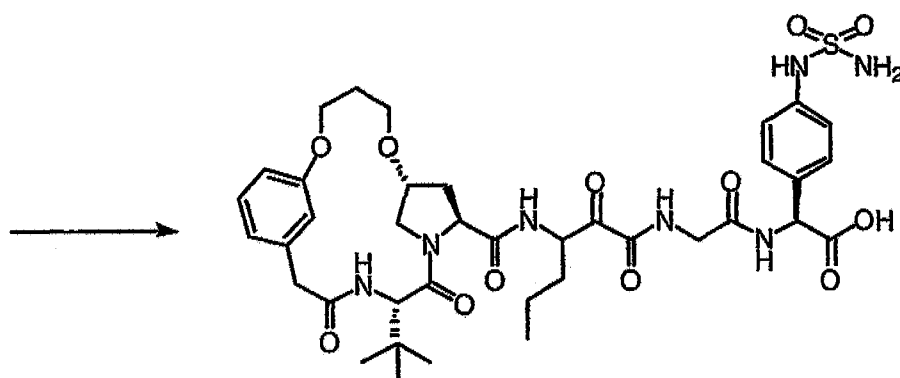
Step J:

- 5 The expected product **18k** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step.

169

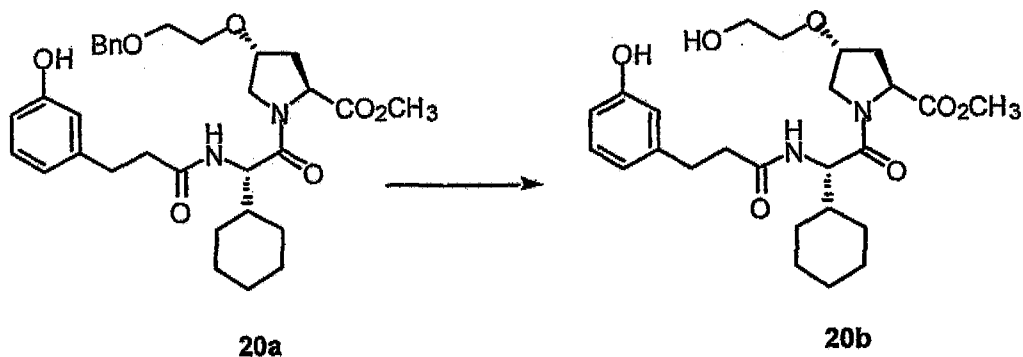
Step A:

18



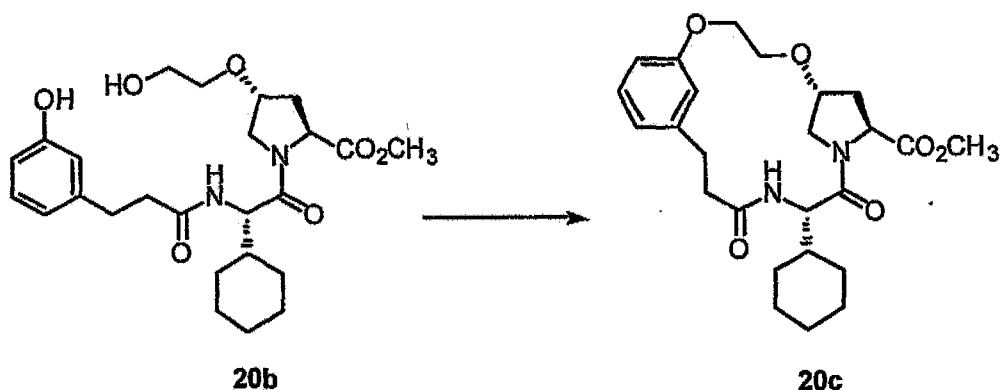
19

- 5 The expected product **19** was synthesized as described earlier for the Example 3, Step A, in quantitative yield.



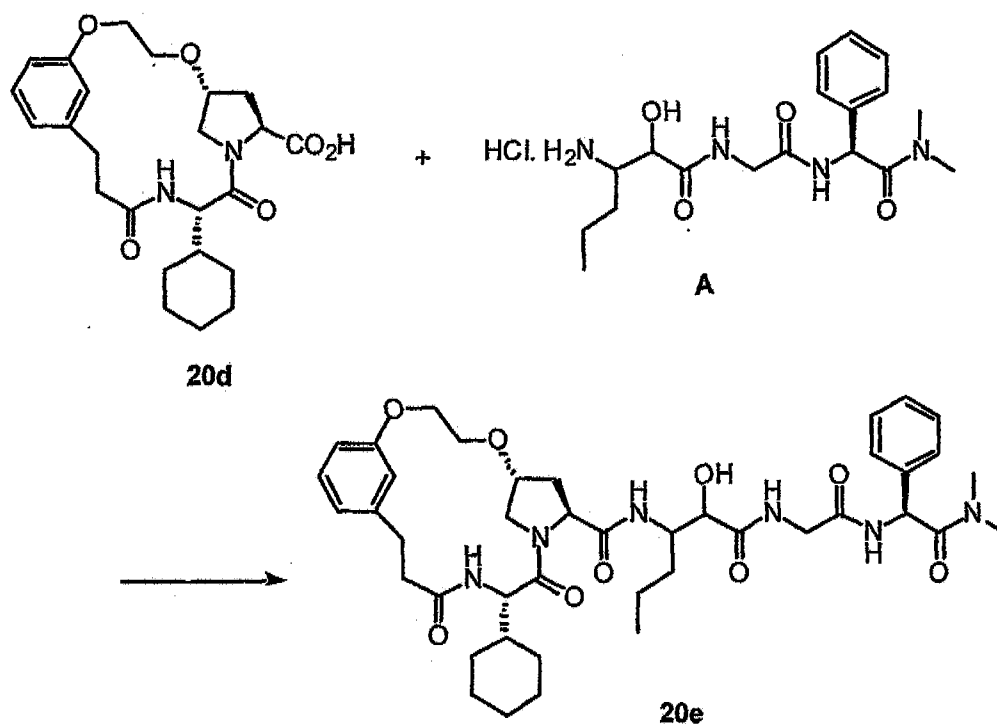
The desired product **20b** was obtained by the method described for Example 1, Step G. The material was purified by flash column chromatography using 98/2 to 96/4 dichloromethane/methanol to provide **20b** in 81% yield. HRMS (FAB) Calcd for $C_{25}H_{37}N_2O_7$: 477.2601 ($M+H$)⁺. Found: 477.2606.

Step C:



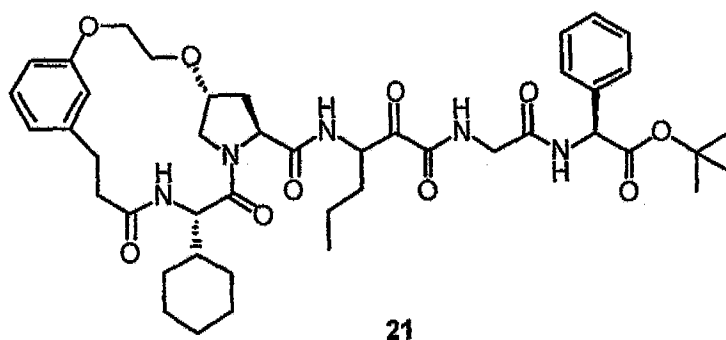
The desired product **20c** was obtained by the method described for Example 1, Step H. Purification by column chromatography using 99/1 dichloromethane/methanol afforded **20c** along with triphenylphosphine oxide. This mixture was taken to the next step. HRMS (FAB) Calcd for $C_{25}H_{35}N_2O_6$: 459.2495 ($M+H$)⁺. Found: 459.2490.

Step D:

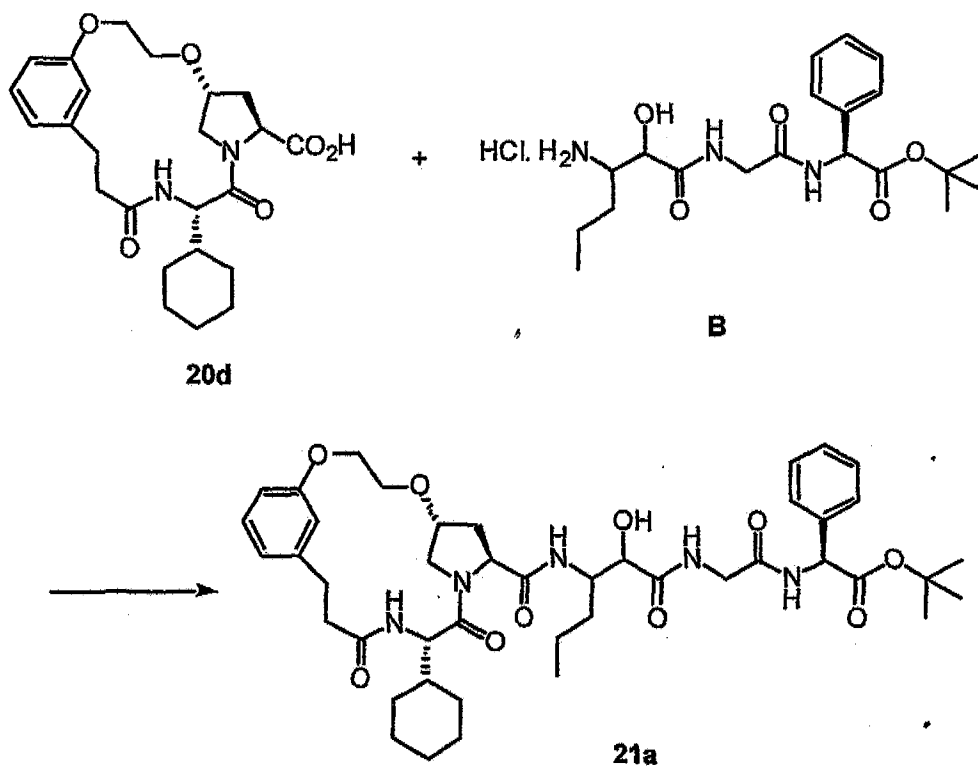


The expected product **20e** was synthesized as described earlier for the Example 1, Step J. The material after work-up was of sufficient purity to be carried forward to the next step.

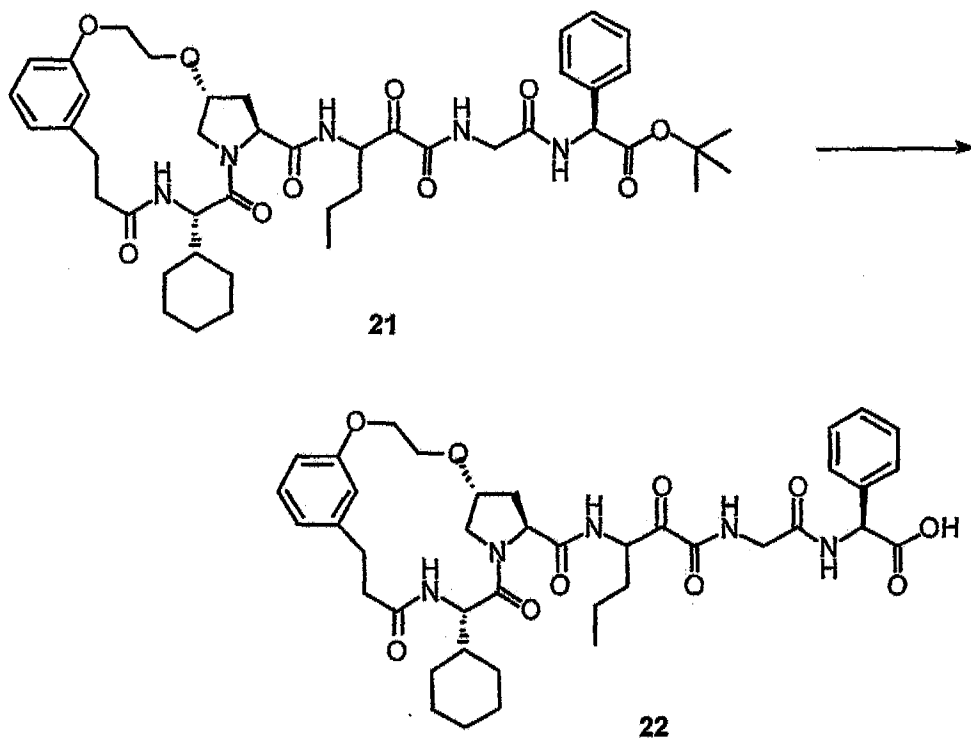
Example 21: Preparation of Compound of Formula 21:



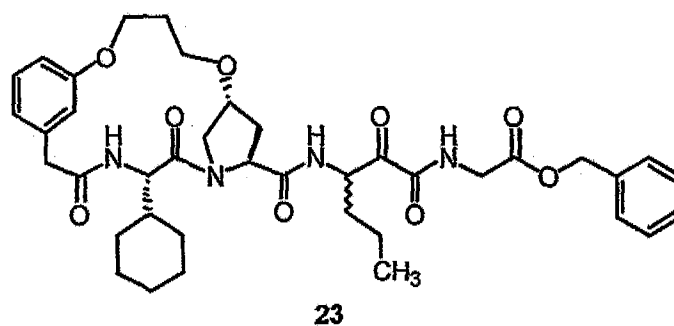
Step A:

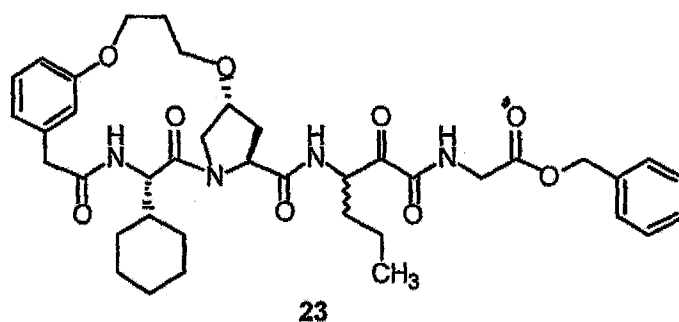
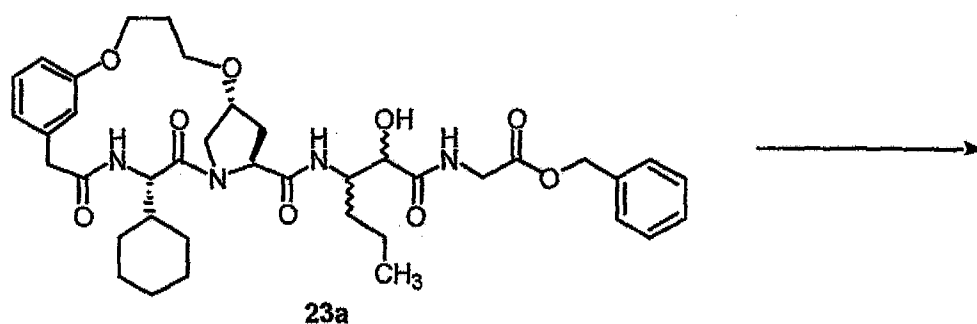


The expected product **21a** was synthesized as described earlier for the Example 2, Step A. The material after work-up was of sufficient purity to be carried forward to the next step.

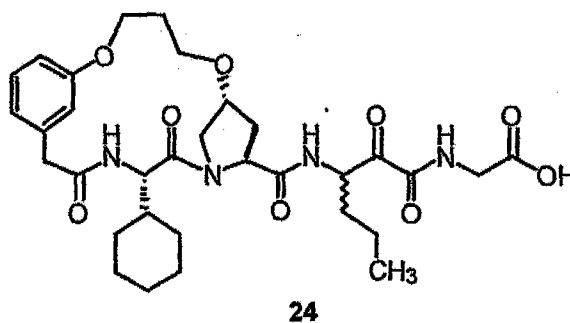
Step A:

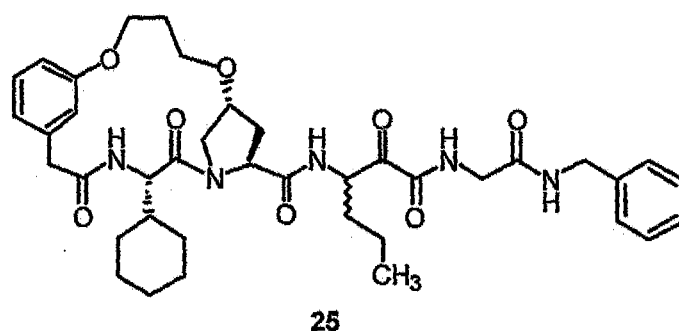
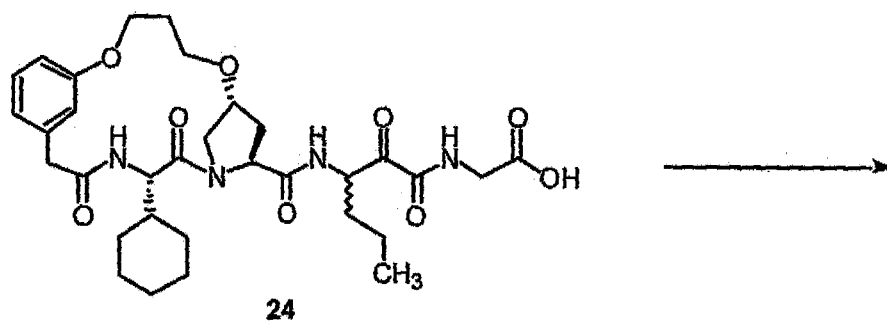
The expected product 22 was synthesized as described earlier for the Example 3, Step A, in quantitative yield. HRMS (FAB) Calcd for $C_{40}H_{52}N_5O_{10}$: 762.3714 (M+H)⁺. Found: 762.3722.

Example 23: Preparation of Compound of Formula 23:

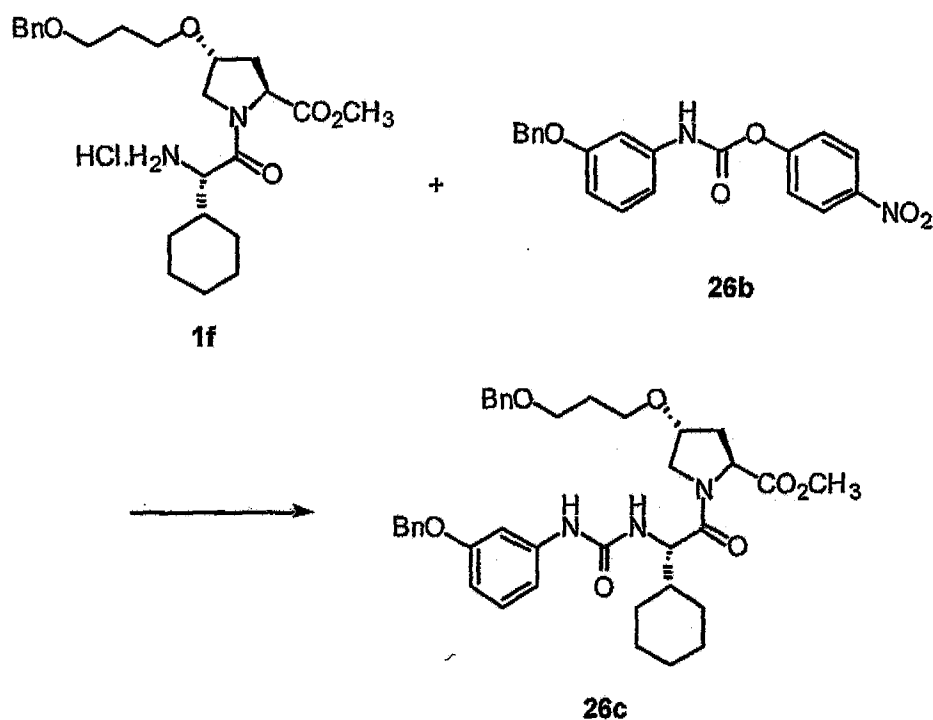
Step B:

The desired compound **23** was prepared in 79 % yield from **23a** according to the method of Example 1, Step K.

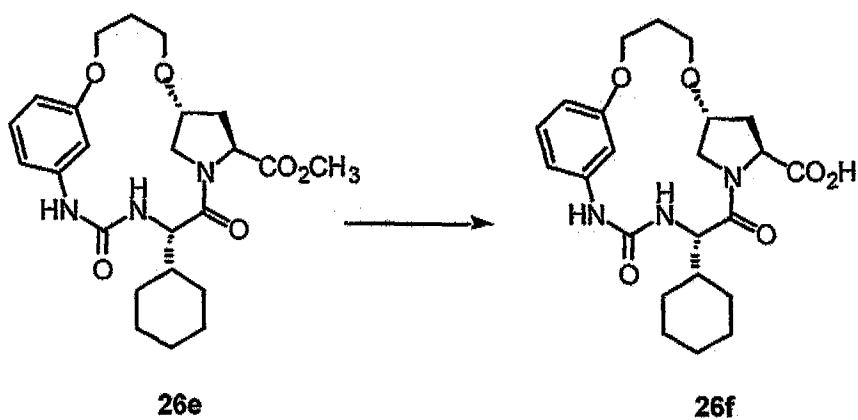
Example 24: Preparation of Compound of Formula 24:

124
~~0026~~
104Step A:

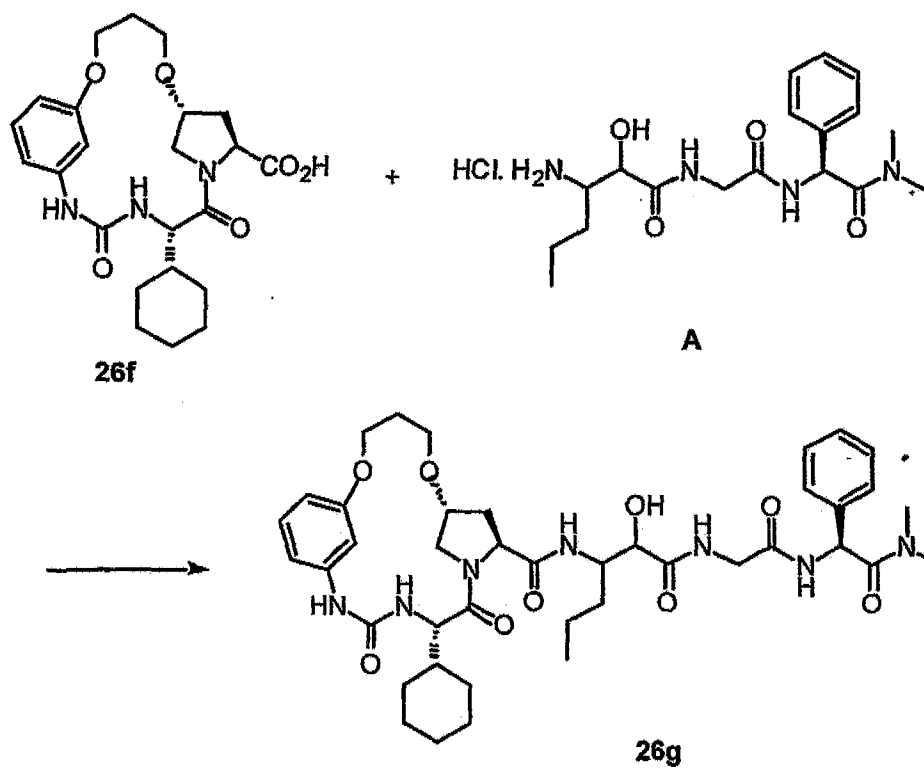
The desired compound **25** was prepared in 53 % yield from **24** according to the method of Example 1, Step J, except substituting benzyl amine for amine **A**.

125
00205
105Step B:

To a solution of **1f** (2.3 g, 5.1 mmol) in dichloromethane/DMF (25/5 mL) at 0°C was added **26b** (2.24 g, 6.1 mmol) followed by triethylamine (0.86 mL, 6.1 mmol). Few crystals of imidazole were added and the reaction mixture stored at -8°C for 16 hrs. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, 10% aqueous citric acid solution, dried (Na₂SO₄), and evaporated *in vacuo*. The crude material was purified by flash column chromatography using 100/0 to 70/30 dichloromethane/ethyl acetate to provide **26c** (1.2 g, 38% yield). HRMS (FAB) Calcd for C₃₈H₄₈N₃O₇: 658.3492 (M+H)⁺. Found: 658.3483.

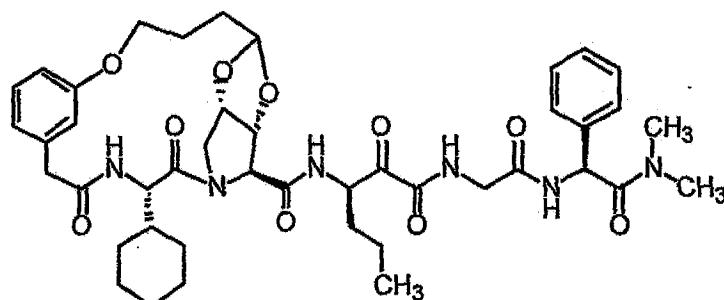
105
~~00106~~
106Step E:

The desired product **26f** was obtained by the method described for Example 1, Step I. HRMS (FAB) Calcd for $\text{C}_{23}\text{H}_{32}\text{N}_3\text{O}_6$: 446.2291 ($\text{M}+\text{H}$)⁺. Found: 446.2290.

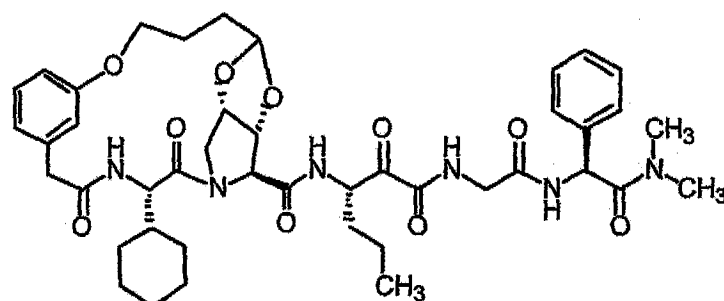
Step F:

using 99/1 to 95/5 dichloromethane/methanol provided **26A** (as a mixture) and **26B** (pure lower R_f isomer). Combined yield = 25%.

Example 27: Preparation of Compound 27:

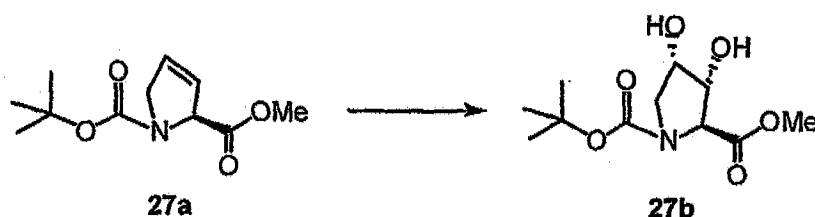


27A



27B

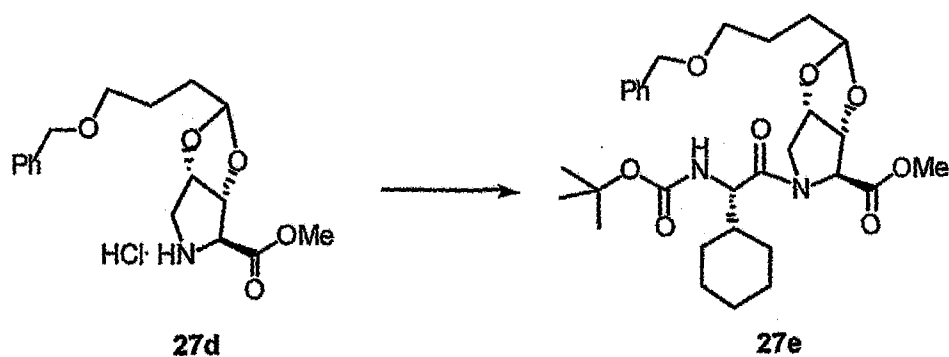
Step A



To the mixture of Boc-3,4-didehydroproline-OMe (**27a**, 5.30 g, 23.4 mmol), *N*-methylmorpholine-*N*-oxide (4.75 g, 35.1 mmol) in acetone (10 mL) and water (15 mL) at rt. was added an Osmium tetroxide solution in tert-butanol (2.5% w/w, 3.5 mL, 0.344 mmol). To this cloudy solution was added THF until the mixture became almost homogeneous. After stirred at rt. overnight, saturated aqueous sodium thiosulfate solution (30 mL) was added and 10 min later, followed by addition of EtOAc (300 mL) and brine (80 mL). After layers were separated, aqueous solution was extracted with EtOAc

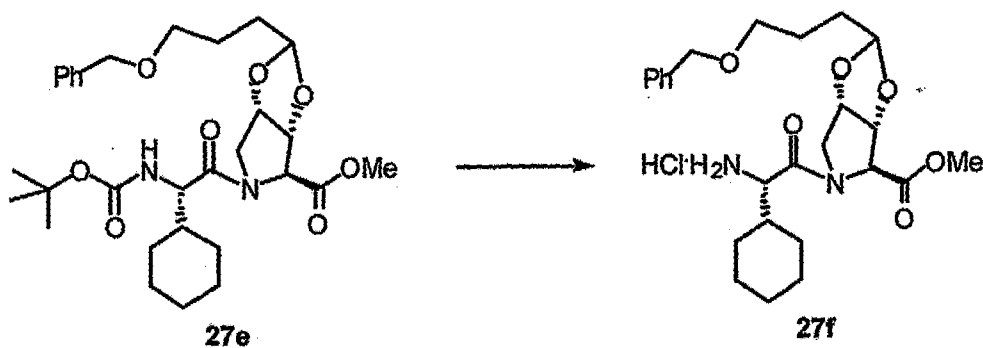
The desired compound **27d** was prepared from **27c** according to the method of Example 1, Step C. It was used in the next reaction without further purification.

Step D

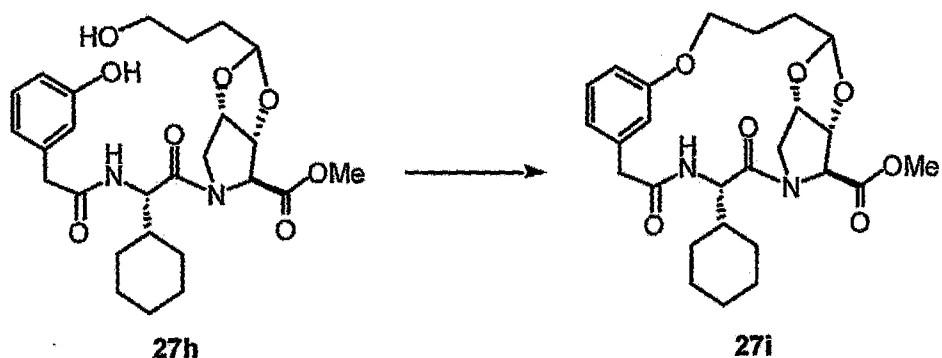


The desired compound was prepared from **27d** according to the method of Example 1, Step D. Flash chromatography (8 to 20 % EtOAc/CH₂Cl₂) afforded **27e**.

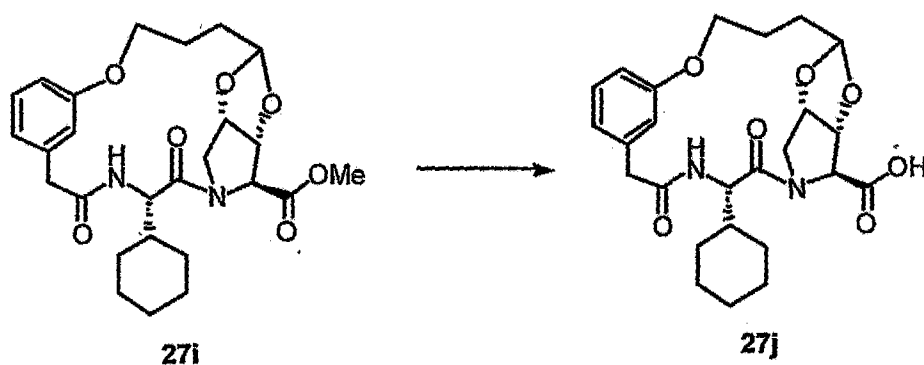
Step E



The desired compound **27f** was prepared from **27e** according to the method of Example 1, Step E. It was used in the next reaction without further purification.

00109
109Step H

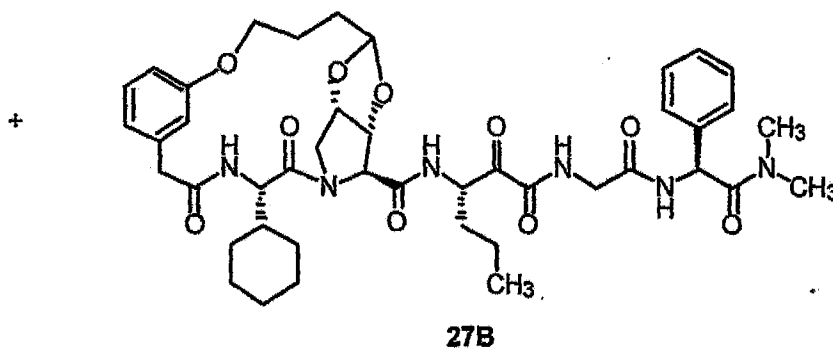
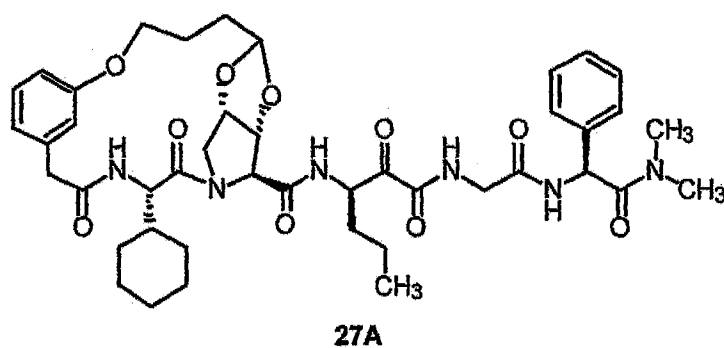
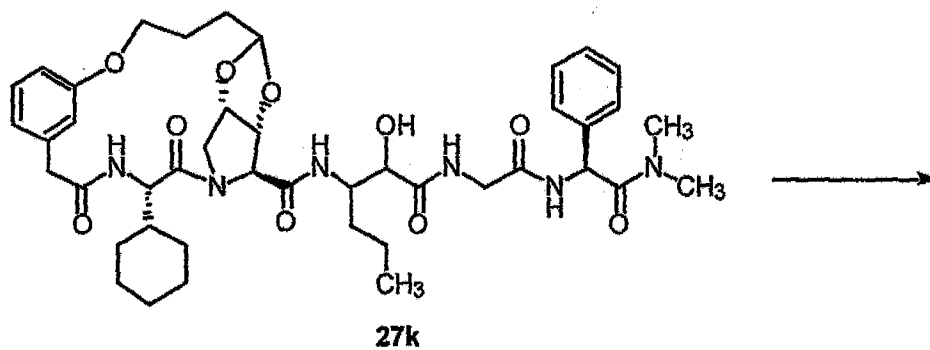
The desired compound was prepared from **27h** according to the method of Example 1, Step H. Flash chromatography (3 to 5 % MeOH/CH₂Cl₂) afforded **27i** as a mixture with triphenylphosphine oxide which was hydrolyzed.

Step I

The desired compound was prepared (72%, 2 steps) from **27i** according to the method of Example 1, Step I.

00117

110

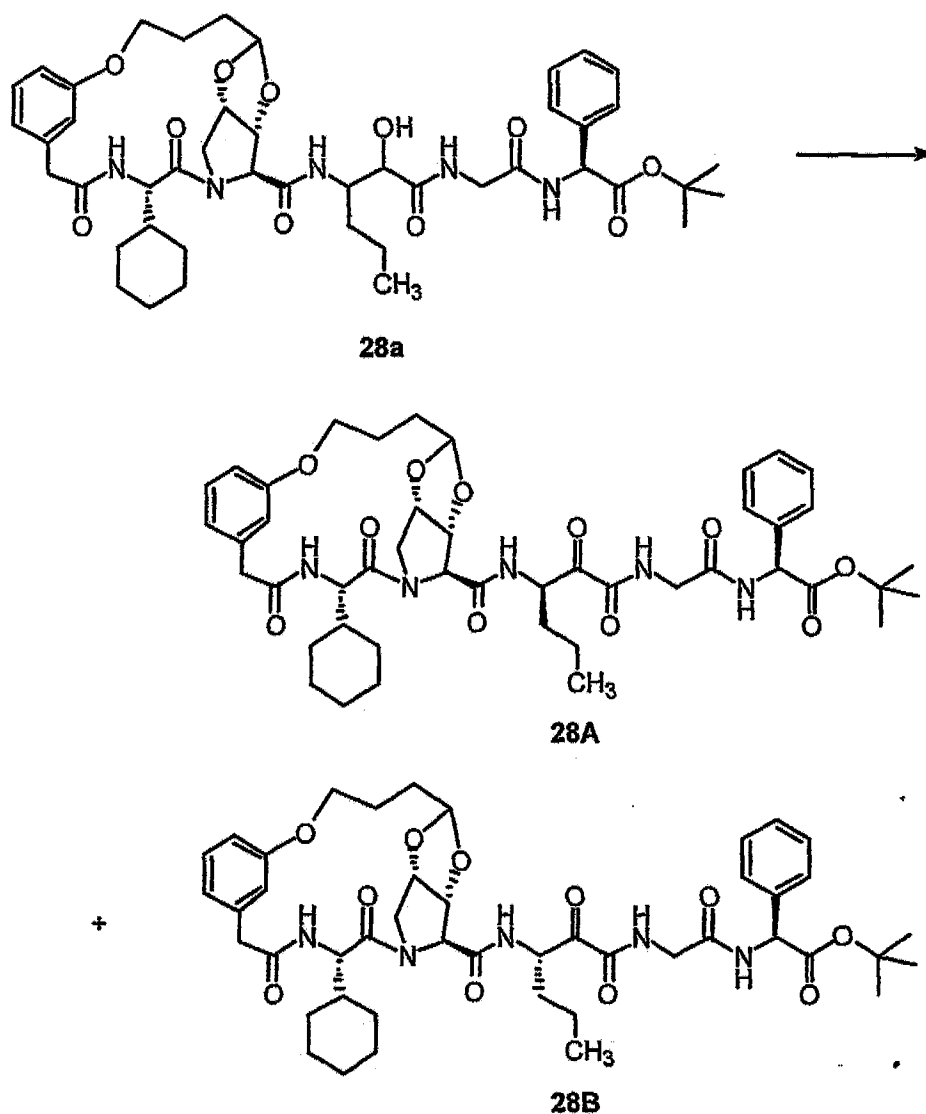
Step K

The desired compound was prepared from **27k** according to the method of Example 1, Step K. Flash chromatography (2 to 5 % MeOH/CH₂Cl₂) afforded pure **27A** and **27B**.

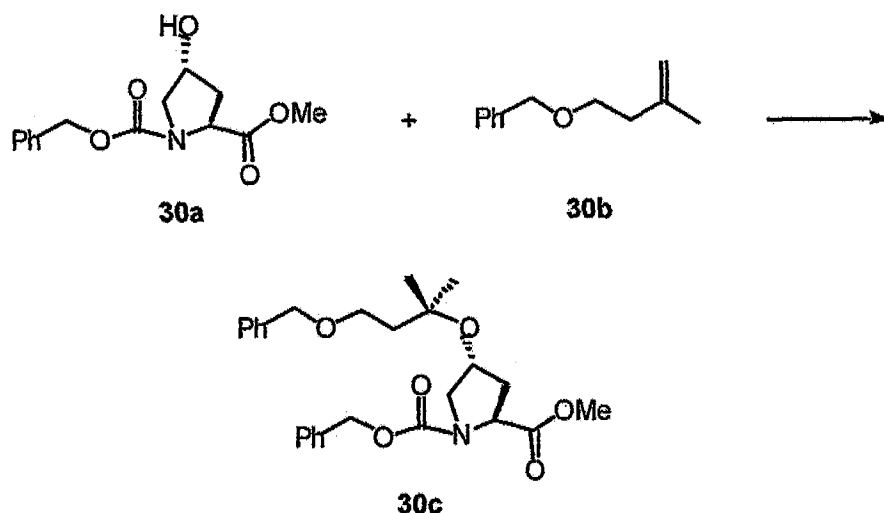
00311
111

The desired compound was prepared from **27j** according to the method of Example 2, Step A. Flash chromatography (3 to 6 % MeOH/CH₂Cl₂) afforded **28a** (50%) as a mixture of inseparable diastereomers.

Step B

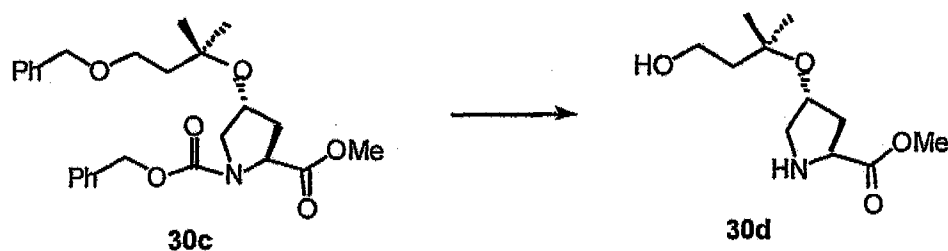


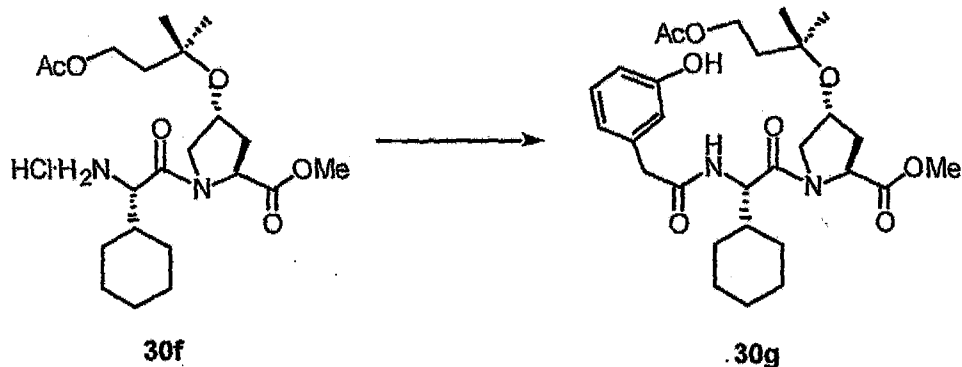
The desired compound was prepared from **28a** according to the method of Example 2, Step B. Flash chromatography (2 to 5 % MeOH/CH₂Cl₂) afforded **28A** and **28B**.

Step A:

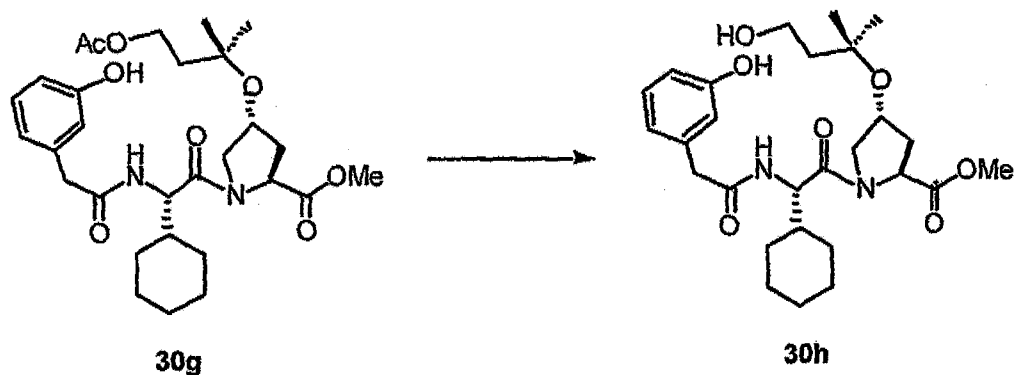
To a solution of the Cbz-HYP-OMe (**30a**) (3.0 g, 10.7 mmol) and 4-benzyloxy-2-methyl-1-butene **30b** (5.30 g, 30.0 mmol) in anhydrous CH_2Cl_2 (80 mL) at 0°C was added trifluoroboron diethyl etherate (0.25 mL, 1.97 mmol). The resulting mixture was stirred at rt. overnight (18 h). Saturated sodium bicarbonate solution (30 mL), brine (50 mL) and EtOAc (300 mL) were added and the layers were separated. The aqueous solution was extracted with EtOAc

(2 X 100 mL) and the combined organic solution was dried (MgSO_4), filtered and concentrated in vacuo to give a yellow oil. Flash chromatography (5 to 20 % EtOAc/ CH_2Cl_2) afforded **30c** (2.00 g, 4.39 mmol, 41 %) as an oil.

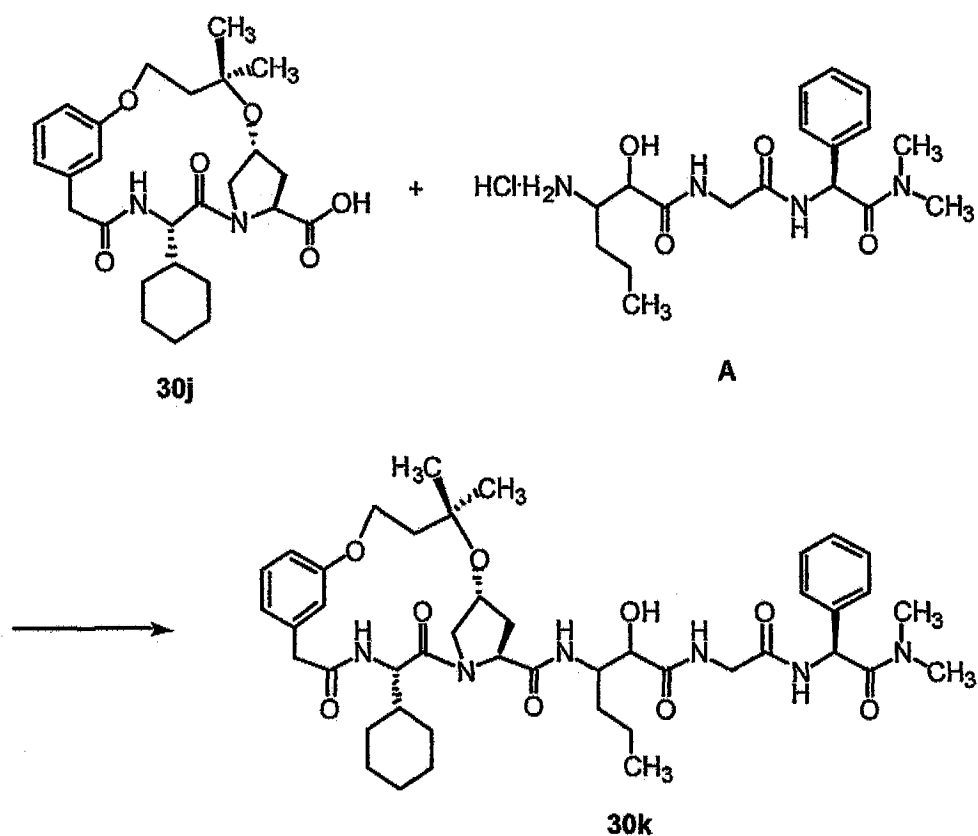
Step B:

Step E:

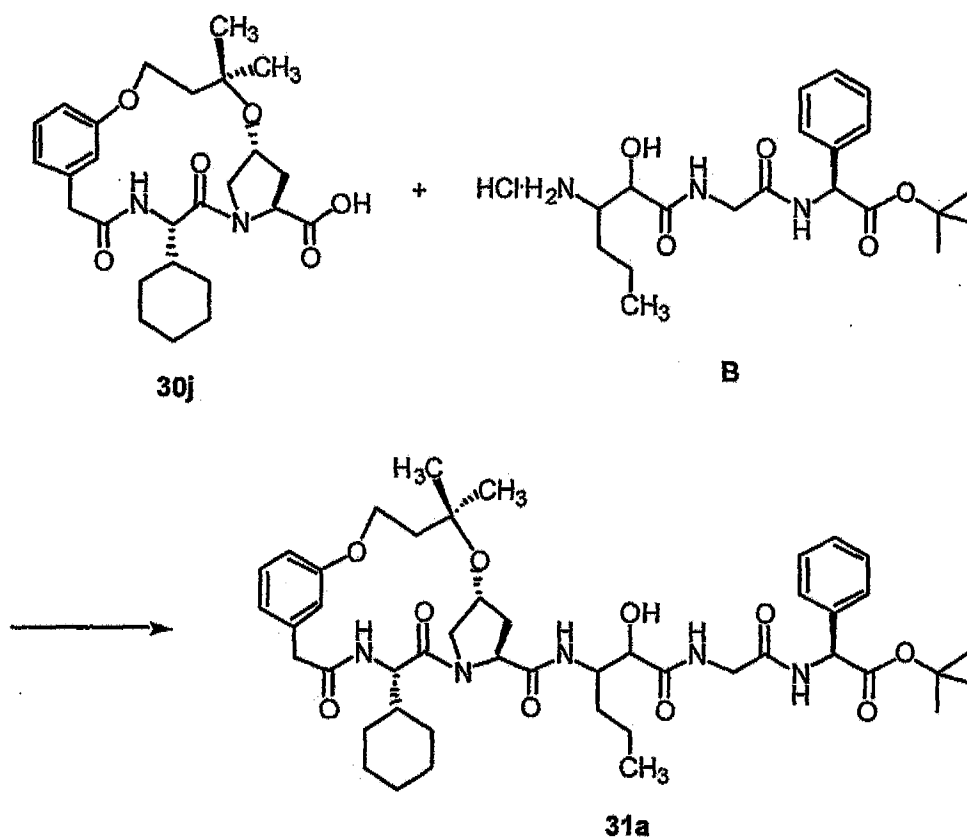
The desired compound **30g** was prepared from **30f** according to the procedure of Example 1, Step E. Flash chromatography (2 to 5 % MeOH/CH₂Cl₂) afforded **30g** (48%, 2 steps).

Step F:

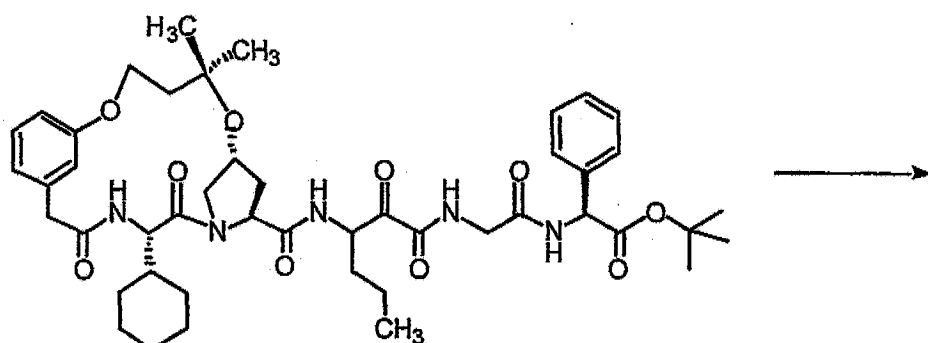
The mixture of **30g** (700 mg, 1.28 mmol) and potassium carbonate (530 mg, 3.84 mmol) in anhydrous methanol (80 mL) was vigorously stirred at rt. The reaction progress was monitored by TLC. After 3 h, it was concentrated in vacuo before EtOAc (200 mL) and water (100 mL) were added and layers were separated. The aqueous solution was extracted with EtOAc (2 X 100 mL). The organic solutions were combined, dried (MgSO₄),

00114
115Step I:

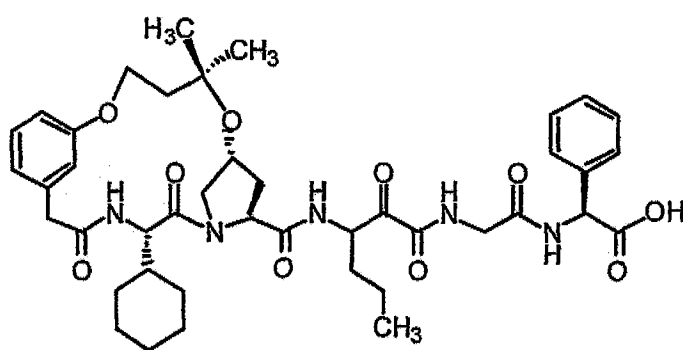
The desired compound was prepared from **30j** according to the procedure of Example 1, Step J. Flash chromatography (3 to 6 % MeOH/CH₂Cl₂) afforded **30k** (58%).

GO 2 13
116Step A

The desired compound was prepared from **30j** and **B** according to the procedure of Example 1, Step J. Flash chromatography (2 to 5 % MeOH/CH₂Cl₂) afforded **31a** (73 %).

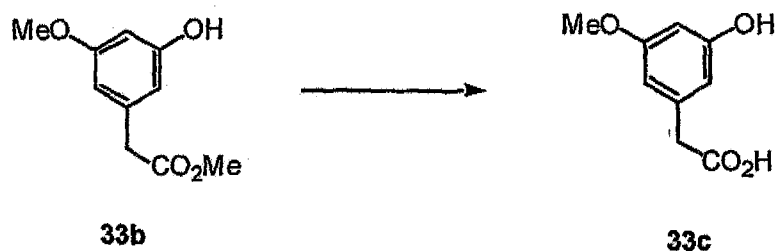
Step A

31

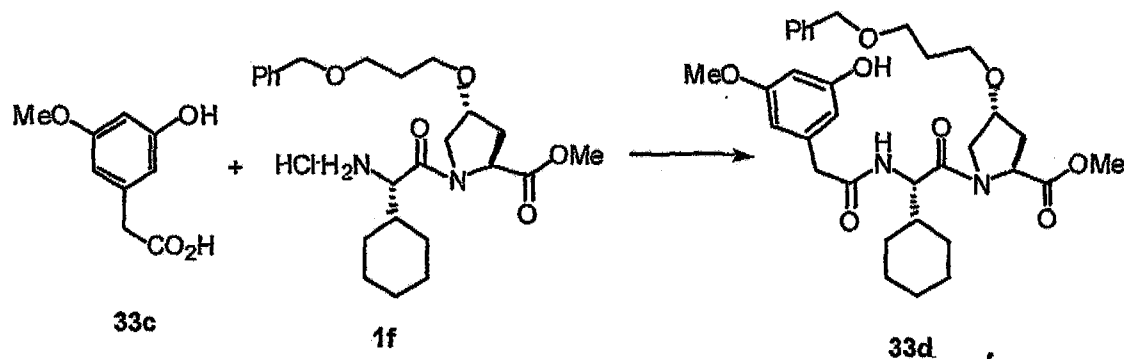


32

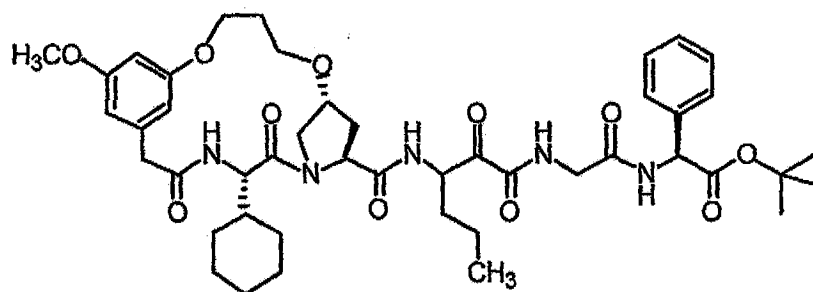
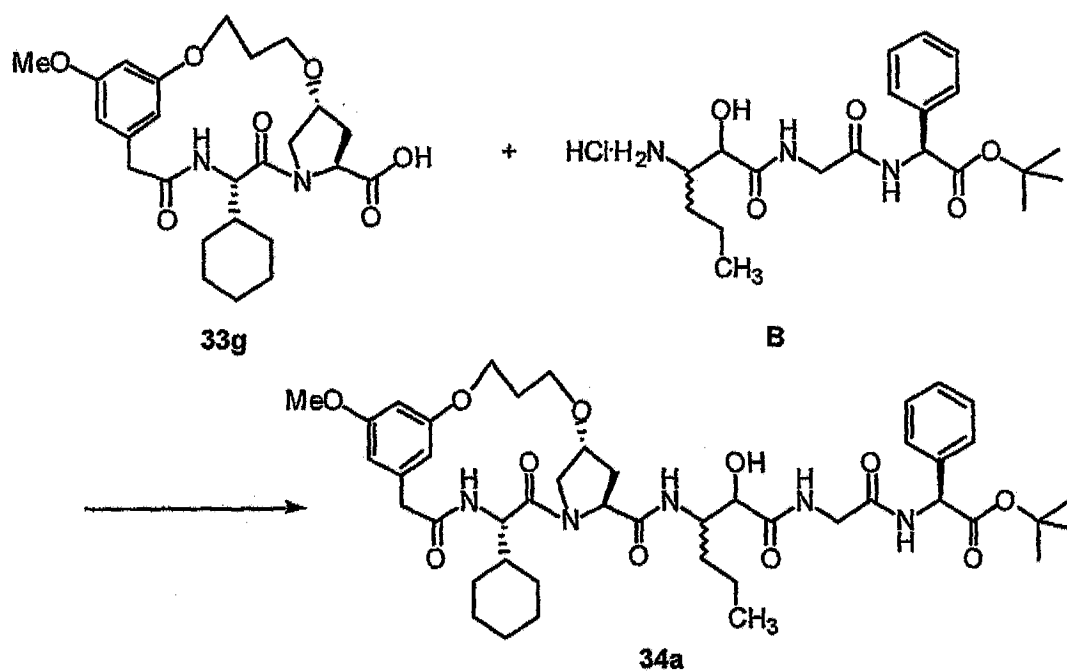
The desired compound **32** can be prepared from **31** according to the procedure of Example 3, Step A.

~~00717~~
118Step B

An aqueous lithium hydroxide solution (0.342 g in 10 mL H₂O) was added to a solution of the methyl ester **33b** in THF (10 mL) and methanol (10 mL) at rt. The progress of the reaction was monitored by TLC. After 4 hr., the volatiles were removed in vacuo, EtOAc (150 mL) and water (30 mL) were added and the aqueous solution was acidified to pH = 1 and saturated with solid sodium chloride. After separation of the layers, the aqueous layer was extracted with EtOAc (2 X 150 mL). Organic solutions were combined, dried with sodium sulfate, filtered and concentrated in vacuo to afford **33c** (1.6 g).

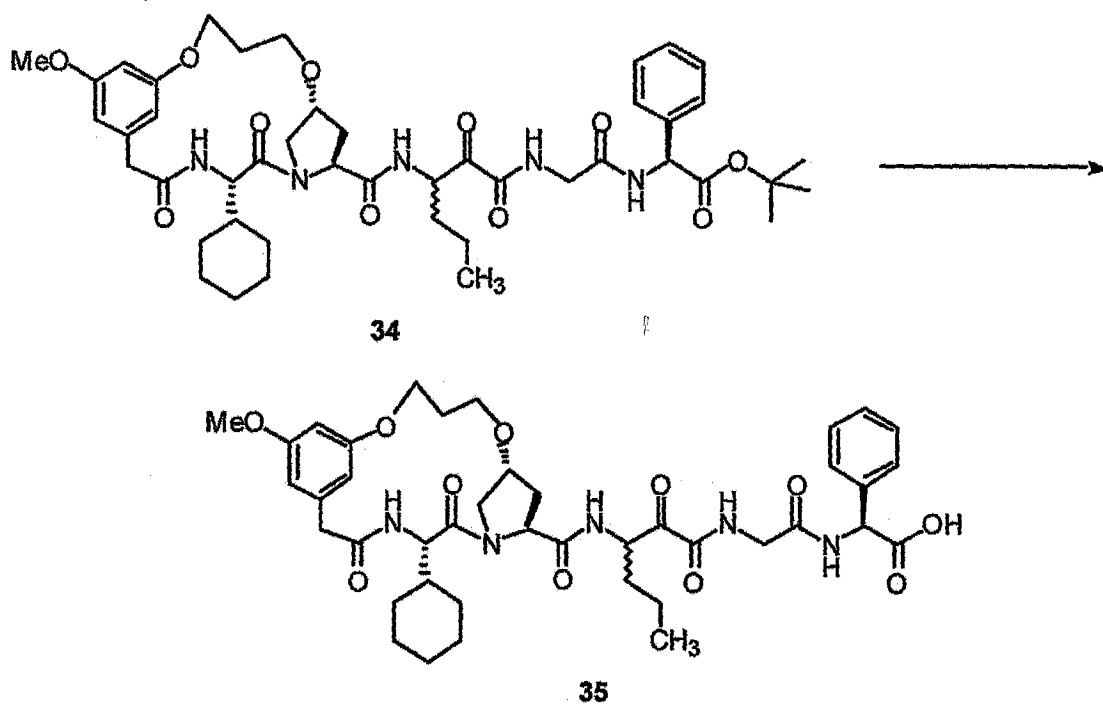
Step C:

The desired compound **33d** was prepared from **33c** and **1f** according to the procedure of Example 1, Step E. Flash chromatography (2 to 5 % MeOH/CH₂Cl₂) afforded **33d** in 90% yield.

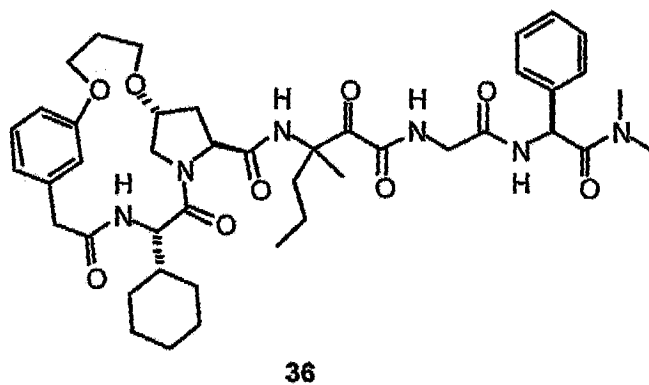
007
120**Example 34: : Preparation of Compound 34:****34****Step A:**

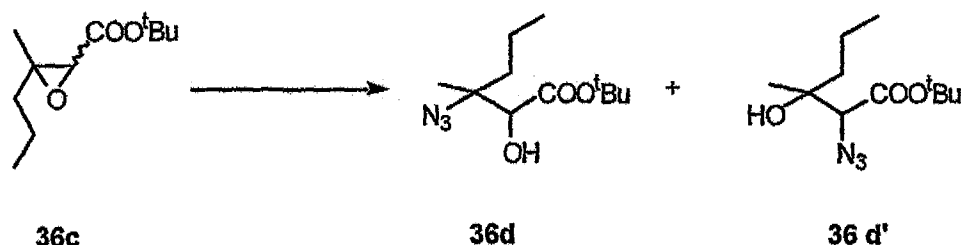
The desired compound **34a** is prepared according to the method of Example 1, Step J, except substituting amine **B** for amine **A**. The product is obtained as a mixture of inseparable diastereomers.

60%
121

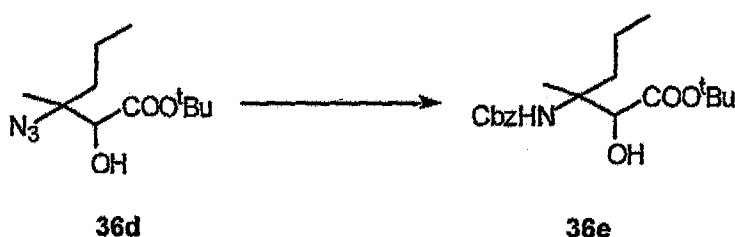
Step A:

The desired compound 35 is prepared from 34 according to the method of Example 3, Step A.

Example 36 : Preparation of Compound 36:

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122**Step C**

A solution of epoxide (4.0 g, 18.4 mmol) in dry ethanol (100 mL) was treated with NaN₃ (12 g, 184 mmol) and NH₄Cl (9.6 g, 184 mmol) and heated at reflux for 36 h. The reaction mixture was diluted with water and the reaction mixture was extracted with ether (300 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by SiO₂ chromatography (EtOAc/Hex 1:19) to yield 1.1 g (28%) of **36d** and 731 mg (18%) of **36d'** as a colorless liquid.

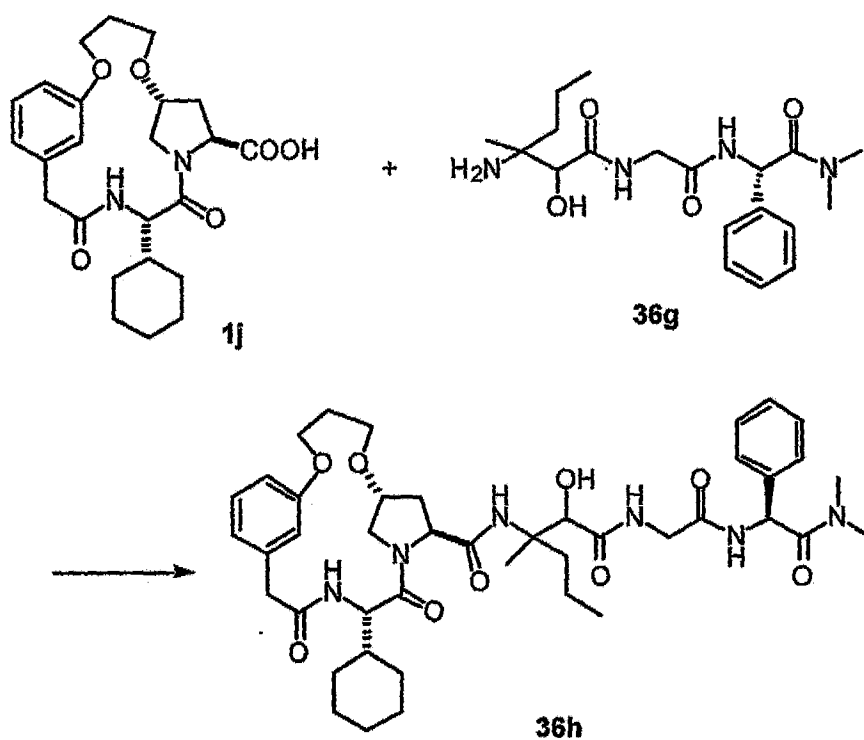
Step D

A solution of azide **36d** (2.1 g, 8.7 mmol) was dissolved in CH₃OH (100 mL) and treated with Pd/C (50 mg) and hydrogenated (40. psi) for 24 h. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated in vacuo. The residue was used for next reaction without further purification.

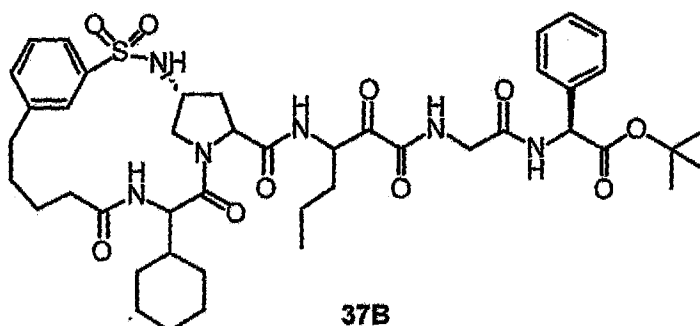
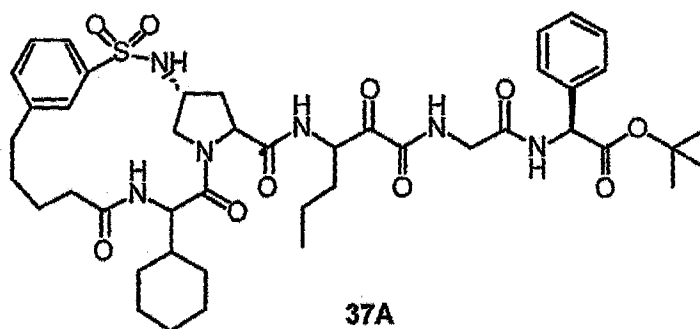
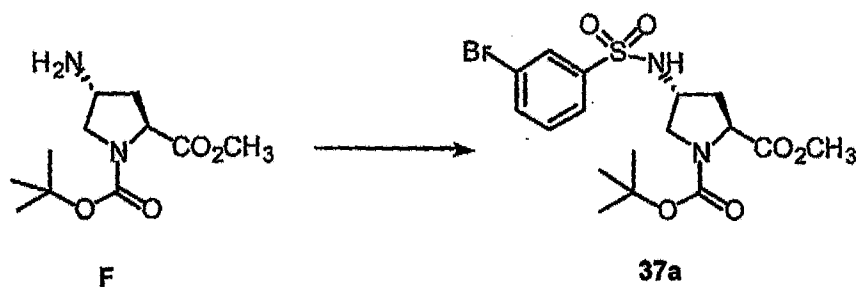
A solution of Cbz-Cl (1.48 g, 8.7 mmol, 1.23 mL) was added dropwise to a mixture of amine and Et₃N (878 mg, 1.25 mL) at -78 °C in CH₂Cl₂ (30 mL). The reaction mixture was warmed to rt. and concentrated in vacuo. The

A solution of **36f** is dissolved in CH₃OH (20 mL) and treated with Pd/C (10 mol%, 20 mg). The reaction mixture will be hydrogenated at 40 psi for 12 h. The reaction mixture is filtered through a plug of Celite and the filtrate is concentrated in *vacuo* and directly used in the next step.

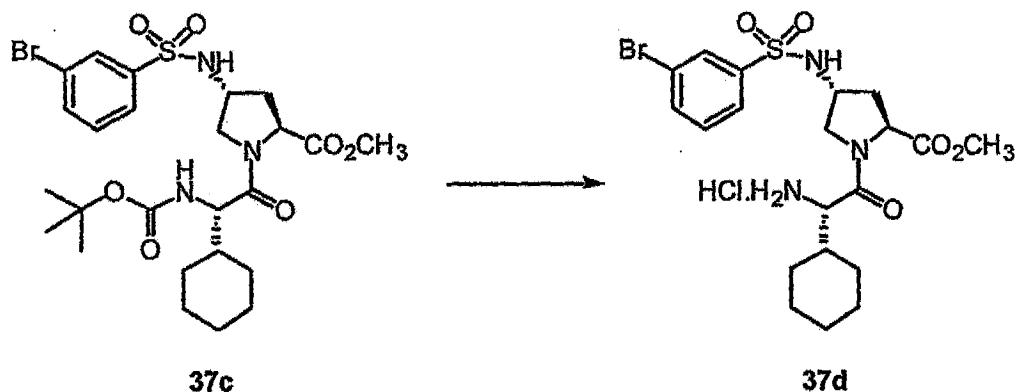
Step G



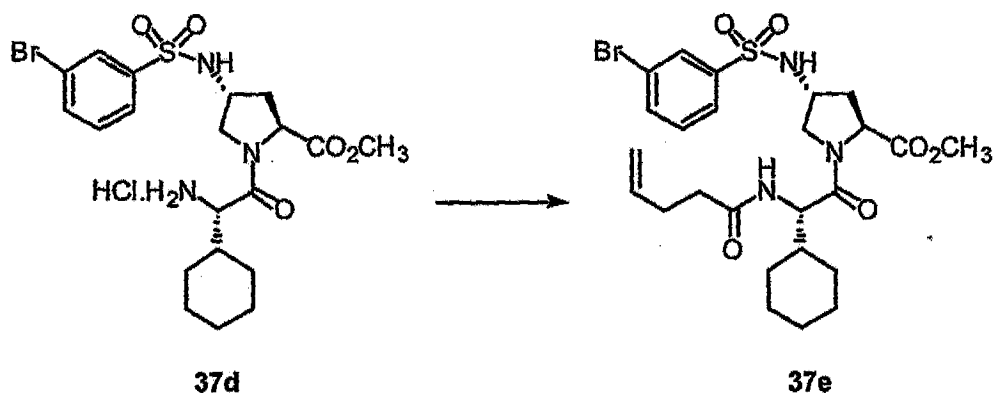
The expected product **36h** is synthesized as described earlier for the Example 1, Step J. The coupled material will be used directly for the next step to synthesize **36A** and **36 B**.

001
124**Example 37: Preparation of Compound 37:****Step A**

To a cold (0°C) solution of F (2.3g, 9.43 mmol) in dichloromethane (20 mL) was added triethylamine (3.97 mL, 28.28 mmol), DMAP (few crystals) and 3-bromobenzenesulfonyl chloride (3.61 g, 14.14 mmol). The reaction mixture was left standing in the refrigerator (0°-5°C) overnight. The reaction mixture was washed with saturated NaHCO₃, and 10% citric acid solution. The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography using 95/5 to 90/10 dichloromethane/EtOAc

125
00123Step D

The desired product **37d** was obtained by the method described for Example 1, Step E. The crude material was used in the next step without purification.

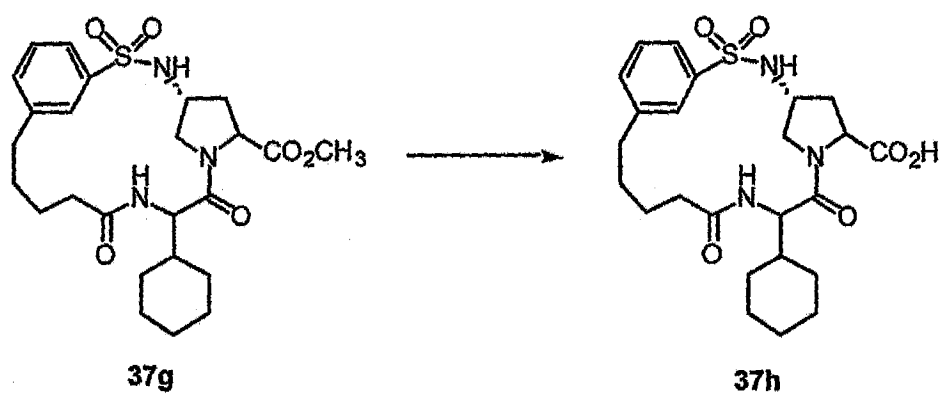
Step E

The desired product **37e** was obtained by the method described for Example 1, Step F using pentenoic acid as the coupling partner. Purification of the residue by column chromatography using 90/10 to 80/20 dichloromethane/EtOAc provided 35% yield of **37e**. HRMS (FAB) Calcd for $C_{25}H_{35}N_3O_6SBr$: 586.1409 (M+H)⁺. Found: 586.1423.

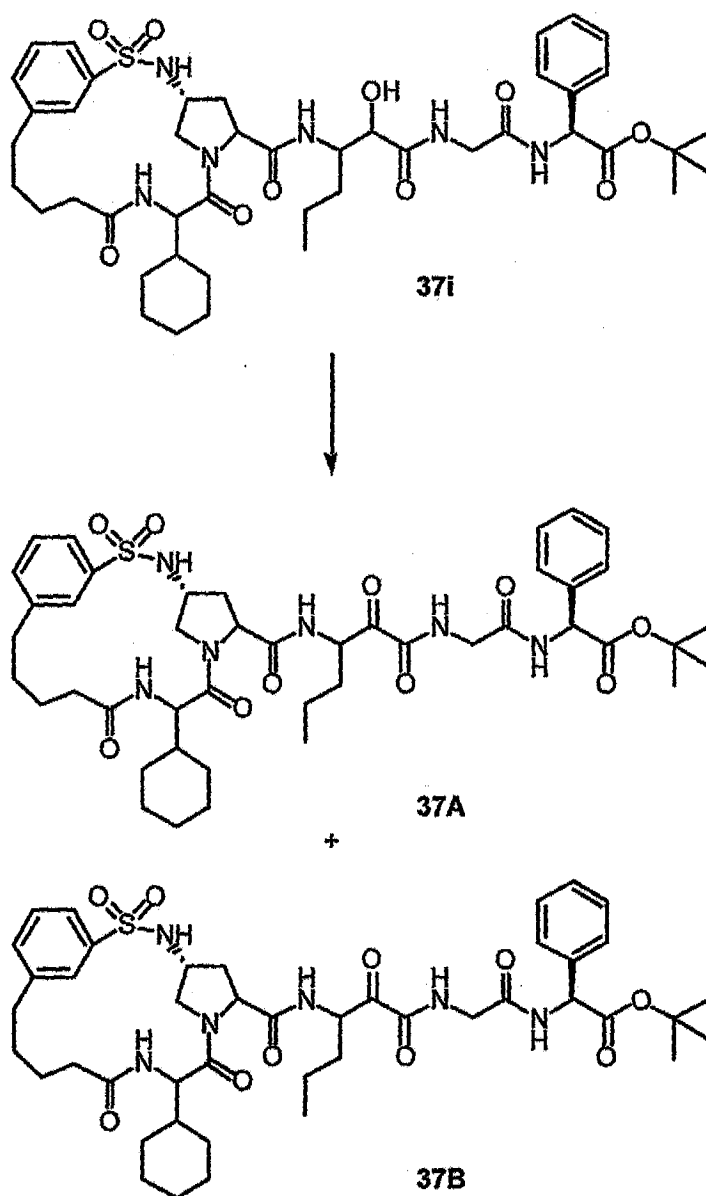
00724
126

The desired product **37g** was obtained by the hydrogenation procedure described for Example 1, Step G in 73% yield. The material was sufficiently pure for further studies. HRMS (FAB) Calcd for $C_{25}H_{36}N_3O_6S$: 506.2325 $(M+H)^+$. Found: 506.2314.

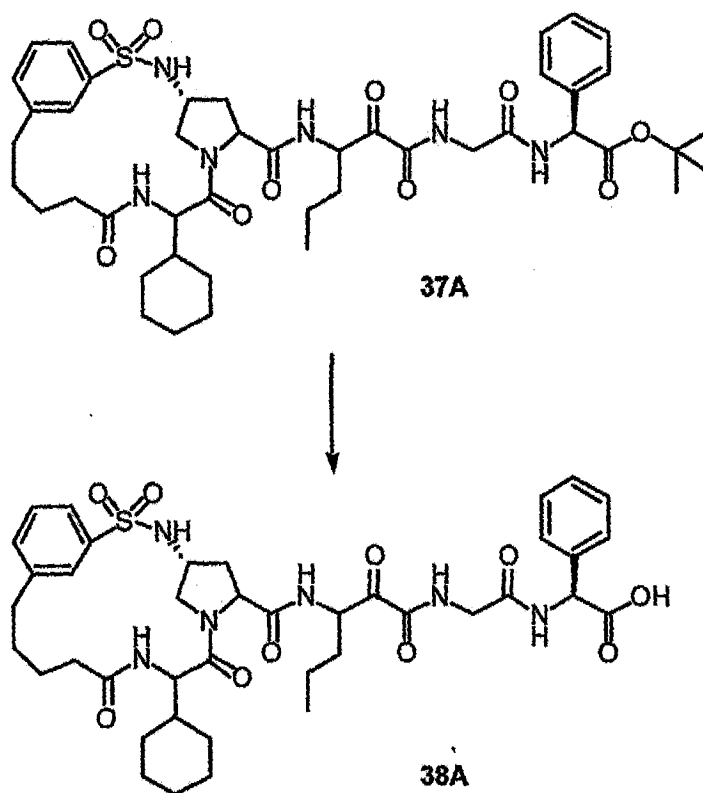
Step H



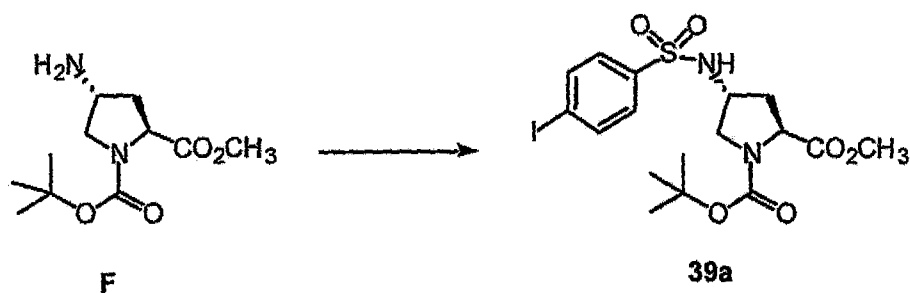
The desired product **37h** was obtained by the procedure described for Example 1, Step H in 84% yield. HRMS (FAB) Calcd for $C_{24}H_{34}N_3O_6S$: 492.2168 $(M+H)^+$. Found: 492.2175.

00125
127Step J

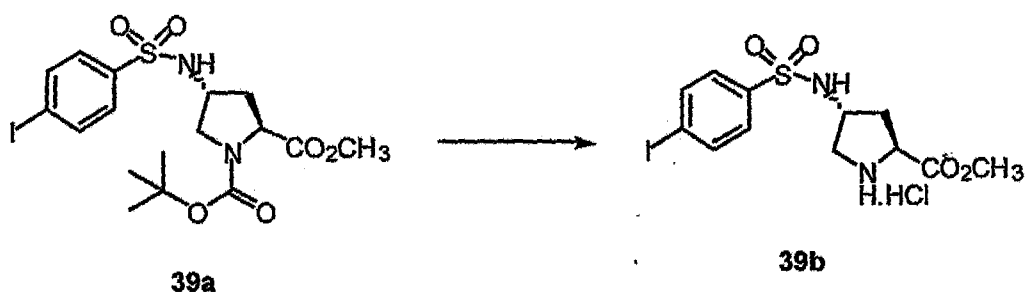
The desired materials **37A** and **37B** were synthesized by the oxidation protocol described for Example 2, Step B. Purification of the residue using 98/2 to 96/4 dichloromethane/MeOH afforded **37A** (61%, less polar) and **37B** (15%, more polar) as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{44}H_{61}N_6O_{10}S$: 865.4170 ($M+H$)⁺. Found: 865.4190 (**37A**), 865.4181 (**37B**).

127
00226
128Step A

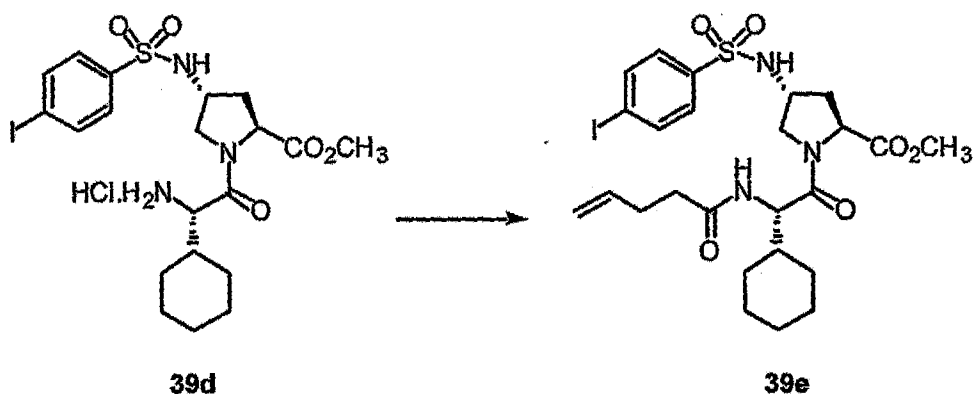
The desired material **38A** was synthesized as described for Example 3, Step A in 91% yield.

129
~~00327~~Step A

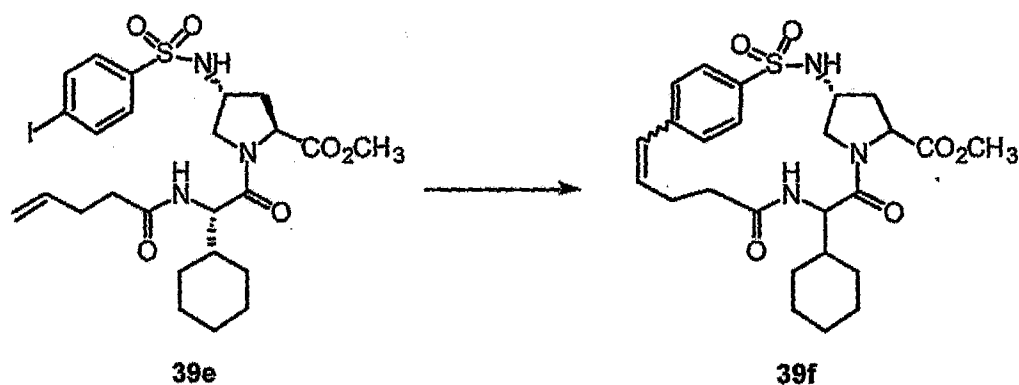
The desired product **39a** was obtained by the method described for Example 37, Step A using pipsyl chloride instead of 3-bromobenzenesulfonyl chloride. Purification of the residue by column chromatography using 95/5 to 90/10 dichloromethane/EtOAc provided 75% yield of **39a**. HRMS (FAB) Calcd for $C_{17}H_{24}N_2O_6Si$: 511.0400 (M+H)⁺. Found: 511.0386.

Step B

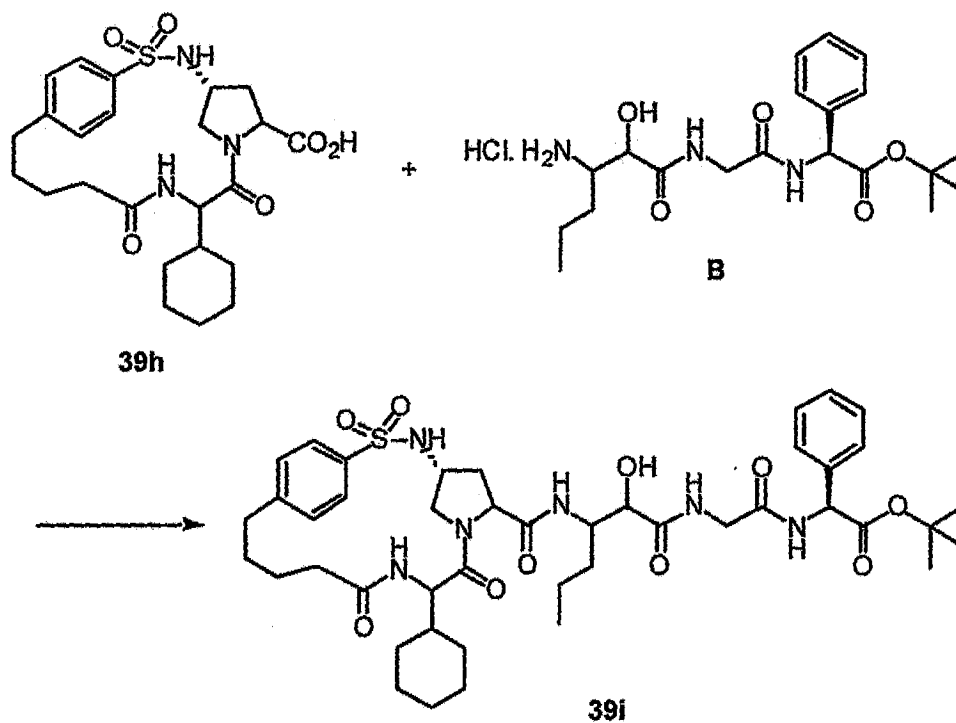
The desired product **39b** was obtained by the method described for Example 1, Step C. The crude material was used in the next step without purification.

Step E

The desired product **39e** was obtained by the method described for Example 1, Step F using pentenoic acid as the coupling partner. Purification of the residue by column chromatography using 98/2 dichloromethane/MeOH provided 76% yield of **39e**.

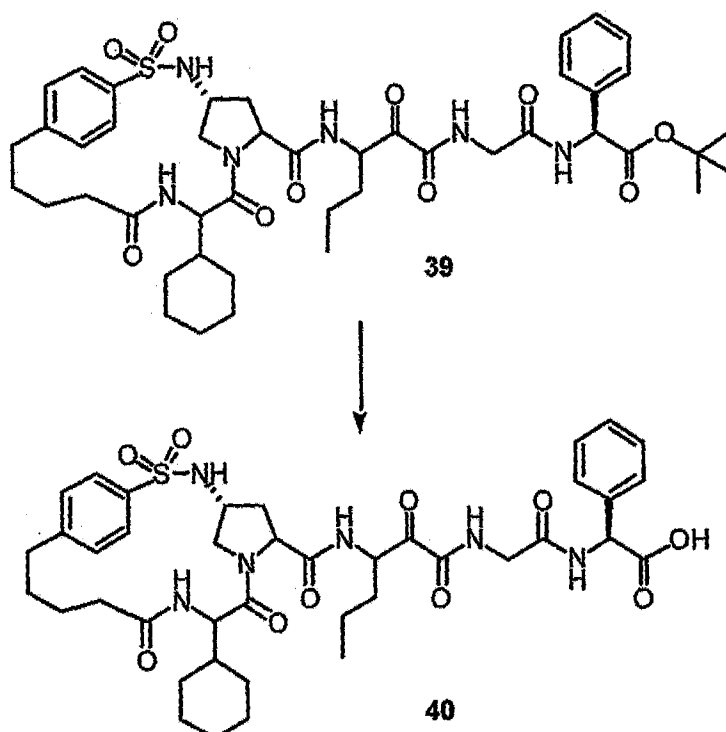
Step F

The desired product **39f** was obtained by the method described for Example 37, Step F. Purification of the residue by column chromatography using 98/2 dichloromethane/MeOH provided 28% yield of **39f** as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{25}H_{34}N_3O_6S$: 504.2168 ($M+H$)⁺. Found: 504.2160.

Step I

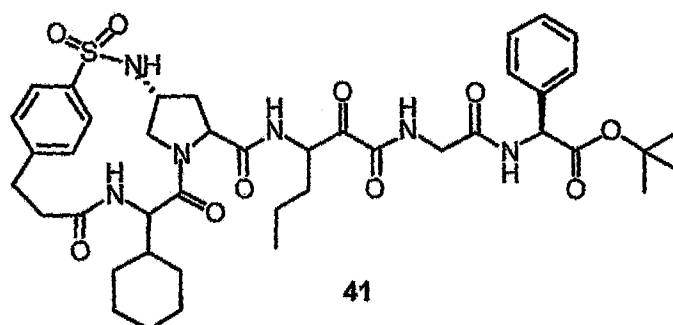
The expected product **39i** was obtained by the method described for Example 2, Step A in 36% yield. The crude material was sufficiently pure for further studies. HRMS (FAB) Calcd for C₄₄H₆₃N₆O₁₀S: 867.4326 (M+H)⁺. Found: 867.4342.

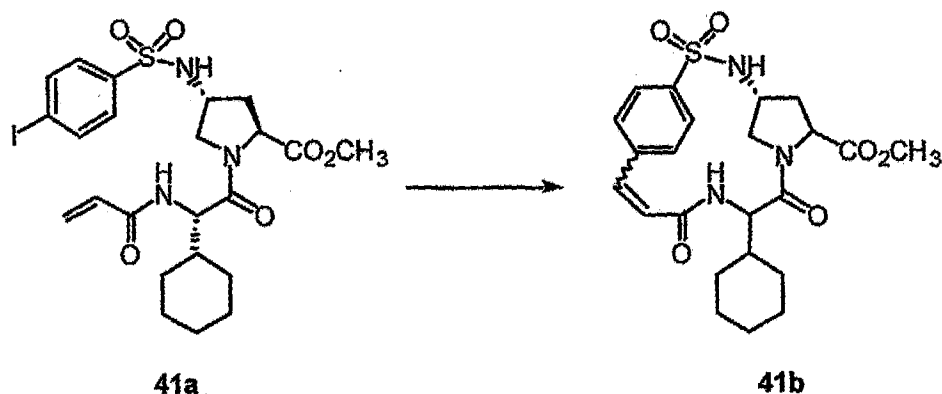
Step A



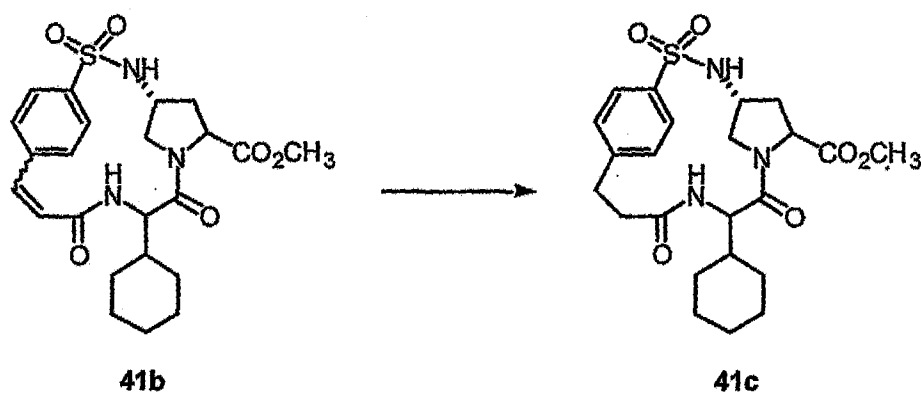
The desired material **40** was obtained by the procedure described for Example 3, Step A in 93% yield as a mixture of diastereomers. HRMS (FAB) Calcd for $C_{40}H_{53}N_6O_{10}S$: 809.3544 ($M+H$)⁺. Found: 809.3544.

Example 41: Preparation of Compound 41:



00131
133Step B

The desired product **41b** was obtained by the method described for Example 37, Step F. The residue was purified using 97/3 dichloromethane/MeOH to afford **41b** in 26% yield. HRMS (FAB) Calcd for $C_{23}H_{30}N_3O_6S$: 476.1855 ($M+H$)⁺. Found: 476.1858.

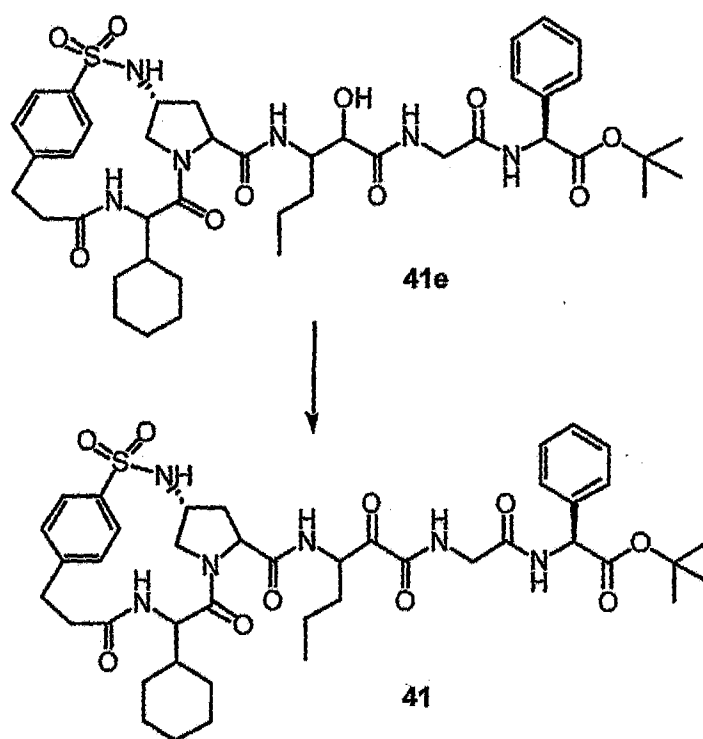
Step C

The desired product **41c** was obtained by the hydrogenation method described for Example 1, Step D in 75% yield. The material was sufficiently pure for further studies.

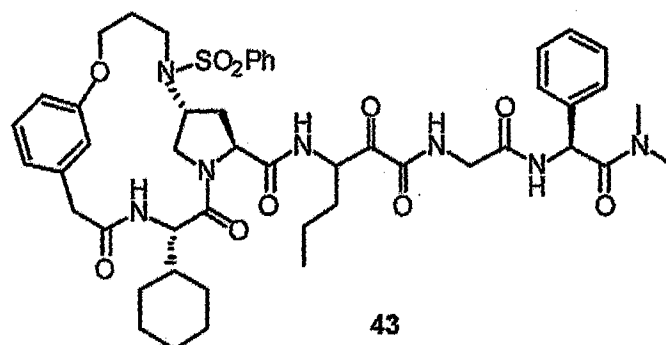
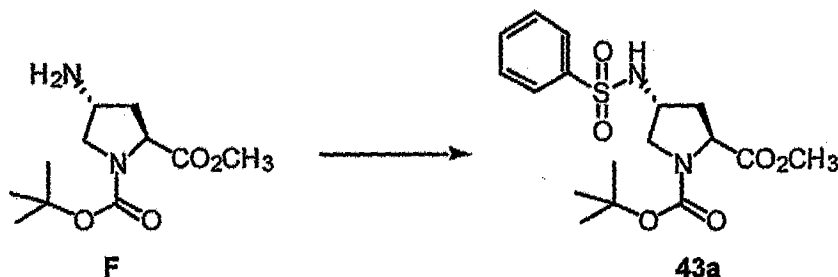
00232
134

The expected product **41e** was obtained by the method described for Example 2, Step A in 63% yield. The crude material was sufficiently pure for further studies.

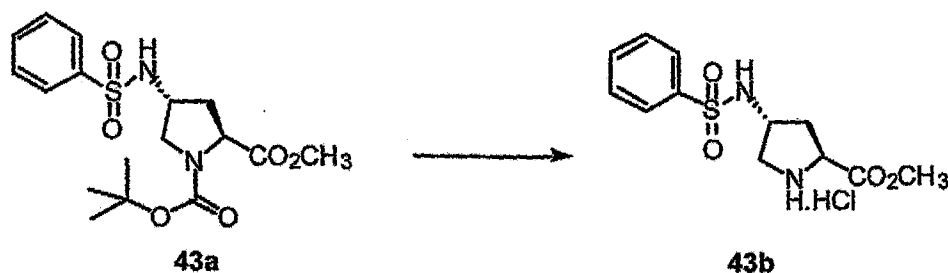
Step F



The desired material **41** was obtained by the oxidation protocol described for Example 2, Step B. Purification of the residue using 98/2 to 95/5 dichloromethane/MeOH afforded **41** in 52% yield as a mixture of diastereomers.

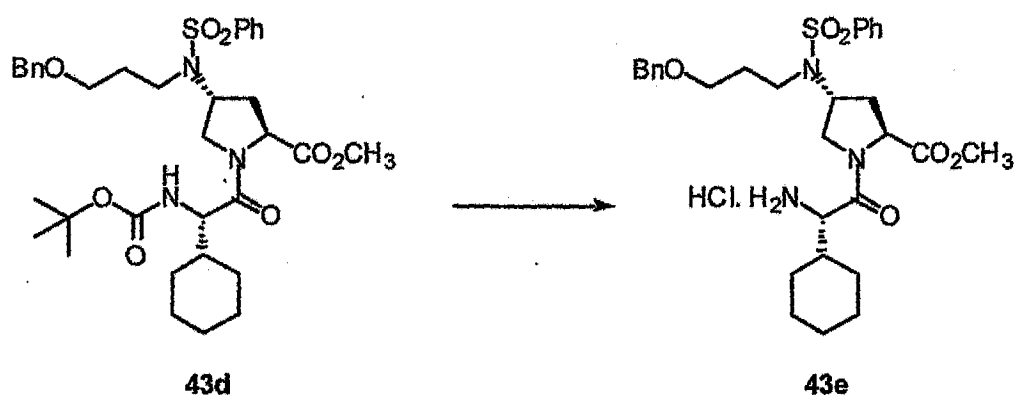
00283
135**Example 43: Preparation of Compound 43:****Step A**

To a cold (0°C) solution of F (5.4 g, 22.1 mmol) in dichloromethane (50 mL) was added triethylamine (6.8 mL, 48.6 mmol), DMAP (few crystals) and benzenesulfonyl chloride (3.29 g, 24.1 mmol). The reaction mixture was left standing in the refrigerator (0-5°C) overnight. The reaction mixture was washed with saturated NaHCO₃, and 10% citric acid solution. The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography using 95/5 dichloromethane/EtOAc to afford 5.0 g (59% yield) of 43a.

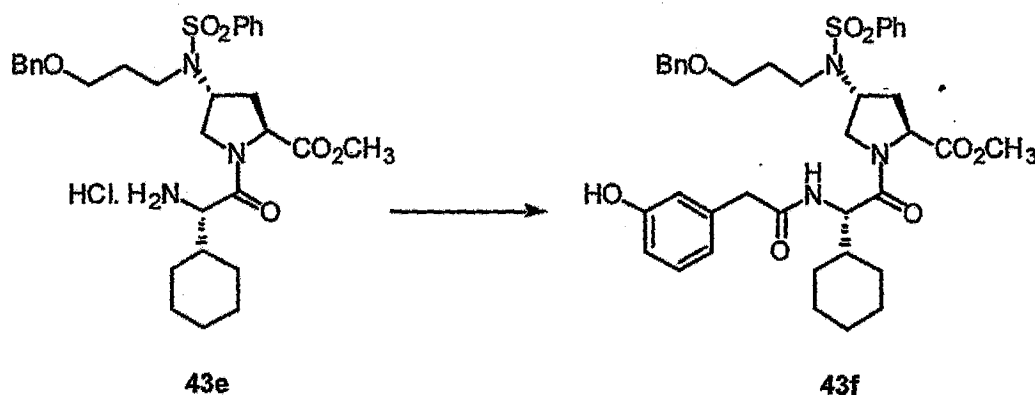
Step B

00136
136

mixture and added Et₂O (50 mL). The precipitated solid material was filtered off. Repeated this operation twice to remove most of the side products. The filtrate was concentrated and purified by flash chromatography using 90/10 to 85/15 dichloromethane/EtOAc to provide 330 mg of **43d**. The recovered starting materials, along with some triphenylphosphine oxide, was resubjected to the above described conditions to provide additional 420 mg of **43d**. Combined yield = 34%. HRMS (FAB) Calcd for C₃₅H₅₀N₃O₈S: 672.3319 (M+H)⁺. Found: 672.3330.

Step E

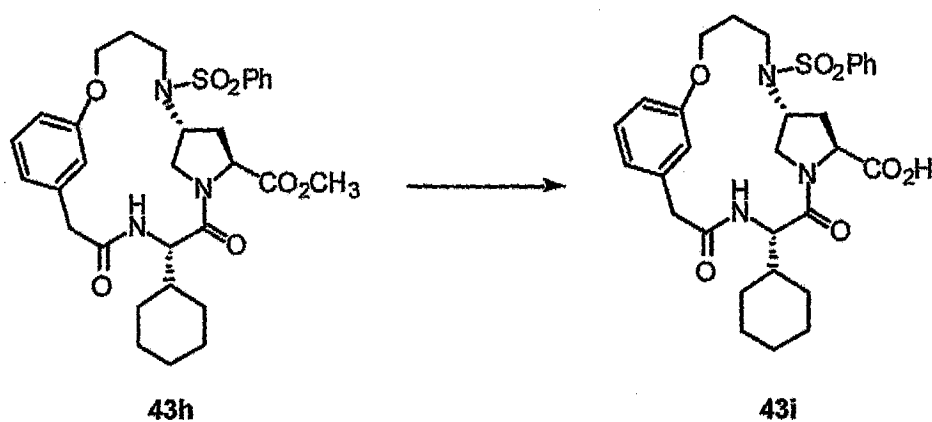
The desired product **43e** was obtained by the method described for Example 1, Step E. The crude product was carried to the next step.

Step F

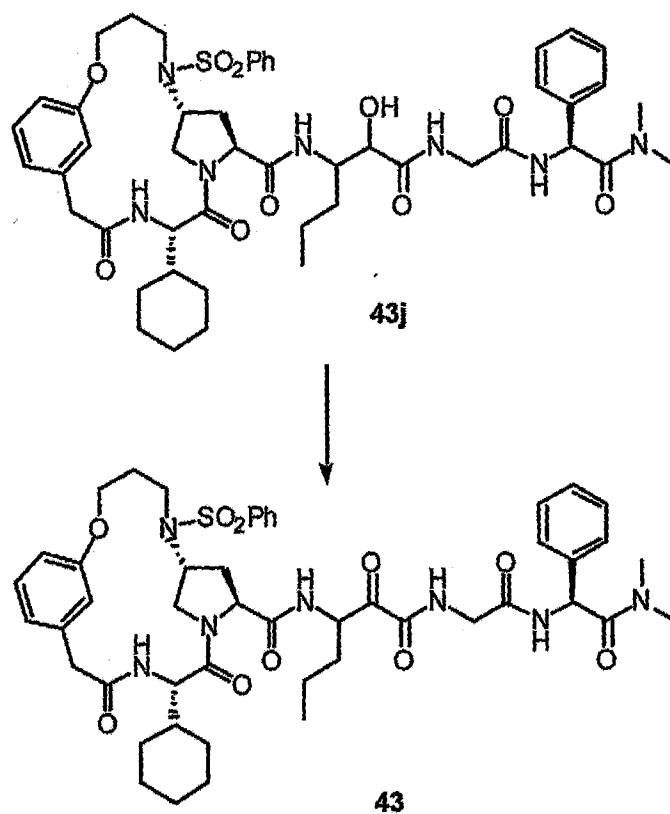
~~00253~~
137

concentrated and Et₂O/EtOAc (50mL/50 mL) was added. The precipitated solids were filtered off and the filtrate was concentrated. The residue was purified by flash chromatography using 85/15 to 80/20 dichloromethane/EtOAc to afford pure **43h** in 20% yield. HRMS (FAB) Calcd for C₃₁H₄₀N₃O₇S: 598.2587 (M+H)⁺. Found: 598.2581.

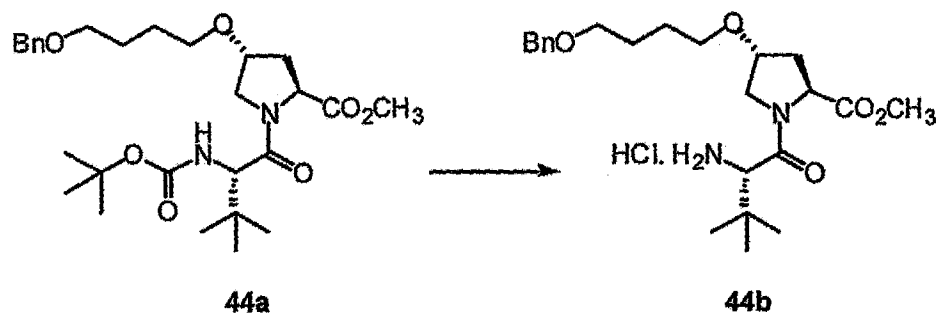
Step I



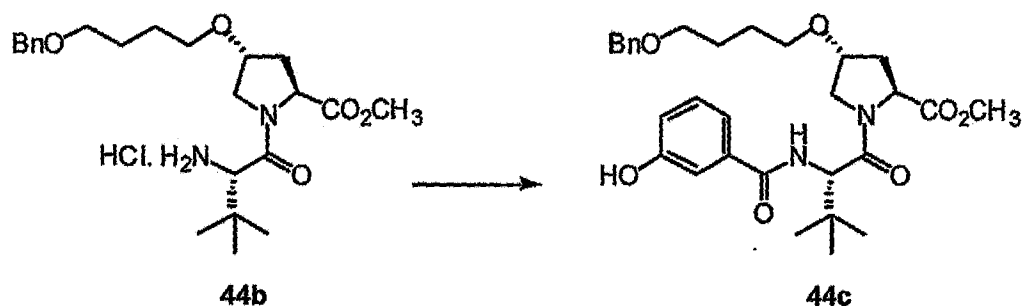
The expected product **43i** was obtained by the procedure described for Example 1, Step I in 92% yield.

~~60,85~~
138Step K

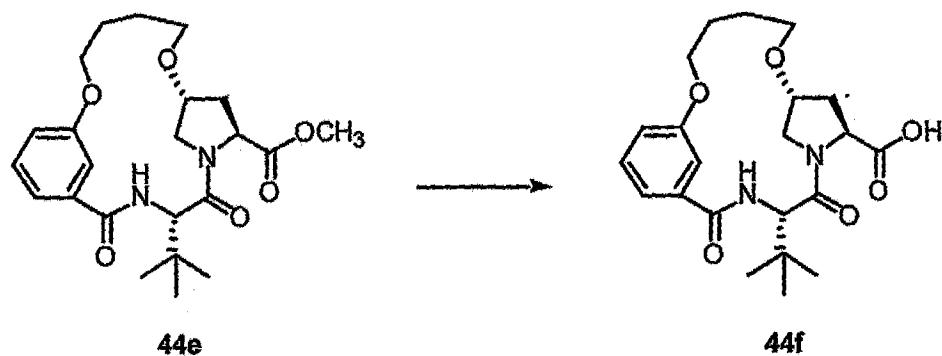
The expected product **43** was obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 97/3 dichloromethane/MeOH afforded **43** as a mixture of diastereomers. Combined yield = 60% (for 2 steps). HRMS (FAB) Calcd for C₄₈H₆₂N₇O₁₀S: 928.4279 (M+H)⁺. Found: 928.4290.

Step B

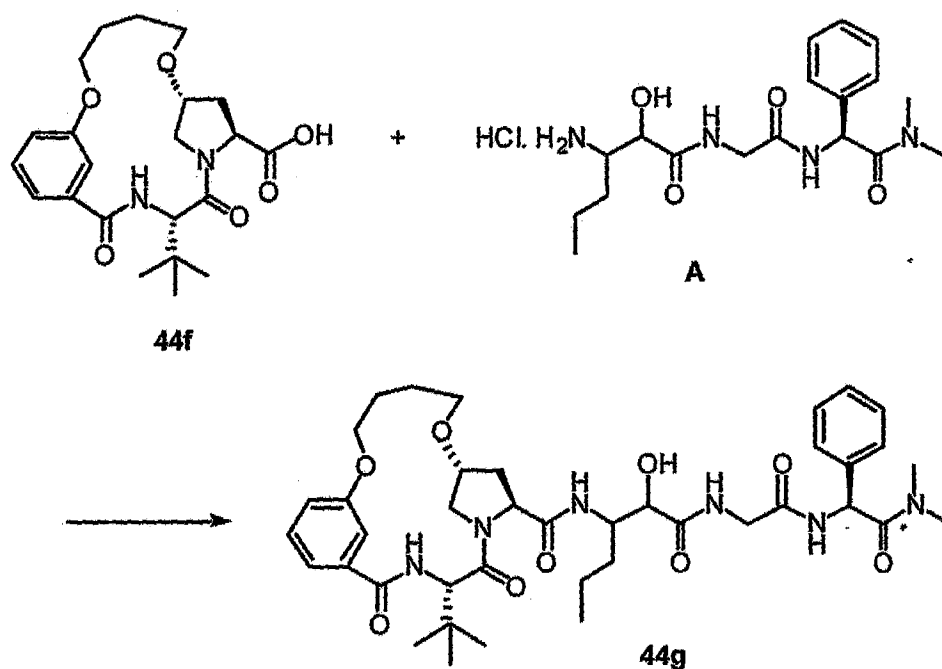
The desired product **44b** was obtained by the method described for Example 1, Step E. The crude material was carried forward without purification.

Step C

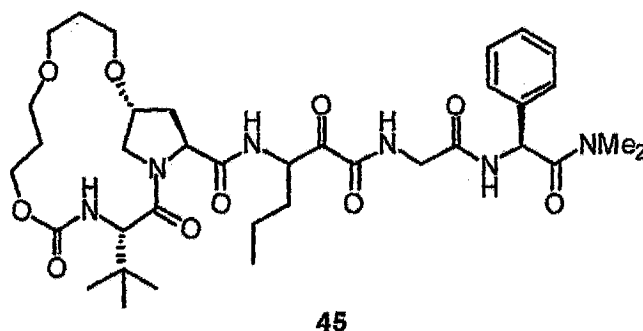
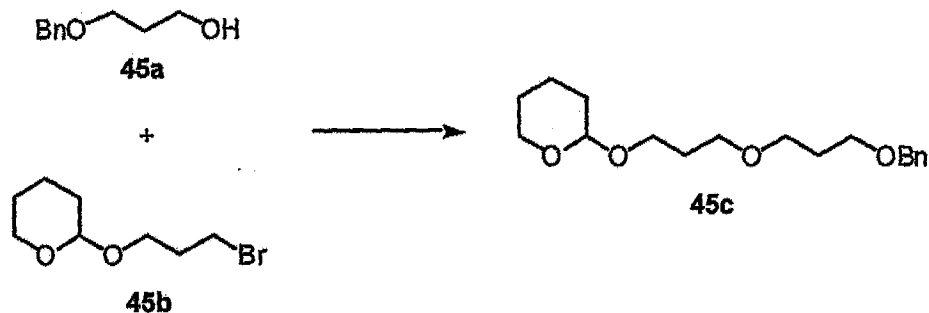
The desired product was obtained by the method described for Example 1, Step F, using 3-hydroxybenzoic acid. The material was purified by flash column chromatography using 85/15 to 65/35 dichloromethane/ethyl acetate to provide **44c** in 81% yield.

Step F

The desired product **44f** was obtained by the method described for Example 1, Step I. Yield of **44f** (for 2 steps) = 11%.

Step G

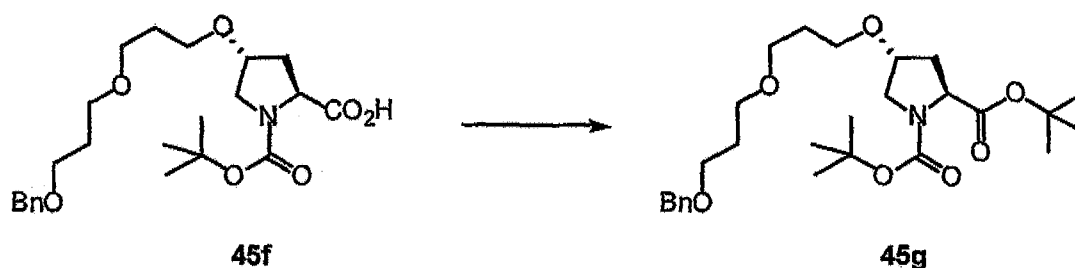
The expected product **44g** was synthesized as described earlier for the Example 1, Step J. The material after work-up was carried forward to the next step.

00233
141**Example 45: Preparation of Compound 45:****Step A**

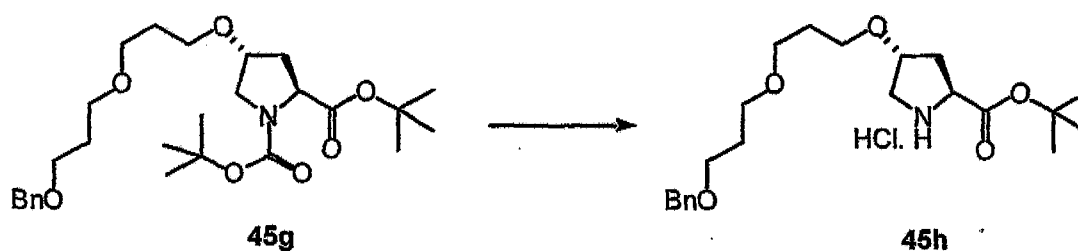
Alkylation of **45a** with **45b** was carried out using the procedure described for Example 1 Step A. The crude product was purified using 85/0/15 to 85/5/10 hexanes/EtOAc/dichloromethane to provide **45c** in 37% yield. HRMS (FAB) Calcd for C₁₈H₂₉O₄: 309.2066 (M+H)⁺. Found: 309.2060.

Step B

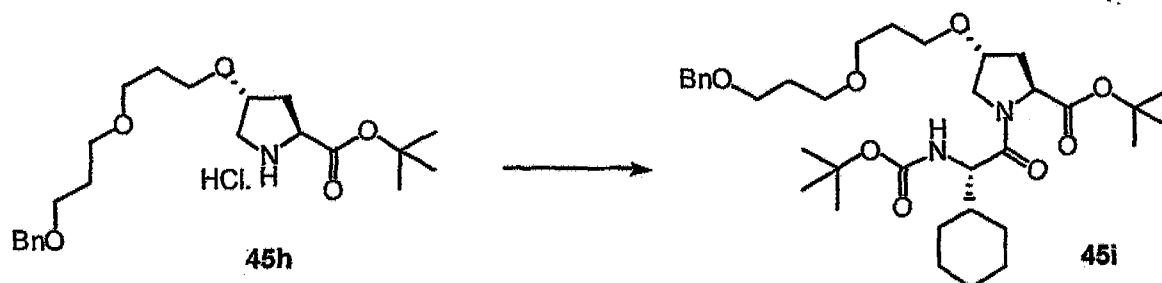
To a solution of **45c** (4.8 g, 15.5 mmol) in MeOH (30 mL) was added pyridinium *p*-toluenesulfonate (780 mg, 3.1 mmol) and refluxed for 3 hrs when

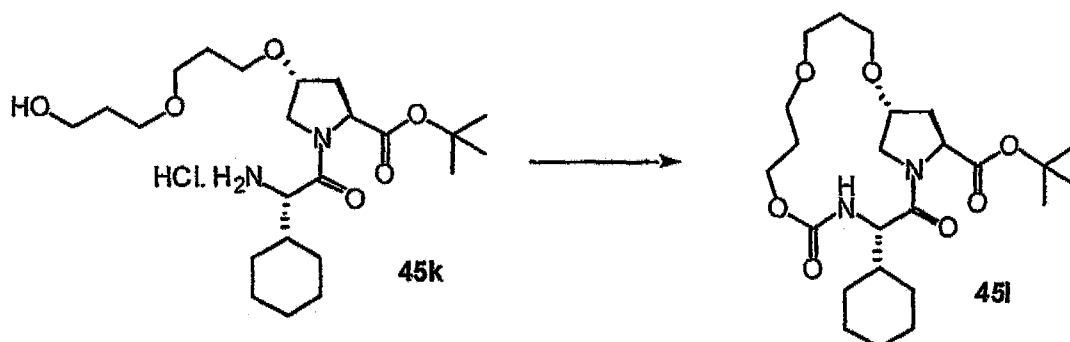
00247
142Step E

The desired product **45g** was obtained by the procedure described for Example 18 Step B using **45f** as the starting material. The residue was purified by flash chromatography using 90/10 dichloromethane/EtOAc to provide **45g** in 61% yield (for 2 steps). HRMS (FAB) Calcd for C₂₇H₄₄NO₇: 494.3118 (M+H)⁺. Found: 494.3107.

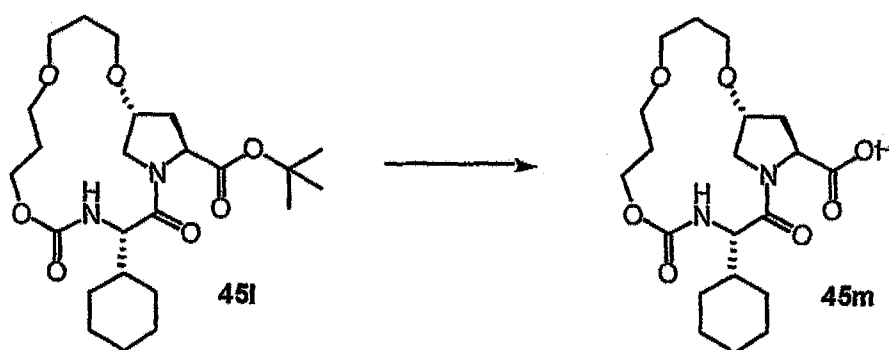
Step F

The desired compound **45h** was prepared by the protocol described for Example 1 Step C. The material was carried forward.

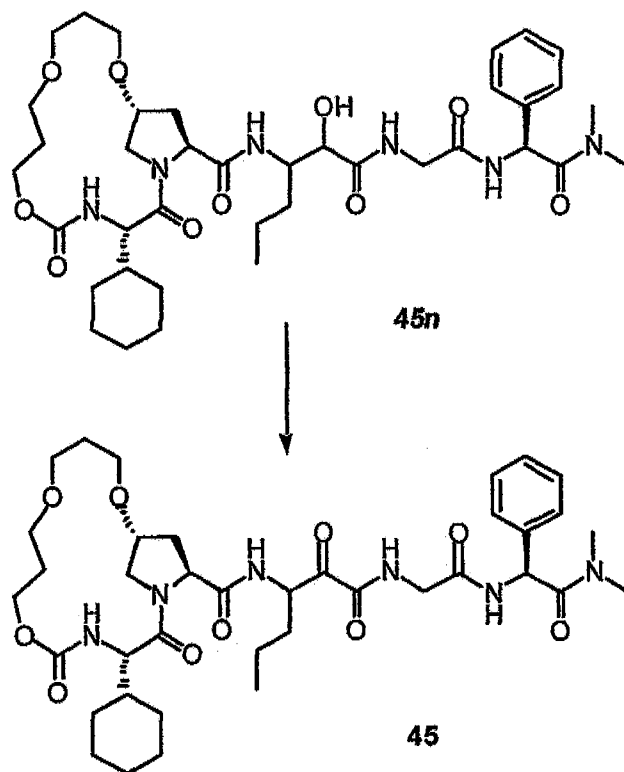
Step G

Step J

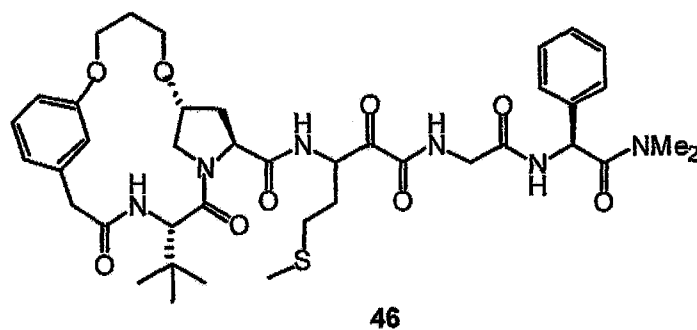
To a cold (0°C) solution of **45k** in dichloromethane is added triethylamine followed by carbonyldiimidazole. Slow warming to ambient temperature overnight is expected to provide the required product **45l**. This product can be purified using conventional flash column chromatography to afford pure **45l**.

Step K

The desired product **45m** is obtained by the procedure described previously for Example 3 Step A.

Step M

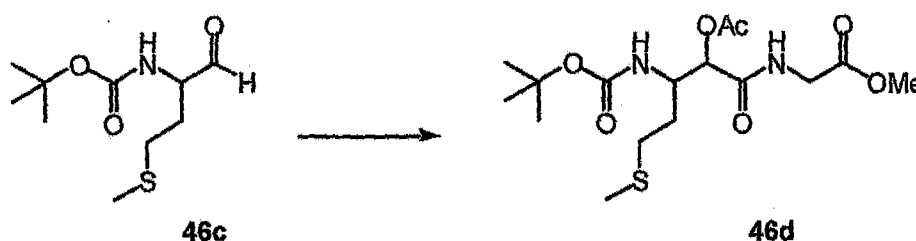
The desired product **45** is obtained by the oxidation protocol described previously for Example 1 Step K. Purification by flash column chromatography will afford pure **45**.

Example 46: Preparation of Compound 46:

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145

by flash column chromatography using 10/90 to 30/70 EtOAc/dichloromethane to provide 4.2 g of **46c** (45% yield - for 2 steps). HRMS (FAB) Calcd for $C_{10}H_{20}NO_3S$: 234.1164 ($M+H$)⁺. Found: 234.1168.

Step C

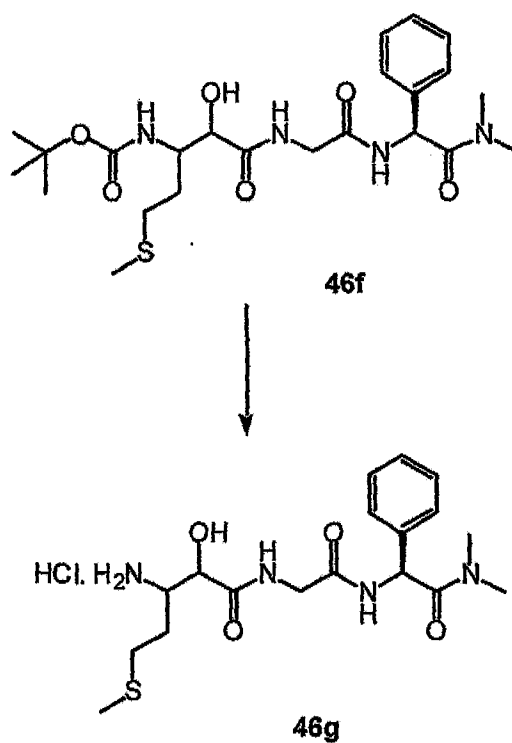


To a cold (-15°C) solution of **46c** (4.2 g, 19.4 mmol) in dichloromethane was added acetic acid (2.14 mL, 38.8 mmol) followed by methyl isocyanoacetate (1.76 mL, 19.4 mmol). The reaction mixture was warmed to room temperature and let stand for 16 hrs. Diluted the reaction with EtOAc and washed with saturated $NaHCO_3$, brine and water. The organic layer was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography using 30/70 EtOAc/dichloromethane afforded pure **46d** (6.5 g) as a white solid in 92% yield. HRMS (FAB) Calcd for $C_{16}H_{29}N_2O_7S$: 393.1695 ($M+H$)⁺. Found: 393.1692.

Step D



To a solution of **46d** (6.5 g, 16.6 mmol) in MeOH (30 mL) was added a solution of lithium hydroxide (1.19 g, 50 mmol) in water (30 mL). After 45 minutes the reaction mixture was concentrated. Aqueous citric acid solution was added till acidic pH (3) and the product was extracted into EtOAc.

Step F

The desired compound **46g** was prepared by the protocol described for Intermediate A, Step 4. The material was carried forward for further studies.

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the pamphlet!

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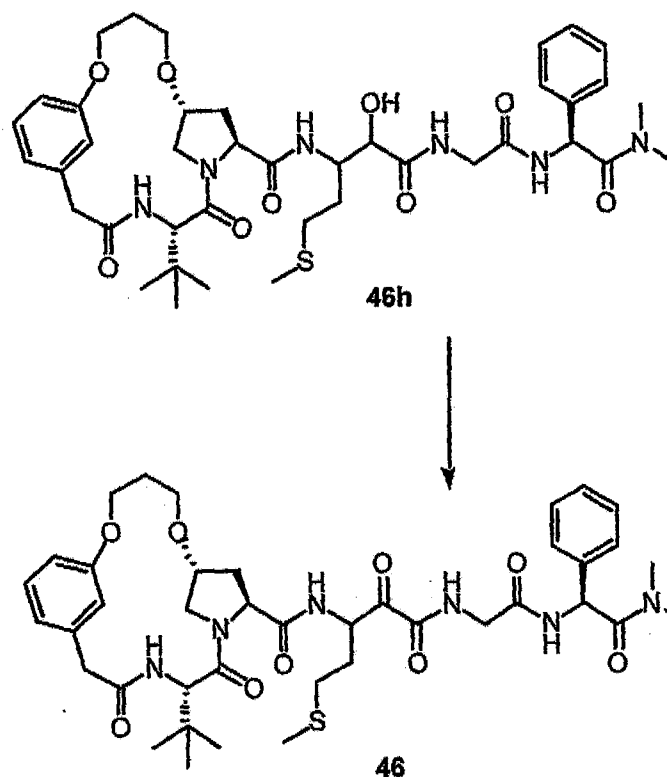
3/3

Date: 18 oct 2001

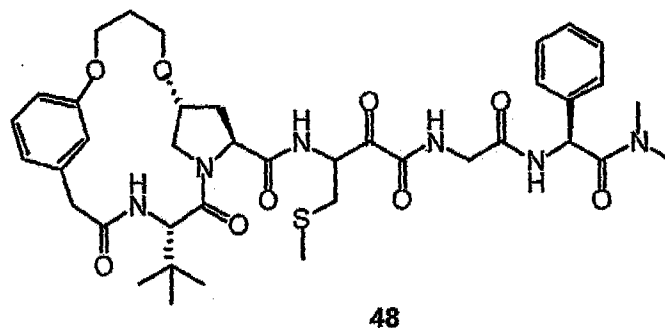
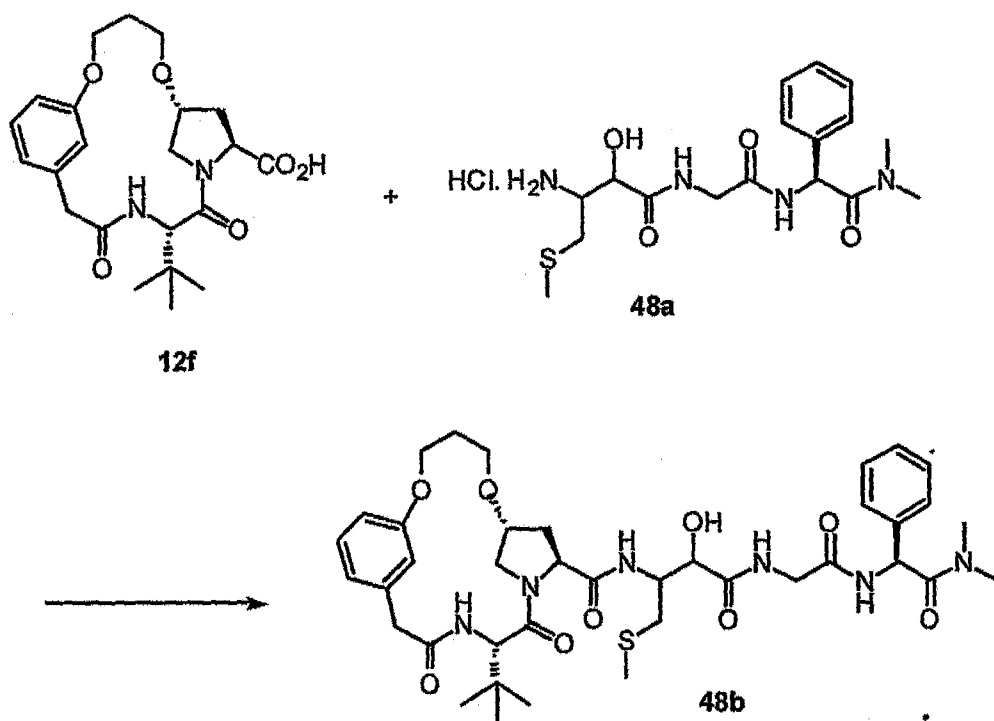
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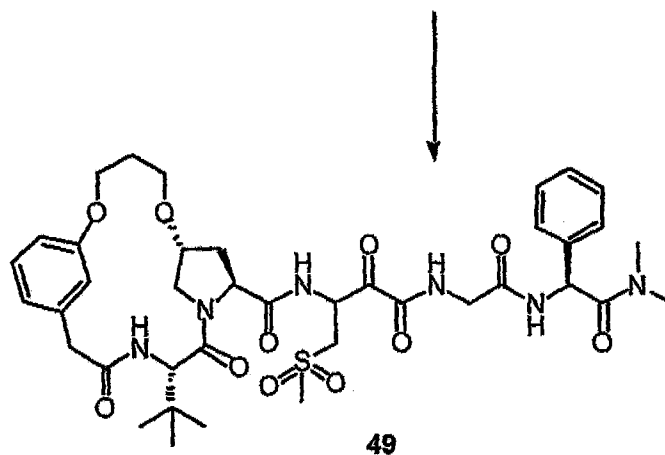
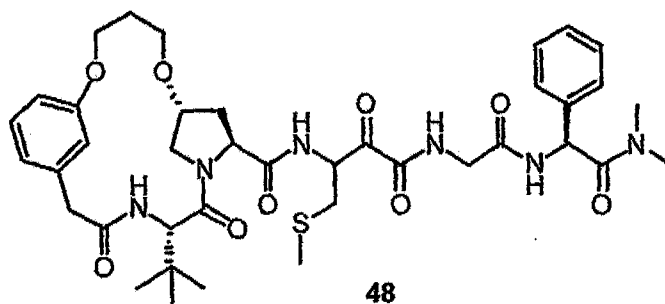
22
147
~~00143~~
~~148~~

148
~~00243~~
147Step H

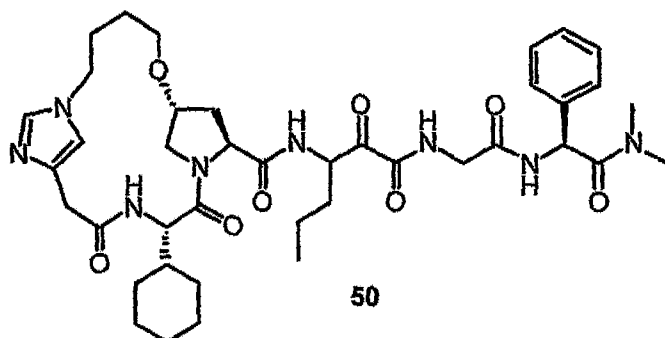
The desired product **46** was obtained by the oxidation protocol described previously for Example 10, Step J. The reaction took 4 days to go to completion. Purification of the residue by flash column chromatography (twice) and preparative TLC using 98/2 dichloromethane/MeOH afforded **46** as a mixture of diastereomers in 12% yield (for 2 steps). HRMS (FAB) Calcd for $C_{40}H_{55}N_6O_9S$: 795.3751 ($M+H$)⁺. Found: 795.3761.

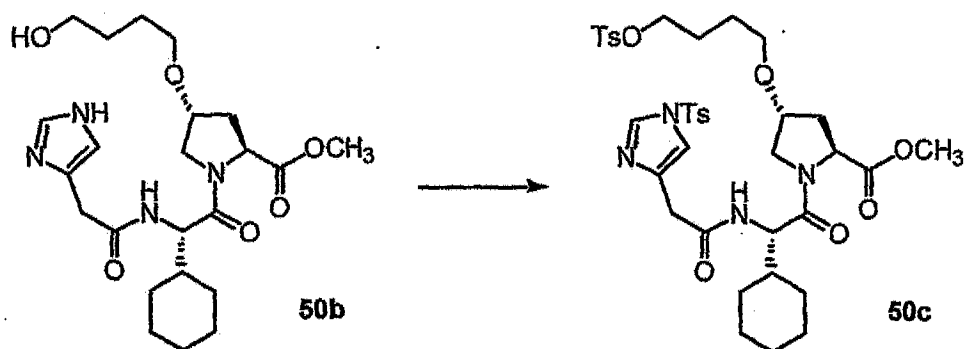
Example 48: Preparation of Compound 48:**Step A**

The desired product **48b** was obtained by the procedure described for Example 1 Step J. The crude material was sufficiently pure for further manipulations. (Note: The precursor **48a** was obtained from commercially available *N*boc-*S*-methylcysteine by similar procedures described for **46g**)

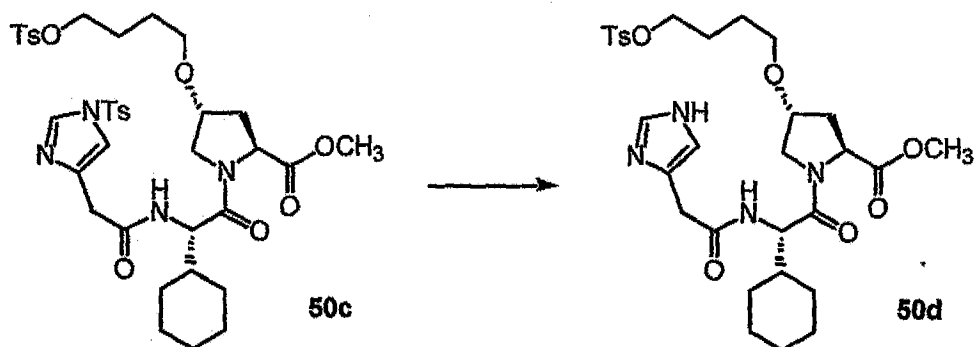
001/50
43Step A

The desired product 49 is obtained by the oxidation protocol described previously for Example 11 Step A.

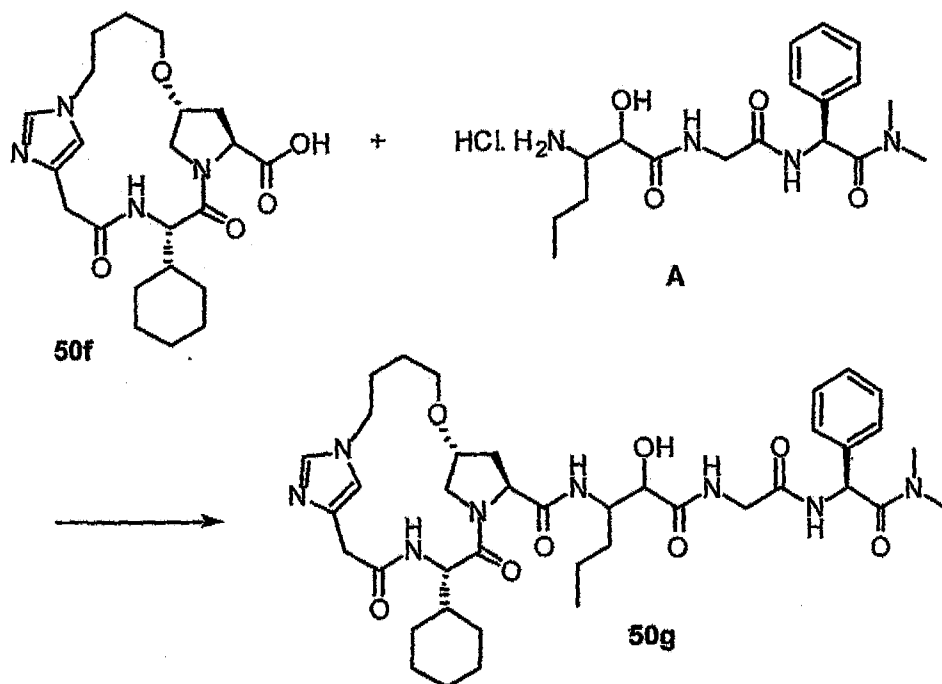
Example 50: Preparation of Compound 50:

150
151
~~00143~~Step C

The desired product **50c** is obtained by the method described for Example 10 Step A using *p*-toluenesulfonyl chloride as the starting material.

Step D

The desired product **50d** is obtained by the treating **50c** with HOBT in THF at ambient temperature over several hrs.

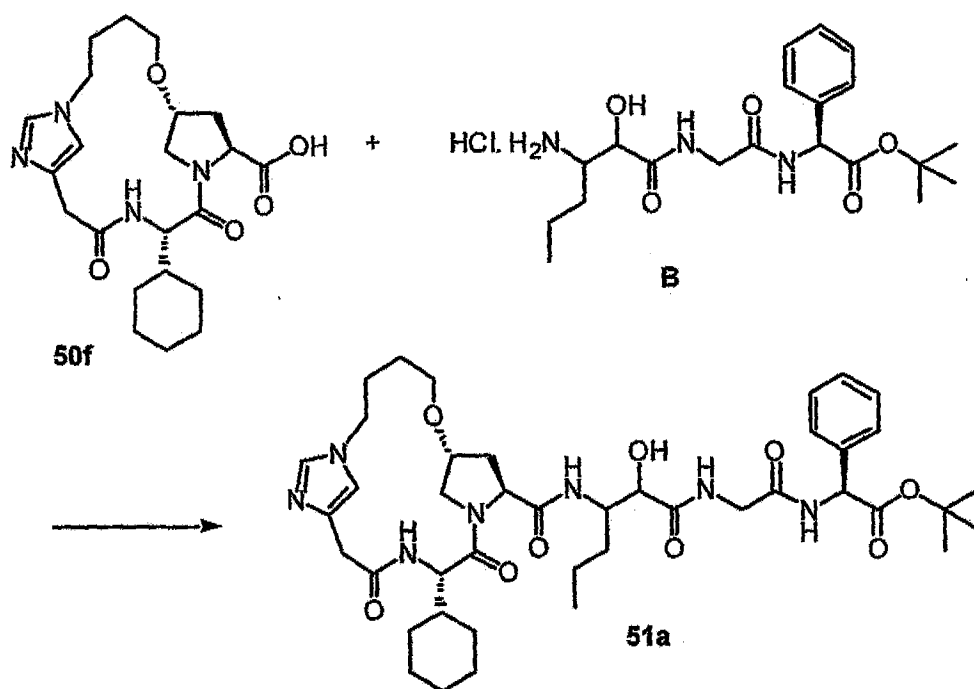
151
00250
152Step G

The expected product **50g** is synthesized as described earlier for Example 1 Step J.

152

00251

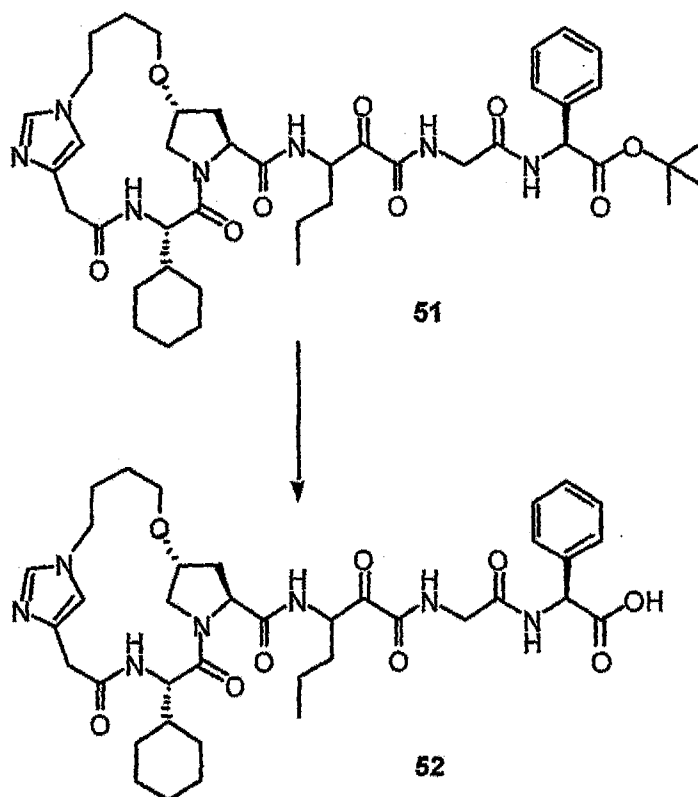
153

Step A

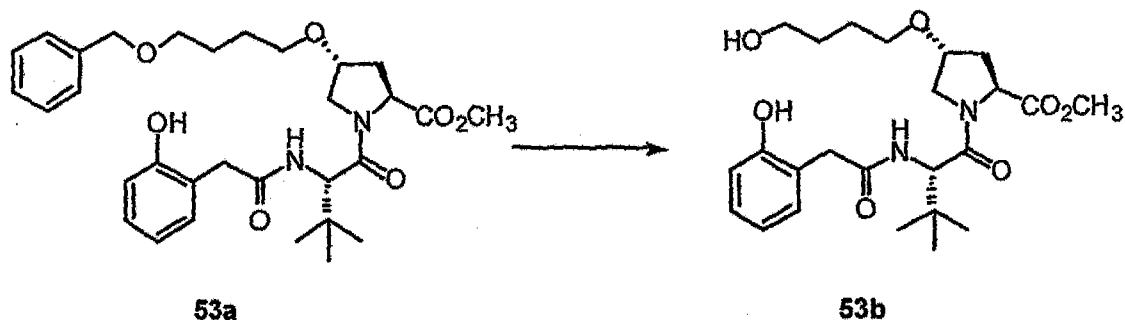
The expected product **51a** is synthesized as described earlier for Example 2 Step A.

154

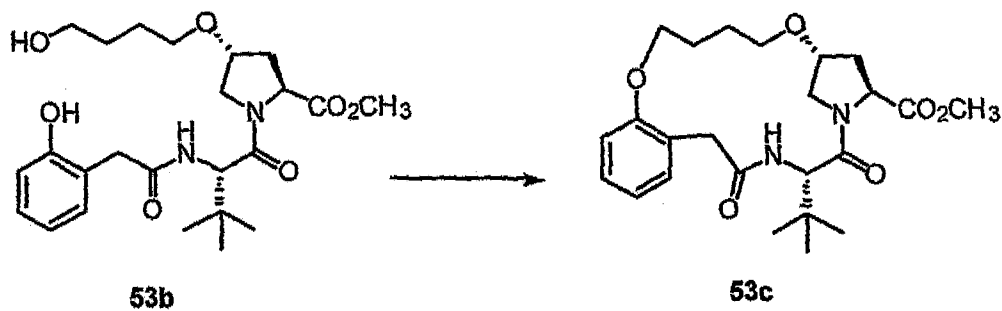
Step A



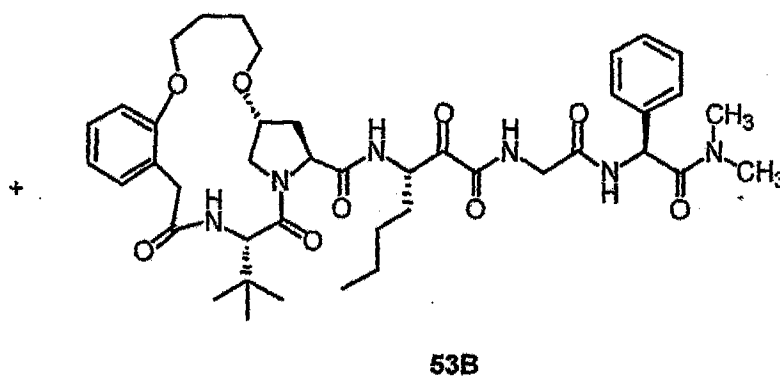
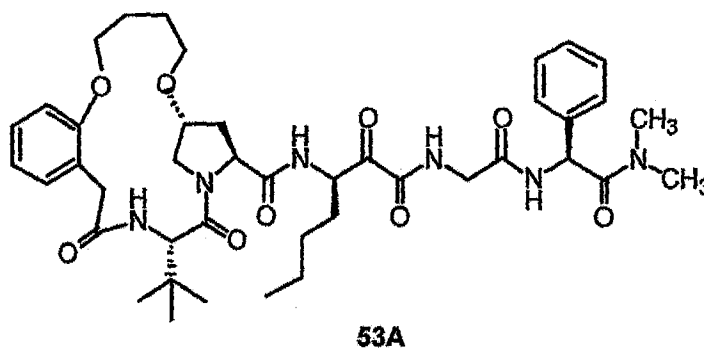
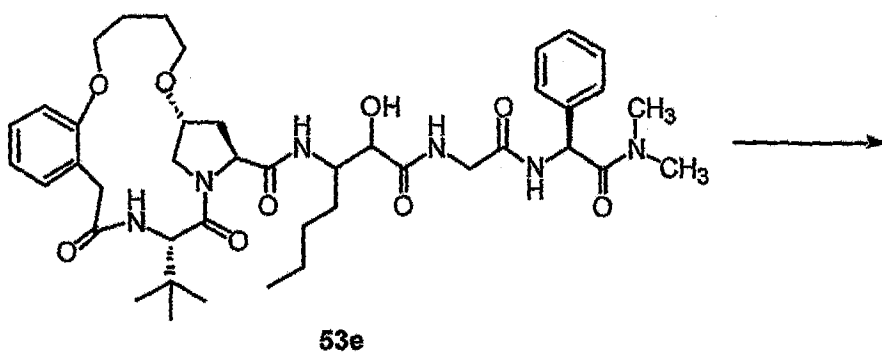
The desired product **52** is obtained by the procedure described previously for Example 3, Step A.

184
00153
155Step B:

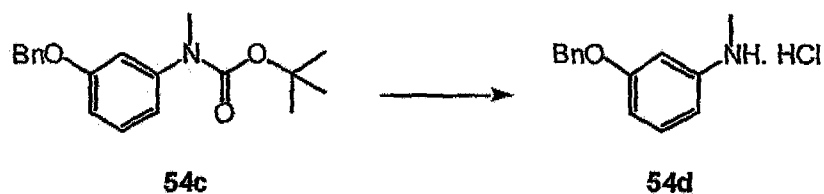
The desired product **53b** was obtained by the method described in Example 1, Step G. The crude material was carried to the next step as is.

Step C:

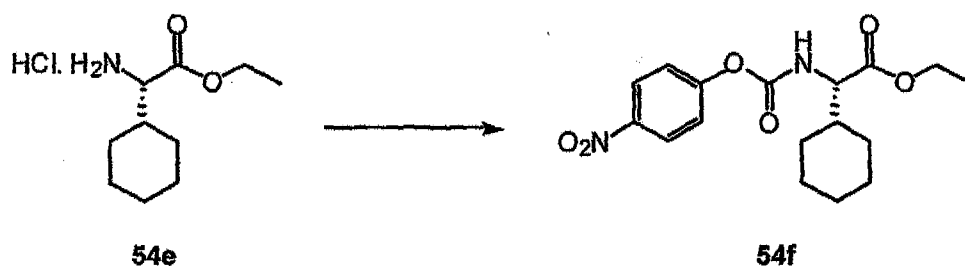
The desired product **53c** was obtained by the method described in Example 1, Step H. Purification by column chromatography using 99/1 dichloromethane/methanol afforded **53c** along with triphenylphosphine oxide. This mixture was taken to the next step.

00154
156Step F:

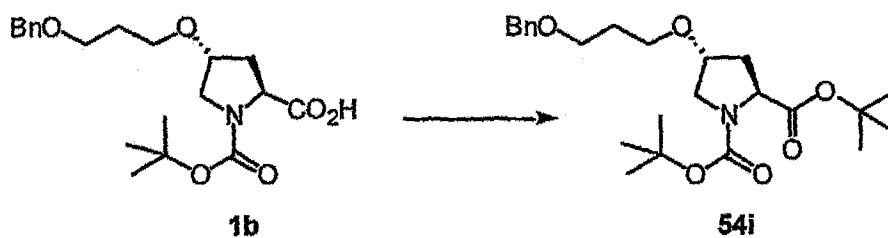
The desired products **53A** and **53B** were obtained by the oxidation protocol described previously for Example 1, Step K. Purification by flash column chromatography using 100/0 to 99/1 dichloromethane/methanol afforded separate isomers **53A** and **53B**, and some mixture.

157
00257
157Step C

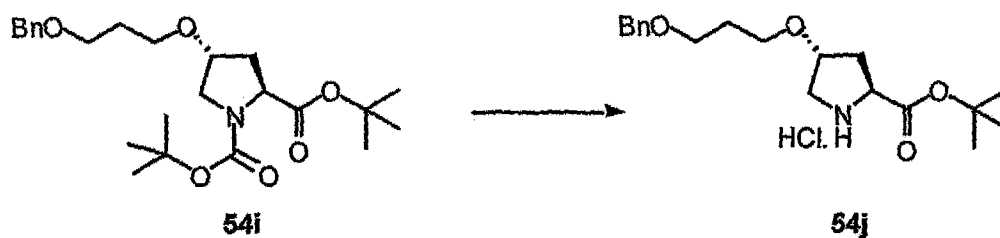
The desired product **54d** was obtained by the procedure described for Example 1 Step C. The crude product was used without further purification.

Step D

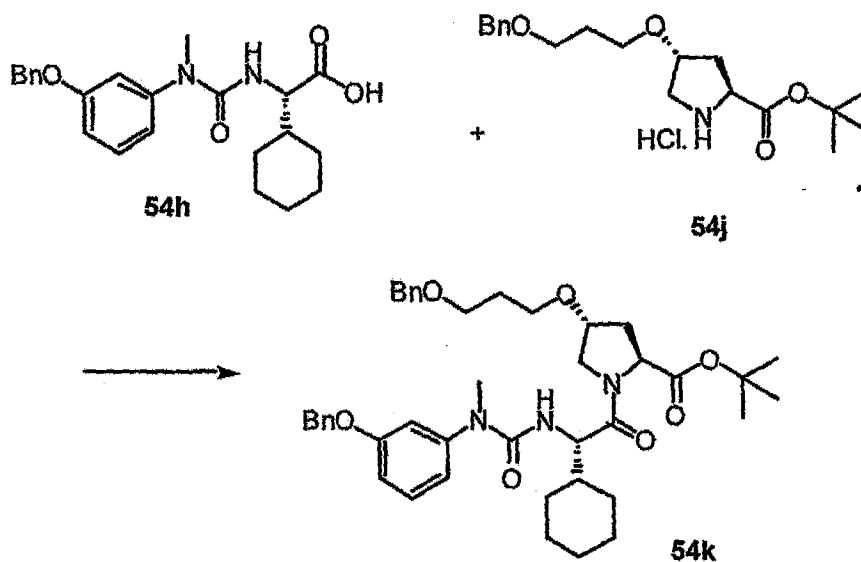
The desired product **54f** was obtained by the procedure described for Example 26 Step A using **54e** as the starting material. The crude product was purified by flash chromatography using 80/20 to 100/0 dichloromethane/hexanes to afford **54f**.

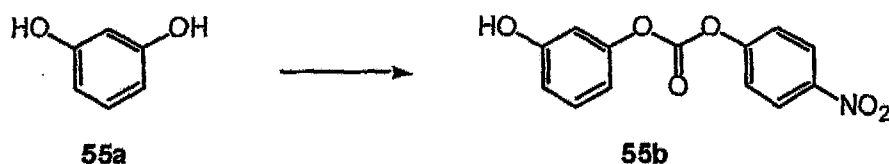
157
00280
158Step G

The desired compound **54i** was prepared by the protocol described for Example 18 Step B.

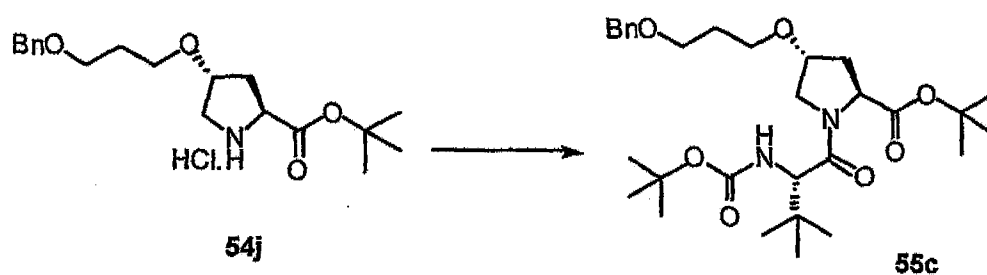
Step H

The desired product **54j** was obtained by the procedure described for Example 1 Step C. The crude material was used without purification.

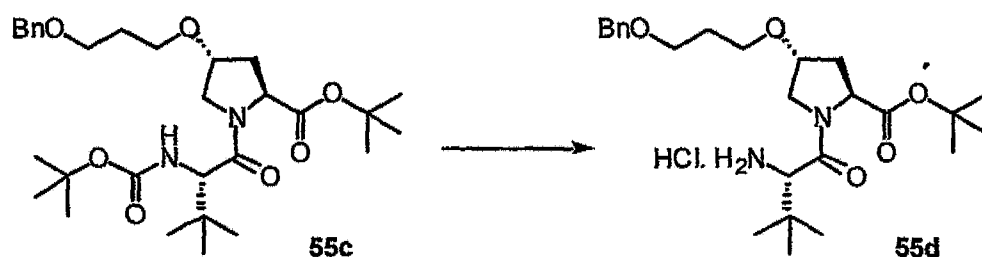
Step I

159
00153
160Step A

Commercially available **55a** was converted to the desired product **55b** using the procedure described for Example 26 Step A in 41% yield.

Step B

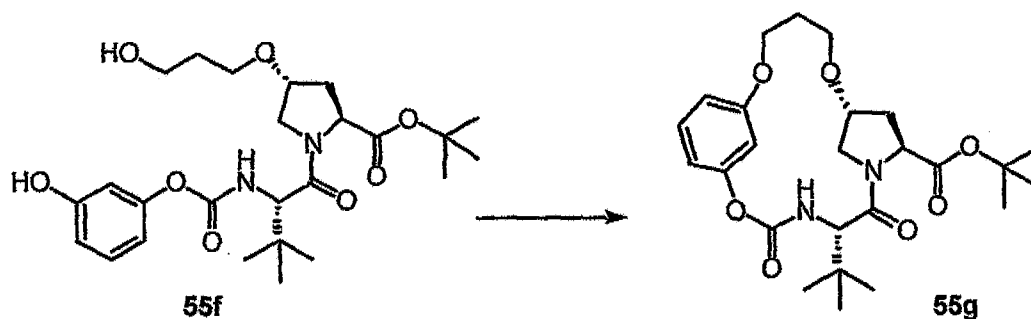
The desired product **55c** was obtained by the coupling protocol described previously for Example 1 Step D using N-boc-t-butylglycine as the coupling partner. Purification using 95/5 dichloromethane/EtOAc afforded **55c** in 57% yield.

Step C

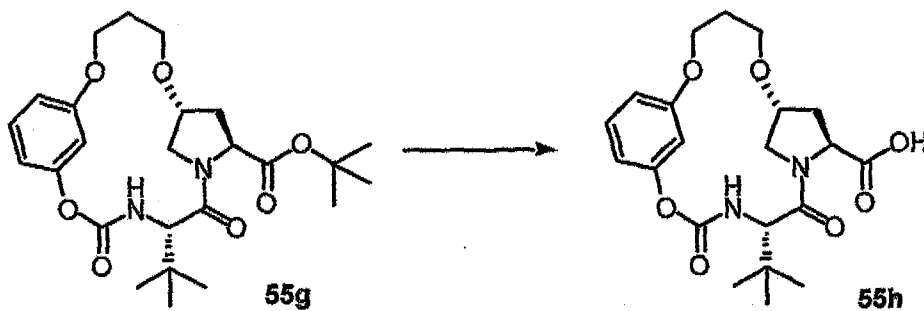
The desired product **55d** was obtained by the procedure described previously for Example 1 Step C. The crude material was carried further.

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Step F

The expected product **55g** was synthesized as described earlier for Example 1 Step H. Purification by flash chromatography using 85/15 dichloromethane/EtOAc provided **55g** in 10% yield.

Step G

The desired product **55h** was obtained by the method described previously for Example 3 Step A. The crude material was carried further without purification.