Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-057907- -00005-0000
Fecha: 2010-10-13 15:20:44 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 32

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [x] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente: 09 057907
Solicitante: NOVARTIS AG
Apoderado: CARLOS REYNALDO OLARTE GARCÍA
Título de la nueva creación o denominación del signo: FORMAS CRISTALINAS DE HEMIFUMARATO DE ALISKIREN
Gaceta: 618

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: **GYNOPHARM S.A.S.**
Dirección: **Carrera 14 Nº 94-44 Piso 7 Torre b**
Nacionalidad o Domicilio: **COLOMBIA**
Lugar de Constitución: **BARRANQUILLA**
Teléfono: **2 36 84 95** Fax:
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [x]
C.E. [ ] Otro [ ]
Cual
Número **802, 006,279-4**

REPRESENTANTE O APODERADO

Nombre: **ELIANA ISAURA MORENO BOHORQUEZ**
Dirección: **CARRERA 13 No. 119-95**
Teléfono: **(571)213 12 13** Fax: **(571)612 19 79**
E-mail: **negocios@optimum-co.com**

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número **51'975.664** TP **83823**

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: **Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN**
No cumple con los requisitos de patentabilidad.
Signo opositor:
Justificación:
La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

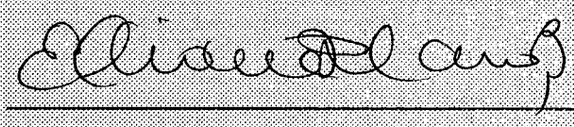
⑤ **Comprobante de pago No.** _____ **Fecha** _____

⑥ **ANEXOS**

- [x] Comprobante de pago de la tasa.
- [x] Poderes, si fuere el caso.
- [x] Pruebas de los fundamentos de la oposición.
- [ ] Documentos que acrediten el legítimo interes, si fuere el caso.
- [x] Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: **ELIANA ISAURA MORENO BOHORQUEZ**

FIRMA: 

C.C. **51.975.664** **TP.** **83823**

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

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 09 057907
Asunto	: Oposición a la solicitud de patente de Invención titulada "FORMAS CRISTALINAS DE HEMIFUMARATO DE ALISKIREN"
Solicitante	: NOVARTIS AG.
Opositora	: GYNOPHARM S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 618 del 19 de julio de 2010

Yo, *ELIANA ISAURA MORENO BOHORQUEZ,* abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *83823* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad GYNOPHARM *S.A.S.* Conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "FORMAS CRISTALINAS DE HEMIFUMARATO DE ALISKIREN", cuyos titulares son NOVARTIS AG, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular ALISKIREN. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 04 de junio de 2009 reivindicando prioridad bajo la solicitud EP20060123642 del 2006-11-07; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 618 del 19 de** julio de 2010, cuya publicación internacional corresponde a la WO2008061622 del 2008-05-29.

2.2. La solicitud colombiana 09 57907 objeto de la presente oposición se refiere a formas cristalinas de HEMIFUMARATO DE ALISKIREN y encarnaciones relacionadas con las mismas, por ejemplo, preparaciones farmacéuticas, los procesos para la fabricación de las formas cristalinas, usos farmacéuticos y similares. Las formas de cristal tienen propiedades particularmente ventajosas, por ejemplo el

ser útiles en la fabricación de preparaciones farmacéuticas para reducción de la presión de sanguínea.

2.3.En primera instancia, se debe advertir que en el capítulo reivindicatorio de la solicitud objeto de la presente oposición, se hace referencia a los usos de la composición en la medicina, no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)*", los usos no están contemplados como patentables; y, Artículo 20.- "*No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso no sería patentable.

2.4.Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*", tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: US2003149303 publicada el 07 de agosto de 2003.

2.5. Ahora bien, el documento D1, se refiere a un procedimiento para la preparación de 2 (S), 4 (S), 5 (S), 7 (S) -2,7 amidas-dialquil-4-hidroxi-5-amino-8-aril-octanoil y sus sales fisiológicamente aceptables, y los nuevos compuestos utilizados como

intermediarios en el proceso de varias etapas. Dicho documento D1 proporciona información detallada sobre cómo obtener cristales de hemifumarato de aliskiren, teniendo en cuenta que la estereoquímica elaborada para el grupo amino citado en el párrafo 001 del mismo documento D1 que corresponde a la preparación de compuestos 2 (8), 4 (8), 5 (8), 7 (8), es la misma estereoquímica del hemifumarato de aliskiren; la solicitud objeto de la presente oposición no es novedosa pues lo reclamado ya era parte de arte anterior.

2.6. Tomando el documento D1 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir de dicho documento D1 por sí solo, formas cristalinas de HEMIFUMARATO DE ALISKIREN y encarnaciones relacionadas con las mismas, por ejemplo, preparaciones farmacéuticas, los procesos para la fabricación de las formas cristalinas, usos farmacéuticos y similares. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 57907 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con ninguno de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud prerendida se riene que:

2.8.1. CARENCIA DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización,*

comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.". A la fecha de prioridad, 07 de noviembre de 2006 ya era conocido, pues como se demostró, eran parte del arte anterior con base en el documento D1, formas cristalinas de HEMIFUMARATO DE ALISKIREN y encarnaciones relacionadas con las mismas, por ejemplo, preparaciones farmacéuticas y los procesos para la fabricación de las formas cristalinas; sobre lo cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.".* A la fecha de prioridad, 07 de noviembre de 2006, a partir del documento D1 por sí solo, un experto en la materia puede llegar de manera evidente a formas cristalinas de HEMIFUMARATO DE ALISKIREN y encarnaciones relacionadas con las mismas, por ejemplo, preparaciones farmacéuticas, los procesos para la fabricación de las formas cristalinas, usos farmacéuticos y similares; sobre lo cual busca protección en el capitulo reivindicatorio.

2.8.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".* La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, en el capitulo reivindicatorio se reclaman usos y estos no son aplicables industrialmente porque primero no se obtiene un

producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos, no cumple con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*. La solicitud pretendida no cumple con ninguno de los tres requisitos de patentabilidad.

2.10. **Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada "FORMAS CRISTALINAS DE HEMIFUMARATO DE ALISKIREN", cuyos titulares son NOVARTIS AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 618 del 19 de julio de 2010.**

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

D1: US2003149303 publicada el 07 de agosto de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **GYNOPHARM S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US2003149303 publicada el 07 de agosto de 2003.

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

Carrera 13 Nº 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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96605417

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/09/29 HORA: 12:48:45

OPERACION: 03C360929069 PAGINA: 1

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad----------
anonima denominada GYNOPHARM S.A. ----------

C E R T I F I C A

Que según Acta No. 22 del 29 de Abril de 2010 correspondiente a la Asamblea de Accionistas en Barranquilla, inscrito(as) en esta Cámara de Comercio, el 24 de Junio de 2010 bajo el No. 160,098 del libro respectivo, la sociedad antes mencionada----------
se transformo en por acciones simplificada bajo la denominación de GYNOPHARM S.A.S.----------

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13
22	2010/04/29	Asamblea de Accionistas en Ba	160,098	2010/06/24
25	2010/08/18	Asamblea de Accionistas en Ba	161,872	2010/08/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.S.----------

SIGLA: .

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/09/29 HORA: 12:48:45

OPERACION: 03C360929069 PAGINA: 2

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CR 49 C No 80 - 125 OF 512.
De la ciudad de Barranquilla.
Correo electrónico: mvenegas@gynopharm.com.co
Pagina Web:

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2087.

C E R T I F I C A

OBJETO SOCIAL: El objeto de la sociedad es el ejercicio de todas las actividades comerciales para: 1)La importacion, exportacion, fabricacion, comercializacion, distribucion y venta de productos farmaceuticos, higienicos, veterinarios e implementos medicos. 2)Cualquier otra actividad licita de comercio relacionada con su objeto social principal y todo lo que se relaciona con la importacion de los bienes y equipos necesarios para el desarrollo de su objeto social. 3)Tener la representacion en Colombia de empresas o sociedades establecidas fuera del territorio colombiano, cuyo objeto sea similar o complementario. En desarrollo de su objeto social principal, la sociedad podra adelantar y celebrar los siguientes actos y contratos: A)Exportar e importar, agenciar, distribuir, comercializar, comprar o vender a comision o consignacion o de cualquier otra forma o modalidad, toda clase de equipos, aparatos, bienes al por mayor o al detal, y servicios relacionados con su actividad. B)Gravar en cualquier forma los bienes de su propiedad muebles o inmuebles, dar en prenda los primeros o hipotecar los segundos para garantizar obligaciones de la sociedad. C)Constituir apoderados que le representen, asociarse con otras compañias de la misma o parecida naturaleza y en general realizar toda clase de operaciones comerciales o civiles y ejecutar o celebrar toda clase de contratos o actos del mismo orden, ya sean industriales, comerciales o financieros encaminados a alcanzar los fines que se proponen. D)Adquirir, enajenar, administrar, recibir o dar en arrendatario o a cualquier titulo, toda clase de bienes muebles e inmuebles. E)Intervenir ante terceros o ante los accionistas mismos como acreedora o como deudora en toda clase de

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/09/29 HORA: 12:48:45

OPERACION: 03C360929069 PAGINA: 3

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operaciones de credito, dando o recibiendo las garantias del caso, cuando haya lugar a ellas; F)Efectuar cualquier clase de operaciones de credito activo o pasivo, tales como constituir depositos, efectuar prestamos. Otorgar o recibir documentos negociables, girar, aceptar, endosar, asegurar y negociar en general titulos valores recibirlos en pago; G)Celebrar y ejecutar en general todos los actos y contratos preparatorios, complementarios o accesorios de todos los anteriores, los que se relacionen con la existencia y funcionamiento de la sociedad, y los que sean conducentes al buen logro de los fines sociales.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********4,000,000,000	**********4,000,000	**********1,000
Suscrito		
$**********2,672,646,000	**********2,672,646	**********1,000
Pagado		
$**********2,672,646,000	**********2,672,646	**********1,000

C E R T I F I C A

ADMINISTRACION: La sociedad tendrá los siguientes órganos de dirección y administración: Asamblea General de Accionistas y Gerencia la cual será asumida por un Gerente y un subgerente quienes tendrán representación legal de la sociedad. Son funciones de la Asamblea General de Accionistas las siguientes entre otras: Nombrar al Gerente y a su suplente y fijar los honorarios a que tenga derecho; Autorizar al Gerente para suscribir actos y contratos en nombre de la sociedad, cuando(i) sean para adquirir, enajenar, recibir o dar en arrendamiento o a cualquier otro título, toda clase de bienes inmuebles de la sociedad o bienes muebles diferentes a los productos comercializados ordinariamente por la sociedad. e (ii) independiente de su objeto, supere en cuantía el equivalente a 300 SMLMV (TRESCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES). Las demás que le correspondan conforme a la ley o a estos estatutos. El Gerente de la sociedad tiene a su cargo la administración inmediata de la sociedad, así como la representación

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legal de la misma y en tal virtud le están asignadas las siguientes funciones y atribuciones entre otras: Llevar la representación de la entidad, tanto judicial como extrajudicialmente. Constituir, para casos especiales, apoderados judiciales o extrajudiciales. Celebrar los actos, operaciones y contratos conducentes al buen logro del objeto de la sociedad. Cuidar de la recaudación e inversión de los fondos de la sociedad. Las demás que le correspondan conforme a la ley y a estos estatutos. El Gerente de la Sociedad deberá contar con autorización previa de la Asamblea General de Accionistas, cuando pretenda suscribir en nombre de la Sociedad (i) actos o contratos para adquirir, enajenar, recibir o dar en arrendamiento o a cualquier otro título, toda clase de bienes inmuebles de la sociedad o bienes muebles diferentes a los productos comercializados ordinariamente por la sociedad, así como (ii) actos o contratos, independiente de su objeto, que supere en cuantía el equivalente a 300 SMLMV (TRESCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES).----------

C E R T I F I C A

Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.S. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Palacios Aragon Luis Alberto	CE.*********319,788

C E R T I F I C A

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.S. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*********351,283

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96605419

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/09/29 HORA: 12:48:45

OPERACION: 03C360929069 PAGINA: 5

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C E R T I F I C A

Que según Acta No. 23 del 25 de Junio de 2010 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A.S. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 14 de Julio de 2010 bajo el No. 160,520 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación

Revisor Fiscal.

DELOITTE &TOUCHE LTDA Ni.*****860,005,813

C E R T I F I C A

Que por Documento Privado del 25 de Junio de 2010, otorgado en Bogota, por DELOITTE & TOUCHE LTDA. inscrito en esta Cámara de Comercio, el 14 de Julio de 2010 bajo el Nro 160,524 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación

Designado: Revisor Fiscal Principal

Aguillon Rojas Sandra Milena CC.******47,436,442

Designado: Revisor Fiscal Suplente

Prada Sanchez Nubia Marcela CC.***1,032,358,923

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficienta a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo,consta que el senor JORGE CASTELLANOS MARTINEZ,identificado con C.C.No.19.460.089,actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Am-

*** CONTINUA ***

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plio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadania No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOFARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOFARM S.A. en el giro ordinario de sus negocios y operaciones sociales.----------

C E R T I F I C A

Que por Escritura Pública No. 2,404 del 28 de Mayo de 2009, otorgada en la Notaria 1a. de Bogota cuya parte pertinente se inscribió en esta Cámara de Comercio, el 02 de Julio de 2009 bajo el No. 3,948 del libro respectivo,----------

consta que el señor LUIS ALBERTO PALACIOS ARAGON con CE No.319788, en su calidad de Representante Legal de GYNOPHARM S.A., manifesto que confiere poder general, amplio y suficiente a la Doctora -------

CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadania numero 52.352.190, para que en nombre de la sociedad GYNOPHARM -----

S.A., promueva y defienda los intereses de la sociedad judicial y extrajudicialmente, en toda especie de gestiones y actuaciones ante las autooridades administrativas o jurisdiccionales en especial ----

para: a) Recibir notificaciones de cualesquiera tipo de actos ------

emanados de las autoridades administrativas o judiciales. b) -------

Presentar recursos por la via administrativa o judicial, renunciar a terminos, desistir, conciliar, transigir y modificar. c) Elevar peticiones y solicitar informacion a las autoridades ----------

administrativas y jurisdiccionales. d) Presentar demandas ante las autoridades administrativas y judiciales.----------

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2010.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en

*** CONTINUA ***

01

96605420

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/09/29 HORA: 12:48:45

OPERACION: 03C360929069 PAGINA: 7

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Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

15

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-057907- -00005-0000

Fecha: 2010-10-13 15:20:44 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 400 OPOSIOBSERVTER Folios: 32

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 86,173
FECHA : OCTUBRE 13 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	380130192	28/09/2010	1,475,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES		295,000.00
		TOTAL :	$	295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

16

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 **del C.S. de la J.**, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **09 057.907,** titulada **"FORMAS CRISTALINAS DE HEMIFUMARATO DE ALISKIREN",** cuyo titular es **NOVARTIS AG,** publicada en la gaceta No. 618 del 19 de julio de 2010.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 30 SEP 2010 días del mes de ___ de 2010.

GYNOPHARM S.A.S.

Cédula de Extranjería: No. 319788.
NIT: 802.006.279-4
Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

REPUBLICA DE COLOMBIA

DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo de Bogotá, LUIS. PALACIOS APAGON

quien exhibio la C.C. C.E. A3197 88

Expedida en [illegible] y declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

30 SEP 2010

BOGOTA, D.C.

FIRMA

HUELLA DEL INDICE DERECHO

NOTARIA DIECIOCHO DEL CIRCULO DE BOGOTA D.C.
LA HUELLA SE AUTENTICA POR SOLICITUD DEL INTERESADO

REPUBLICA DE COLOMBIA
JOSE MIGUEL [illegible] YO PINEROS
NOTARIO 18 DEL CIRCULO DE BOGOTA D.C.

CC: 241100

US 20030149303A1

(19) **United States**

(12) **Patent Application Publication** (10) Pub. No.: **US 2003/0149303 A1**

Stutz et al. (43) Pub. Date: **Aug. 7, 2003**

(54) **PROCESS FOR THE PREPARATION OF SUBSTITUTED OCTANOYL AMIDES**

(76) Inventors: **Stefan Stutz**, Basel (CH); **Peter Herold**, Basel (CH); **Felix Spindler**, Starrkirch-Wil (CH)

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Publication Classification

(51) **Int. Cl.**[7] **C07C 233/53**; C07D 305/12

(52) **U.S. Cl.** **564/164**; 549/321

(57) **ABSTRACT**

Compounds of formula (II) are simultaneously halogenated in the 5 position and hydroxylated in the 4 position under lactonization, the halolactone is converted into a hydroxy-lactone and then the hydroxy group into a leaving group, the leaving group is replaced with azide, the lactone amidated and then the azide converted to the amine group, in order to obtain compounds of formula (I).

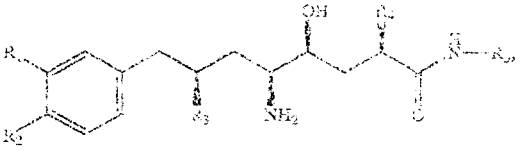
PROCESS FOR THE PREPARATION OF SUBSTITUTED OCTANOYL AMIDES

[0001] The invention relates to a process for the preparation of 2(S),4(S),5(S), 7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryl-octanoyl amides and their physiologically acceptable salts; and the new compounds used as intermediates in the multistage process.

[0002] In EP-A-0 678 503, δ-amino-γ-hydroxy-ω-aryl-alkanecarbox-amides are described, which exhibit renin-inhibiting properties and could be used as antihypertensive agents in pharmaceutical preparations. The manufacturing procedures described are unsatisfactory in terms of the number of process steps and yields and are not suitable for an industrial process. A disadvantage of these processes is also that the total yields of pure diastereomers that are obtainable are too small.

[0003] It has now been surprisingly found that these alkane-carboxamides can be prepared both in high total yields and in a high degree of purity, and that selectively pure diastereomers are obtainable, if the double bond of 2,7-dialkyl-8-aryl-4-octenic acid or 2,7-dialkyl-8-aryl-4-octenic acid ester is simultaneously halogenated in the 5 position and hydroxylated in the 4 position under lactonization, the halolactone is converted to a hydroxylactone and then the hydroxy group is converted to a leaving group, the leaving group substituted with azide, the lactone amidated and then the azide converted to the amine group. Apart from the high yields and stereoselectivities in the individual process steps, particular attention is drawn to the fact that substantially fewer by-products are formed in the azidation step.

[0004] A primary object of the invention is a process for the preparation of compounds of formula I,

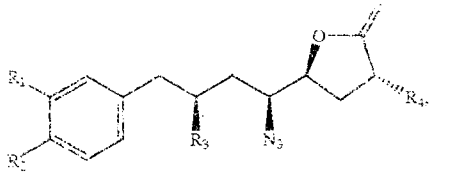


[0005] wherein

[0006] R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_3halogenalkyl, C_1-C_6alkoxy, C_1-C_3alkoxy-C_1-C_6alkyl, or C_1-C_3alkoxy-C_1-C_3alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_5 is C_1-C_6alkyl, C_1-C_5hydroxyalkyl, C_2-C_6alkoxy-C_1-C_6-alkyl, C_2-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, C_2-C_6-dialkylamino-C_1-C_6-alkyl, C_2-C_6-alkanoylamido-C_1-C_6-alkyl, HC(O)C—C_1-C_5-alkyl, C_1-C_6alkyl-C—(O)C—C_1-C_6alkyl, H_2N—C(O)—C_1-C_6alkyl, C_1-C_6alkyl-HN—C(O)—C_1-C_6alkyl or (C_1-C_6alkyl)$_2$N—C(O)—C_1-C_6-alkyl, comprising

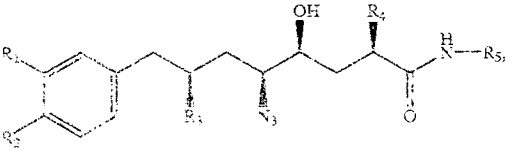
[0007] a) the reaction of a compound of formula II,

(II)



[0008] with an amine of formula R_5—NH_2 to form a compound of formula III,

(III)

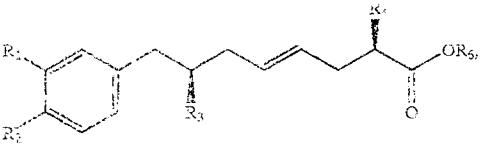


[0009] and

[0010] b) reduction of the azide group of the compound of formula III to the amine group and isolation of the compounds of formula I, if necessary with the addition of a salt-forming acid, comprising the preparation of compounds of formula II by reacting

[0011] c1) a compound of formula IV,

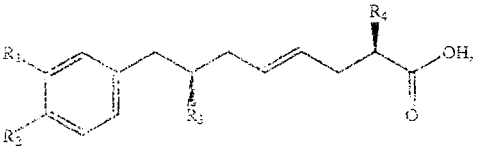
(IV)



[0012] wherein R_6 is C_1-C_{20}alkyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkyl-C_1-C_6alkyl, C_6-C_{14}aryl or C_6-C_{14}-aryl-C_1-C_6alkyl, with a halogenation agent to form a compound of formula VI, or

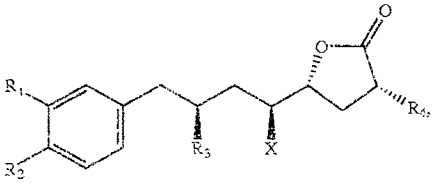
[0013] c2) a carboxylic acid of formula V, or a salt of this carboxylic acid,

(V)



[0014] with a halogenation agent to form a compound of formula VI,

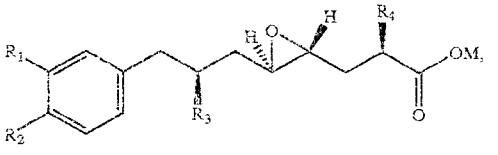
(VI)



[0015] wherein X is Cl, Br or I,

[0016] d) reaction of the compound of formula VI in the presence of an alkali metal or alkaline earth metal hydroxide or an alcohol to form a compound of formula VII,

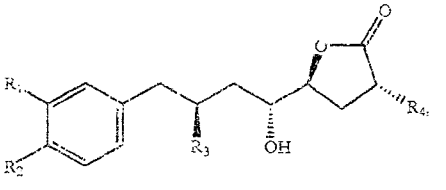
(VII)



[0017] wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group,

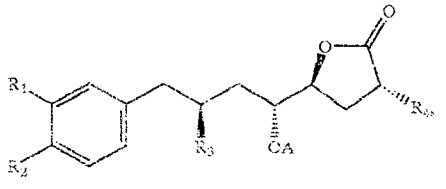
[0018] e) hydrolysis of the compound of formula VII in the presence of an acid to form a compound of formula VIII,

(VIII)



[0019] f) substitution of the hydrogen atom of the hydroxyl group in the compound of formula VIII and conversion thereof to a leaving group AO to form compounds of formula IX,

(IX)



[0020] g) and then reaction of the compound of formula IX with an oxidation agent to form a compound of formula II, or

[0021] h) reaction of the compound of formula VIII directly with a zinc azide/-bis-pyridine complex in the presence of a tertiary phosphine and an azodicarboxylate, if necessary in an organic solvent, to form a compound of formula II.

[0022] As an alkyl, R_1 and R_2 may be linear or branched and preferably comprise 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl.

[0023] As a halogenalkyl, R_1 and R_2 may be linear or branched and preferably comprise 1 to 4 C atoms, especially 1 or 2 C atoms. Examples are fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-chloroethyl and 2,2,2-trifluoroethyl.

[0024] As an alkoxy, R_1 and R_2 may be linear or branched and preferably comprise 1 to 4 C atoms. Examples are methoxy, ethoxy, n- and i-propyloxy, n-, i- and t-butyloxy, pentyloxy and hexyloxy.

[0025] As an alkoxyalkyl, R_1 and R_2 may be linear or branched. The alkoxy group preferably comprises 1 to 4 and especially 1 or 2 C atoms, and the alkyl group preferably comprises 1 to 4 C atoms. Examples are methoxymethyl, 1-methoxyeth-2-yl, 1-methoxyprop-3-yl, 1-methoxybut-4-yl, methoxypentyl, methoxyhexyl, ethoxymethyl, 1-ethoxyeth-2-yl, 1-ethoxyprop-3-yl, 1-ethoxybut-4-yl, ethoxypentyl, ethoxyhexyl, propyloxymethyl, butyloxymethyl, 1-propyloxyeth-2-yl and 1-butyloxyeth-2-yl.

[0026] As a C_1-C_6alkoxy-C_1-C_6alkyloxy, R_1 and R_2 may be linear or branched. The alkoxy group preferably comprises 1 to 4 and especially 1 or 2 C atoms, and the alkyoxy group preferably comprises 1 to 4 C atoms. Examples are methoxymethyloxy, 1-methoxyeth-2-yloxy, 1-methoxyprop-3-yloxy, 1-methoxybut-4-yloxy, methoxypentyloxy, methoxyhexyloxy, ethoxymethyloxy, 1-ethoxyeth-2-yloxy, 1-ethoxyprop-3-yloxy, 1-ethoxybut-4-yloxy, ethoxypentyloxy, ethoxyhexyloxy, propyloxymethyloxy, butyloxymethyloxy, 1-propyloxyeth-2-yloxy and 1-butyloxyeth-2-yloxy.

[0027] In a preferred embodiment, R_1 is methoxy- or ethoxy-C_1-C_4alkyloxy, and R_2 is preferably methoxy or ethoxy. Particularly preferred are compounds of formula I, wherein R_1 is 1-methoxyprop-3-yloxy and R_2 is methoxy.

[0028] As an alkyl, R_3 and R_4 may be linear or branched and preferably comprise 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl. In a preferred embodiment, R_3 and R_4 in compounds of formula I are in each case isopropyl.

[0029] As an alkyl, R_5 may be linear or branched in the form of alkyl and preferably comprise 1 to 4 C atoms. Examples of alkyl are listed hereinabove. Methyl, ethyl, n- and i-propyl, n-, i- and t-butyl are preferred.

[0030] As a C_1-C_6hydroxyalkyl, R_5 may be linear or branched and preferably comprise 2 to 6 C atoms. Some examples are 2-hydroxyethy-1-yl, 2-hydroxyprop-1-yl, 3-hydroxyprop-1-yl, 2-, 3- or 4-hydroxybut-1-yl, hydroxypentyl and hydroxyhexyl.

[0031] As a C_1-C_6alkoxy-C_1-C_6alkyl, R_5 may be linear or branched. The alkoxy group preferably comprises 1 to 4 C atoms and the alkyl group preferably 2 to 4 C atoms. Some examples are 2-methoxyethy-1-yl, 2-methoxyprop-1-yl, 3-methoxyprop-1-yl, 2-, 3- or 4-methoxybut-1-yl, 2-ethoxyethy-1-yl, 2-ethoxyprop-1-yl, 3-ethoxyprop-1-yl, and 2-, 3- or 4-ethoxybut-1-yl.

[0032] As a C_1-C_6alkanoyloxy-C_1-C_6alkyl, R_5 may be linear or branched. The alkanoyloxy group preferably comprises 1 to 4 C atoms and the alkyl group preferably 2 to 4 C atoms. Some examples are formyloxymethyl, formyloxyethyl, acetyloxy-ethyl, propionyloxyethyl and butyroyloxyethyl

[0033] As a C_1-C_6aminoalkyl, R_5 may be linear or branched and preferably comprise 2 to 4 C atoms. Some examples are 2-aminoethyl, 2- or 3-aminoprop-1-yl and 2-, 3- or 4-aminobut-1-yl.

[0034] As C_1-C_6alkylamino-C_1-C_6alkyl and C_1-C_6dialkylamino-C_1-C_6-alkyl, R_5 may be linear or branched. The alkylamino group preferably comprises C_1-C_4alkyl groups and the alkyl group preferably 2 to 4 C atoms. Some examples are 2-methylaminoeth-1-yl, 2-dimethylaminoeth-1-yl, 2-ethylaminoeth-1-yl, 2-ethylaminoeth-1-yl, 3-methylaminoprop-1-yl, 3-dimethylaminoprop-1-yl, 4-methylaminobut-1-yl and 4-dimethylaminobut-1-yl.

[0035] As a C_1-C_6alkanoylamido-C_1-C_6alkyl, R_5 may be linear or branched. The alkanoyl group preferably comprises 1 to 4 C atoms and the alkyl group preferably 1 to 4 C atoms. Some examples are 2-formamidoeth-1-yl, 2-acetamidoeth-1-yl, 3-propionylamidoeth-1-yl and 4-butyroylamidoeth-1-yl.

[0036] As a HO(C)C—C_1-C_5alkyl, R_5 may be linear or branched and the alkyl group preferably comprises 2 to 4 C atoms. Some examples are carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl.

[0037] As a C_1-C_4alkyl-O—(O)C—C_1-C_6alkyl, R_5 may be linear or branched, and the alkyl groups preferably comprise independently of one another 1 to 4 C atoms. Some examples are methoxycarbonylmethyl, 2-methoxycarbonyleth-1-yl, 3-methoxycarbonylprop-1-yl, 4-methoxycarbonylbut-1-yl, ethoxycarbonylmethyl, 2-ethoxycarbonyleth-1-yl, 3-ethoxycarbonyl-prop-1-yl, and 4-ethoxycarbonylbut-1-yl.

[0038] As a H_2N—C(O)—C_1-C_5alkyl, R_5 may be linear or branched, and the alkyl group preferably comprises 2 to 6 C atoms. Some examples are carbamidomethyl, 2-carbamidoeth-1-yl, 2-carbamido-2,2-dimethyleth-1-yl, 2- or 3-carbamidoprop-1-yl, 2-, 3- or 4-carbamidobut-1-yl, 3-carbamido-2-methylprop-1-yl, 3-carbamido-1,2-dimethylprop-1-yl, 3-carbamido-3-ethylprop-1-yl, 3-carbamido-2,2-dimethylprop-1-yl, 2-, 3-, 4- or 5-carbamidopent-1-yl, 4-carbamido-3,3- or -2,2-dimethylbut-1-yl.

[0039] As a C_1-C_6alkyl-HN—C(O)—C_1-C_6-alkyl or (C_1-C_6alkyl)$_2$N—C(O)—C_1-C_6alkyl, R_5 may be linear or branched, and the NH-alkyl group preferably comprises 1 to 4 C atoms and the alkyl group preferably 2 to 6 C atoms. Examples are the carbamidoalkyl groups defined hereinabove whose N atom is substituted, with one or two methyl, ethyl, propyl or butyl.

[0040] A preferred subgroup of compounds of formula I is that in which R_1 is C_1-C_4alkoxy or C_1-C_4alkoxy-C_1-C_4alkyloxy, R_2 is C_1-C_4alkoxy, R_3 is C_1-C_4alkyl, R_4 is C_1-C_4alkyl and R_5 is $H_2NC(O)$—C_1-C_4alkyl which if necessary is N-monosubstituted or N-di-C_1-C_4alkyl substituted.

[0041] A more preferred subgroup of compounds of formula I is that in which R_1 is methoxy-C_2-C_4-alkyloxy, R_2 is methoxy or ethoxy, R_3 is C_2-C_4alkyl, R_4 is C_2-C_4alkyl and R_5 is $H_2NC(O)$—C_1-C_5alkyl.

[0042] An especially preferred compound of formula I is that in which R_1 is 3-methoxy-prop-3-yloxy, R_2 is methoxy, R_3 and R_4 are 1-methyleth-1-yl, and R_5 is $H_2NC(O)$—$[C(CH_3)_2]$—CH_2—.

[0043] As an alkyl, R_6 may be linear or branched and comprise preferably 1 to 12 C atoms, 1 to 8 C atoms being especially preferred. R_6 is particularly preferred as a linear C_1-C_4alkyl. Some examples are methyl, ethyl and the isomers of propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, hexadecyl, octacyl and eicosyl. Especially preferred are methyl and ethyl.

[0044] As a cycloalkyl, R_6 may preferably comprise 4 to 8 ring-carbon atoms, 5 or 6 being especially preferred. Some examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and cyclododecyl.

[0045] As a cycloalkyl-alkyl, R_6 may comprise preferably 4 to 8 ring-carbon atoms, 5 or 6 being especially preferred, and preferably 1 to 4 C atoms in the alkyl group, 1 or 2 C atoms being especially preferred. Some examples are cyclopropyl methyl, cyclobutyl methyl, cyclopentyl methyl or cyclopentyl ethyl, and cyclohexyl methyl or cyclohexyl ethyl.

[0046] As an aryl, R_6 is preferably phenyl or naphthyl.

[0047] As an aralkyl, R_6 is preferably benzyl or phenyl ethyl.

[0048] In formula VII, M may be an alkaline earth metal, for example Mg, Ca or Sr. Equivalent in the context of the invention means the charge equalization of cation and anion. M is preferably an alkali metal, for example Li, Na or K. Particular preference is for M as Li. If M is the residue of an alcohol minus a hydroxyl group, it may be the R_6 group, including the embodiments and preferences described hereinbefore, in particular alkyl and cycloalkyl.

[0049] Residue A in the leaving group AO is preferably the residue of an organic acid, for example C_1-C_8acyl, particular preference being for C_1-C_8sulfonyl. The acyl residue may be a carboxylic acid, such as formic acid, acetic acid, propionic acid, butyric acid and benzoic acid substituted if necessary with C_1-C_4alkyl, C_1-C_4alkoxy or halogen. The sulfonyl residue A may correspond for example to formula R_7—SO_2—, wherein R_7 is C_1-C_8alkyl, C_1-C_8halogenalkyl, C_3-C_8cycloalkyl, or phenyl or benzyl either unsubstituted or substituted with C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4halogenalkyl or halogen. Some examples of sulfonyl residues are methyl, ethyl, phenyl, methylphenyl, dimethyl phenyl, trimethyl phenyl, trifluoromethyl phenyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl and trifluoromethyl sulfonyl.

[0050] The individual process steps may be carried out in the presence of solvent. Suitable solvents are water and

organic solvents, especially polar organic solvents, which can also be used as mixtures of at least two solvents. Examples of solvents are hydrocarbons (petroleum ether, pentane, hexane, cyclohexane, methylcyclohexane, benzene, toluene, xylene), halogenated hydrocarbon (dichloromethane, chloroform, tetrachloroethane, chlorobenzene); ether (diethyl ether, dibutyl ether, tetrahydrofuran, dioxane, ethylene glycol dimethyl or diethyl ether); carbonic esters and lactones (methyl acetate, ethyl acetate, methyl propionate, valerolactone); N,N-substituted carboxamides and lactams (dimethylformamide, dimethylacetamide, N-methylpyrrolidone); ketones (acetone, methylisobutylketone, cyclohexanone); sulfoxides and sulfones (dimethylsulfoxide, dimethylsulfone, tetramethylene sulfone); alcohols (methanol, ethanol, n- or i-propanol, n-, i- or t-butanol, pentanol, hexanol, cyclohexanol, cyclohexanediol, hydroxymethyl or dihydroxymethyl cyclohexane, benzyl alcohol, ethylene glycol, diethylene glycol, propanediol, butanediol, ethylene glycol monomethyl or monoethyl ether, and diethylene glycol monomethyl or monoethyl ether; nitriles (acetonitrile, propionitrile); tertiary amines (trimethylamine, triethylamine, tripropylamine and tributylamine, pyridine, N-methylpyrrolidine, N-methylpiperazine, N-methylmorpholine) and organic acids (acetic acid, formic acid).

[0051] Process Step a)

[0052] The reaction of compounds of formula II to form compounds of formula III with a compound R_5NH_2 by opening of the lactone ring can be carried out with or without solvent. The reaction is expediently carried out in the presence of alcohols or amines, which can form activated carbonic esters or carboxamides. Such compounds are well-known. These may be 2-hydroxypyridine, N-hydroxycarboxamides and imides, and carboximides (N-hydroxysuccinimide). Organic solvents are used as solvent, tertiary amines being of advantage, for example trimethylamine or triethylamine. The reaction temperature may range for example from approximately 40° C. to 150° C. and preferably from 50° C. to 120° C.

[0053] Process Step b)

[0054] Reduction of the azide group to the amine group in the compounds of formula III takes place in a manner known per se (see Chemical Reviews, Vol. 88 (1988), pages 298 to 317), for example using metal hydrides or more expediently using a catalytic method with hydrogen in the presence of homogeneous (Wilkinson catalyst) or heterogeneous catalysts, for example Raney nickel or precious metal catalysts such as platinum or palladium, if necessary on substrates such as carbon. The hydrogenation can also be carried out if necessary catalytically under phase transfer conditions, for example with ammonium formate as hydrogen donor. It is of advantage to use organic solvents. The reaction temperature may range for example from approximately 0° C. to 200° C. and preferably from 10° C. to 100° C. Hydrogenation may be carried out at normal pressure or increased pressure up to 100 bar, for example, and preferably up to 50 bar.

[0055] The compounds of formula I may be converted to addition salts in a manner known per se by treatment with monobasic or polybasic, inorganic or organic acids. Hemifumarates are preferred.

[0056] Process Step c1)

[0057] Suitable chlorination, bromination and iodination agents are elemental bromine and iodine, in particular N-chlorine, N-bromine and N-iodocarboxamides and dicarboximides. Preferred are N-chloro, N-bromo and N-iodophthalimide and especially chloro, N-bromo and N-iodosuccinimide, as well as tertiary butyl hypochlorite and N-halogenated sulfonamides and sulfonimides, for example chloramine T. The reaction is advantageously carried out in organic solvents miscible with water, such as tetrahydrofuran or dioxane in the presence of at least an equivalent volume of water. The reaction takes place first at low temperatures, for example −20 to 10° C., and then at elevated temperatures, for example 30 to 100° C. The presence of inorganic or organic acids may be advantageous. Suitable acids are for example formic acid, acetic acid, methanesulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, toluenesulfonic acid, H_2SO_4, H_3PO_4, hydrogen halides, acid ion exchange resins, and acids immobilized on solid carriers. The halolactone may be isolated for example by extraction with organic solvents.

[0058] Process Step c2)

[0059] Suitable chlorination, bromination and iodination agents are elemental bromine and iodine, in particular N-chloro, N-bromo and N-iodocarboxamides and dicarboximides. Preferred are N-chloro, N-bromo and N-iodophthalimide and especially chloro, N-bromo and N-iodosuccinimide, as well as tertiary butyl hypochlorite and N-halogenated sulfonamides and sulfonimides, for example chloramine T. The reaction is advantageously carried out in organic solvents, such as halogenated hydrocarbons (chloroform, dichloromethane). The reaction temperature may range for example from approximately −70° C. to ambient temperature and preferably from −30° C. to 10° C. The halolactone may be isolated for example by extraction with organic solvents.

[0060] Suitable salts of carboxylic acids of formula V are for example alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, as well as ammonium salts. The ammonium salts may derive from ammonia, primary, secondary or tertiary amines, or they may be quaternary ammonium salts. The amines may be acyclic or cyclic and comprise heteroatoms from the C and S group. The amines may comprise 1 to 18 C atoms, 1 to 12 being preferred and 1 to 8 especially preferred. Quaternary ammonium salts may comprise 4 to 18 C atoms, 4 to 12 being preferred and 4 to 8 especially preferred. Some examples of amines are methylamine, dimethylamine, triethylamine, ethylamine, diethylamine, triethylamine, propylamine, dipropylamine, Tripropylamine, isopropylamine, butylamine, dibutylamine, tributylamine, phenylamine, methylethylamine, methyldiethylamine, phenylmethylamine, benzylamine, cyclopentylamine, cyclohexylamine, piperidine, N-methyl-piperidine, morpholine, pyrrolidine, and 2-phenylethylamine. Salt formation allows a more efficient purification of the carboxylic acids of formula V with regard to their optical and chemical purity, especially when crystalline salts are formed with the selection of amines. The salts may be converted before the reaction to the carboxylic acids of formula V. However, the salts may also be used directly for halolactonization. In this case, the addition of acids, for example trifluoroacetic acid or other strong acids, is recommended, as described under process step c1).

[0061] The halolactonization is surprisingly stereoselective, and the desired cis-halolactones are formed in yields of up to 90% or more.

[0062] Process Step d)

[0063] The reaction of a compound of formula VI with at least equimolar quantities of alkali or alkaline earth metal hydroxides is expediently carried out in a polar organic solvent, for example alcohols such as isopropanol, and at low temperatures of, for example, −20 to 30° C. Aqueous solutions of hydroxides are preferably used, lithium hydroxide being especially preferred. The compound of formula VII does not need to be isolated, but the reaction mixture can be used directly in process step e). The desired stereoisomer is also formed in this step at high yields of up to 90% or more.

[0064] The reaction of a compound of formula VI with at least equimolar quantities of an alcohol, especially a C_1-C_8alkanol and in particular methanol or ethanol, is expediently carried out in a polar organic solvent, for example ethers or the alkanols used for esterification, and at low temperatures of, for example −20 to 30° C. Bases are preferably used as well, for example alkali metal hydrogencarbonates or alkali metal carbonates, potassium hydrogencarbonate being especially preferred. The compound of formula VII does not need to be isolated, but the reaction mixture can be used directly in process step e). The desired stereoisomer is also formed in this reaction at high yields of up to 90% or more.

[0065] Process Step e)

[0066] Lactonization of the compounds of formula VII to form compounds of formula VIII is expediently carried out at a temperature of −20 to 50° C. and in the presence of a preferably polar solvent, such as an alcohol (isopropanol) or ether (tetrahydrofuran, dioxane). It is advantageous to use inorganic acids, especially mineral acids such as hydrochloric acid, hydrobromic acid or sulfuric acid. The hydroxylactone of formula VII may be isolated for example by extraction with organic solvents. The desired stereoisomer is also formed in this step at high yields of up to 90% or more.

[0067] Process Step f)

[0068] Conversion of the hydroxy group to a leaving group may be carried out in organic solvents, preferably polar organic solvents, and at temperatures of −20 to 50° C. Acid halogenides, such as acid chlorides and acid bromides, are preferably used as reagents. Sulfonyl chlorides or bromides are especially preferred. The reaction is advantageously carried out in the presence of equivalent quantities of a base for bonding of the acid. Suitable bases are in particular tertiary amines, such as trimethylamine or triethylamine and dimethylaminopyridine. The hydroxylactone of a compound of formula VII may be isolated for example by extraction with organic solvents. The yields are up to 90% or more.

[0069] Process Step g)

[0070] Suitable azidation agents are for example metal azides, especially alkaline earth metal azides and alkali metal azides, as well as silyl azides. Especially preferred azidation agents are lithium azide, sodium azide and potassium azide. The reaction may be carried out in organic solvents, such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), dimethylformamide (DMF), 1,3-dimethylimidazolidinone (DMI), toluene or methylcyclohexane. The reaction temperature may range for example from approximately 20° C. to 150° C. and preferably from 50° C. to 120° C. It may be expedient to include the use of phase transfer catalysts. The preparation and synthetic use of azides are described for example by E. F. V. Scriven in Chemical Reviews, Vol. 88 (1988), pages 298 to 317 The yield amounts to an outstanding 70% or more.

[0071] In one variant, the introduction of the leaving group in process step f) and the azidation in process step g) may be carried out simultaneously in one reaction vessel.

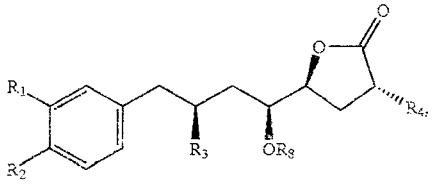
[0072] Process Step h)

[0073] In one variant, the azidation may also be carried out directly with the hydroxyl compound of formula VIII. This reaction has been described by David. L. Hughes in Organic Preparations and Procedures Int. (1996), 28 (2), pp. 127-164 and by M. C. Viaud et al. in Synthesis (1990), pp. 130 to 131. The azidation is carried out with at least equimolar quantities of zinc azide/bis-pyridine in the presence of, for example, triphenylphosphine in quantities of 2 equivalents or more, and approximately equal quantities of an azodicarboxylate such as azodiisopropylcarboxylate. The reaction is carried out in an organic solvent, especially an aromatic hydrocarbon, such as benzene, toluene or xylene. The reaction temperature may be −20 to 80° C.

[0074] Some intermediates prepared using the process according to the invention are new and represent further objects of the invention.

[0075] A further object of the invention is thus a compound of formula X,

(X)



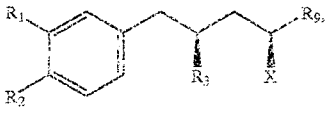
[0076] wherein

[0077] R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_5alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C1-C6alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoyl-R_{C1}-C_5alkanoyloxy-C1- c6alkyl, C1-C6aminoalkylamno C3.-c6-alkyl, C1-C6-dialkylai 1., -C6-alkanoyl-amido - C -C6-al kyl, 6-lyl, C, -C6alkyl -O- (0)C-C, -s - C6alk C6alkyl, C_1-C_6alkyl-HN-C(0) -C_1-C_6alkyl or

[0078] R_8 is hydrogen or R_8O is a leaving group.

[0079] For residues R_1, R_2, R_3, and R_4 in compounds of formula X, the embodiments and preferences described hereinbefore apply.

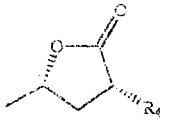
[0080] XI,



(XI)

[0081] wherein

[0082] X is halogen and Rg is a residue of form a

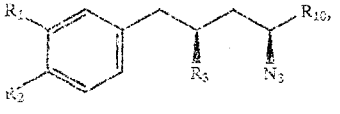


[0083] and

[0084] R_1 and R_2 are, inde ndently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, $_1$-Csalkoxy, C_1-C_6alkoxy-Cl7C_6alkyl, or C_1-C6alkoxy-C_1-0$_6$a1 loxy, R3 is C_1-Caikyl, R_4 is C_1-C_6alkyl, and R_5 is Cl-C.a yl, C_1-C_6hydroxyalkyl, Cl-Cfalkoxy-C_1-C_6-alkyl, C_1-C_6alkano oxy-C_1-C_6alkyl, C_1-C_6aminoalkyvl C_1-C_6alkylamino-C_1-C_6-al#,1, C_1-C_6-dialkylamino-C_1-C6-alkylEC1-C_6-alkanoyl-amico $_1$-C_6-alkyl, HO(0)C-C_1-C_5-alkyl, Ci C6alkyl-0-(0)C-C-C_6 yl, H_2N-C (0) -C_1-C_5alkyl, C_1-C_6alkyl -HN-C(0) C_1-C_5alkyl or

[0085] compounds of formula XI, the embodimenis and pretere described hereinbefore apply.

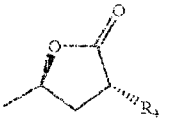
[0086] An object of the invention is also a compound of formula XII,



(XII)

[0087] wherein

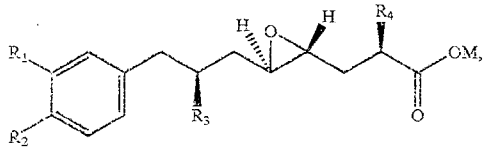
[0088] R_{2} is a residue of formula



[0089] and

[0090] R_1 and R_2 are, indepen ently of one another, H, Cl-Calkyl, C_1-C_5halogenalkyl, CC lalkoxy, O_1-C_6alkoxy-C_1-C_5alkyl, or Cl-C_5alkoxy-CL-C_5alkyloy, R_3 is C_1-C_5alkyl, R_4 is C_1-C_6alkyl, and R5 is CL-C_6alkyl, C_1-C_6hydroxyalkyl, C_2-C_5alkoxy-CL-C_5-alkyl, C_1-C_5alkanoyloxy C r-C_6alkyl, C1-C6aminoalkyl, C_1-C_6alkylamino-C_1-C_6-alkyl, O_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_5-alkanoyl-amido-CC$_6$- ikyl, HO (0) C-C_1-C_6-alkyl, C_1-C_6alkyl-O- (0)C-Cl-C_5alkyl, -CN-C(O)l-O-C_5alkyl, C1-C6alkyl-HN-C(O)-C1-C6alkyl or (0$_2$C$_6$al l)$_2$N-C(O) -C_1-C_5-alkyl. For esidues R_1, R_2, R_3, and R_4 in compounds of formula XII, t embodiments and prefe.rences described hereinbefore 4 pply. .

[0091] An object of the invention in a broader sense is a compound of formula VII,



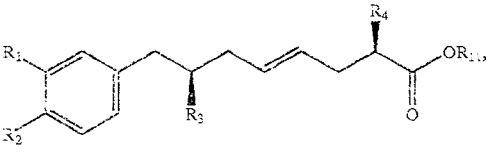
(VII)

[0092] wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group, and

[0093] R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_3-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, amino-C1-C6-alkyl, C1-C6-dialkylam l Cl-Cr,-alkanoyl-amido-C1-C6-alkyl, HO.-c - a lk, C1-C6alkyl-0- (0)C-Cl-C6a -Calkyl, C_1-C_6alkyl-HN-C (0) -C_1-C_6alkyl or.

[0094] For residues R_1, R_2, R_3, and R_4, as well as for M, in compounds of formula VII, the embodiments and preferences described hereinbefore apply.

[0095] An object of the invention is a compound of formula XIII



(XIII)

[0096] wherein R_{11} is an alkali metal, an equivalent alkaline earth metal, hydrogen or the residue ot an alcohol minus a hydroxyl group, and

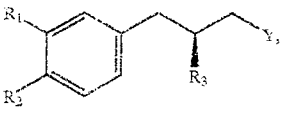
[0097] R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_5halogenalkyl, C_1-C_6alkoxy, C_1-C_5alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_5alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_5alkyl, alkyl, C_1-C_5alkanoyloxy-C_1-C_6alkyl, Cl- Cl C6alkylamino-C_1-C_6-alkyl, c_1-c_6- mino-C_1-C6-alkyl, CL-C_6-alkanoyl-amido-Cl- 1 O H(O)C-C_1-C_6-alkyl, C_1-C_6alkyl-O-(0) C i- H_2N-C (0) -C_1-C_6alkyl. C_1-C_6alkyl-HN-C (0) -C_1

[0098] For residues R_1, R_2, R_3, R_4, and R_{11} in compounds of formula XIII, the embodiments and preferences described hereinbefore apply.

[0099] The carboxylic acids of formula V used in process step c) may be prepared in a manner known per se by hydrolysis of hydrolysable acid derivatives such as carbonic esters, carboxamides or carboxylates. The hydrolysis may be carried out with acids or bases. Hydrolysis with a base is preferred, for example with alkali metal hydroxides (LIOH, KOH and NaOH), which can be added as aqueous solution or as a solid. The reaction is advantageously carried out in water, organic solvents (alcohols and ethers) or mixtures thereof. The reaction temperature may range up to the boiling temperature of the solvent used. After removal of the solvent, the residue of the reaction is expediently taken up with an aqueous acid, such as hydrochloric acid, and the compound of formula V is extracted (for example with ethers) and purified. The hydrolysis is quantitative, and the pure compound of formula V is obtained in yields of more than 90%. It is possible to carry out the hydrolysis at the same time as the halolactonization in one reaction vessel. The hydrolysis may also be carried out enzymatically.

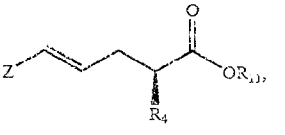
[0100] The compounds of formula XIII are obtainable by reacting a compound of formula XIV

(XIV)



[0101] with a compound of formula XV,

(XV)



[0102] wherein R_1 to R_4, and R_{11} are as defined hereinbefore, including the preferences, Y is Cl, Br or I, and Z is Cl, Br or I, in the presence of an alkali metal or alkaline earth metal. Y and Z are preferably Br and especially Cl.

[0103] The coupling of Grignard reagents with alkenyl halogenides in an ether such as tetrahydrofuran or dioxane as solvents in the presence of catalytic quantities of a soluble metal salt or metal complex, for example an iron, nickel or palladium salt or an iron, nickel or palladium complex (such as iron trichloride, iron acetonyl acetate iron benzoyl acetonate, nickel acetonyl acetate, and iron, nickel or palladium complexes with tertiary phosphines or diertiary diphosphines such as triphenylphosphine, tricyclohexylphosphine, 1, 2-diphenylphosphinoetnane, 1, 2-diphenylphosphinopropane, 1, 2-diphenylphosphinofuran, and 1, 2-diphenylphosphinobutane is known. Examples of metal complexes and metal complex salts are dichloronickel(1,2-diphenylphosphinoethane) and dichloropalladium(1,2-diphenylphosphinoethane). The presence of an additive stabilizing the metal salts or metal complexes and metal complex salts- can be of advantage. Examples are DMPU, N-methylpyrrolidone, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-morpholine, amines such as triethylamine and tetramethylethylenediamine, as well as mixtures of at least two of these additives. When using iron acetonylacetate, the addition of a mixture of DMPU and tetramethylethylendiamine has proved successful. When using dichloronickel(1,2-diphenylphosphinoethane), the addition of triethylamine has proved to be of advantage.

[0104] The reaction is described by G. Cahiez et al. in Synthesis (1998), pp. 1199-1200. The reaction temperature may for example be −50 to 80° C., preferably −20 to 50° C. Catalytic quantities may for example be 0.1 to 20% by weight in relation to a compound of formula XIV. It is expedient to carry out the reaction so that initially a compound of formula XIV is converted to a Grignard compound (for example with magnesium) and then adding a solution of a compound of formula XV, metal salt, metal complex, or metal complex salt and the stabilizing additive, or vice versa.

[0105] It may be of advantage if only catalytic quantities of an additive stabilizing the metal complexes, for example triethylamine or DMPU, are used. Catalytic quantities may for example be 0.1 to 10 mol percent, preferably 1 to 5 mol percent, in relation to compounds of formula XIV or XV.

[0106] Compounds of formula XIV in the form of their racemates or enantiomers are known or capable of being prepared according to analogous processes. For example, RIR_2phenylaldehyde may be reacted with R_3diethoxyphosphorylacetic acid ester to form 2-R_3-3-(R_1R_2phenyl)acrylic acid esters, these may then be hydrogenated to form the corresponding propionic acid esters, the ester group saponified and the carboxylic acid reduced to alcohol, and finally the hydroxyl group substituted with halogen. Enantiomers are obtainable by separating the racemates of the carboxylic acids with for example quinine or by enzymatic resolution of the racemates of the corresponding carbonic esters. Details are described in the examples. A possible asymmetric synthesis of compounds of formula XIV is described in EP-A-0 678 503.

[0107] The compounds of formula XV are obtainable by reacting for example carbonic esters or derivatives of formula $R_4CH_2COOR_{11}$ with 1,3-dihalogenpropene in the presence of strong amine bases such as alkali metal amides (Li-N(i-propyl)$_2$ or lithium hexamethyldisilazane) to form compounds of formula XV, or by preparing through derivatization in a manner known per se carboxylic acids, carboxylic acid halogenides, carboxamides and carboxylic acid salts from e.g. the carbonic esters of formula XV. The desired enantiomers can be obtained from the racemates in a manner known per se by separating the racemates, for example by crystallization from addition salts of carboxylic acids using optically active bases. It is more advantageous to separate the racemates by treating esters of formula XV with esterases.

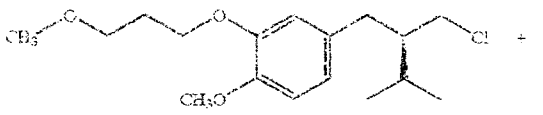
[0108] With the choice of carbonic esters and carboxylic acids of formulae IV and V, the compounds of formula I, which per se are complex compounds, can be prepared in a convergent and simple manner, which is especially true for this enantioselective or diastereoselective synthesis. The total yield from all process steps a) to h) may amount to 40% or more, which makes industrial application feasible.

[0109] The following examples explain the invention in more detail.

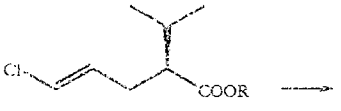
[0110] A) Preparation of Compounds of Formula IV

EXAMPLE A1

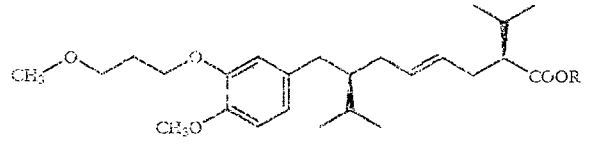
[0111]



A'



A1: R = Ethyl
A2: R = Methyl



B1: R = Ethyl
B2: R = Methyl

[0112] A mixture of 9.75 g magnesium powder and 100 ml tetrahydrofuran is heated to reflux, and 0.50 ml 1,2-dibromoethane then added over a period of 1 minute (visible exothermic reaction). A solution of 34.63 g A', 3.80 ml 1,2-dibromoethane and 300 ml tetrahydrofuran is added dropwise over a period of 30 minutes at 62-64° C. The mixture is agitated for another 30 minutes under reflux and then cooled down to ambient temperature. The reaction mixture is filtered under argon until clear and the resulting Grignard solution added dropwise over a period of 10 minutes to a solution of 20.47 g A1, 0.24 ml N-methylpyrrolidone, 0.88 g iron(III) acetylacetonate in 230 ml tetrahydrofuran at −5 to 0° C. The reaction mixture is stirred for a further 1 minute at 0° C., and 400 ml 2N hydrochloric acid is then added. The mixture is now extracted with diethyl ether (3×300 ml) and the organic phases washed consecutively with water (1×300 ml) and saturated aqueous sodium chloride solution (1×200 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated by evaporation on a Rotavapor. By means of flash chromatography (SiO_2 60F; diethyl ether/hexane 1:4), title compound B1 is obtained from the residue as a slightly yellowish oil (33.8 g, 75%). TLC R_f=0.15 (diethyl ether-hexane 1:4). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.75-0.9 (m, 12H), 1.15 (t, 3H), 1.40 (m, 1H), 1.50 (m, 1H), 1.70-2.45 (m, 10H), 3.30 (s, 3H), 3.50 (t, 2H), 3.80 (s, 3H), 3.90-4.10 (m, 4H), 5.25 (m, 2H), 6.60 (m, 2H), 6.70 (d, 1H) ppm.

EXAMPLE A2

[0113] By analogy with example A1, the derivative is prepared by reacting A' with A2:

[0114] ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90-1.00 (m, 12H), 1.40-2.55 (m, 12H), 3.40 (s, 3H), 3.60 (t, 2H), 3.65 (s, 3H), 3.85 (s, 3H), 4.15 (t, 2H), 5.40 (m, 2H), 6.65-6.75 (m, 2H), 6.80 (d, 1H) ppm.

EXAMPLE A3

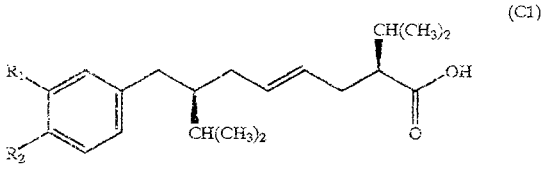
[0115] A mixture of 38.9 g magnesium powder and 400 ml tetrahydrofuran is heated to reflux, and 2.0 ml 1-bromo-2-chloroethane then added over a period of 1 minute (visible exothermic reaction). A solution of 126.0-8 g A1, 14.6 ml 1-bromo-2-chloroethane and 700 ml tetrahydrofuran is added dropwise over a period of 35 minutes at 62-64° C. The mixture is stirred for another 30 minutes under reflux and then cooled down to ambient temperature. The reaction mixture is filtered under argon until clear and the resulting Grignard solution added dropwise over a period of 20 minutes to a solution of 80.3 g A2, 5.58 ml triethylamine, and 2.11 g NidppeCl$_2$ in 700 ml tetrahydrofuran at 20 to 22° C. The reaction mixture is stirred for a further 1 minute at 20° C., and 1 l 1N hydrochloric acid is then added, at 15° C. Extraction is now performed with tert-butyl methyl ether (2×1 l), and the organic phases are washed consecutively with saturated aqueous sodium chloride solution/water (1:9) (2×1.2 l) and saturated aqueous sodium chloride solution (1×300 ml). The combined organic phases are dried over sodium sulfate, filtered and concentration by evaporation on a rotary evaporator. A2 which has not been converted is distilled off from the residue at 75° C. under a vacuum. Crude title compound B2 obtained in this way (171.4 g) is further reacted in example B2.

[0116] B) Preparation of Compounds of Formula V

Example B1

Preparation of Carboxylic Acid

[0117]



(C1)

[0118] To a solution of 22.4 g B1 and 150 ml tetrahydrofuran/methanol/water (3:1:1) 3.6 g lithium hydroxide is added and then stirred for 48 hours under reflux. The reaction mixture is concentrated by evaporation, 500 ml 1N HCl (cold) is added to the residue, and extraction performed with tert-butyl methyl ether (3×500 ml). The organic phases are washed with saturated, aqueous NaCl solution (200 ml), dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F/ethyl acetate/hexane 1:1), title compound C1 is obtained from the residue as a slightly yellowish oil (19.2 g, 94%). TLC R_f=0.22 (diethyl ether-hexane 2:1).

[0119] ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80-1.0 (m, 12H), 1.50 (m, 1H), 1.70 (m, 1H), 1.80-2.60 (m, 10H), 3.40 (s, 3H), 3.65 (t, 2H), 3.85 (s, 3H), 4.15 (m, 2H), 5.45 (n, 2H), 6.70 (m, 2H), 6.80 (d, 1H) 7.60-9.0 (bs, 1H) ppm.

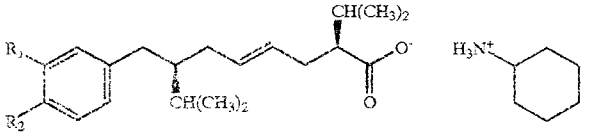
[0120] Title compound C1 can be prepared from B2 by analogy with example B1.

EXAMPLE B2

Preparation of Carboxylic Acid-Cyclohexylamine Salt

[0121]

(C2)



[0122] To a solution of 171.4 g (crude) B2 and 1.07 l dioxane, 0.67 l water and 0.4 l 2N KOH are added and the mixture is then stirred under reflux for 23 hours. The reaction mixture is concentrated by evaporation, 0.6 l water is added to the residue which is washed with tert-butyl methyl ether (2×500 ml) (organic phases are discarded). The aqueous phase is acidified with 0.24 l 4N HCl and then extracted with tert-butyl methyl ether (2×0.6 l). The organic phases are washed with aqueous NaCl solution (0.6 l), dried over sodium sulfate and concentrated on a rotary evaporator. The residue is dissolved in 2 l n-hexane, 38.5 ml cyclohexylamine is added and the mixture stirred for 20 hours at room temperature. The resulting suspension is cooled to 0° C., and title compound C2 is obtained by filtration in the form of white crystals (165.6 g, 79.6%)

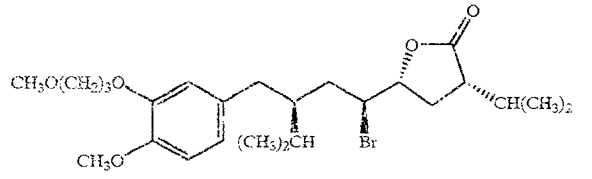
[0123] C) Preparation of Compounds of Formula VI

EXAMPLE C1

Preparation of

[0124]

(D1)



[0125] A solution of 2.66 g C1 and 26.6 ml dichloromethane is cooled to −15° C. Then 4×0.232 g N-bromosuccinimide is added in portions every 2 minutes. The reaction mixture is stirred for another 30 minutes at −15° C. and then, over a period of 5 minutes, is introduced to 30 ml of 40% sodium hydrogen sulfite solution cooled to 0° C. The mixture is diluted with water (10 ml) and extracted with dichloromethane (2×30 ml). The organic phases are washed consecutively with water (1×30 ml) and concentrated aqueous NaCl solution (1×30 ml), then dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/hexane 1:1) 2.98 g title compound D1 is obtained from the residue (content of title compound=approx. 89%); TLC R_f=0.34 (cis-lactone) and 0.38 (trans-lactone) with diethyl ether/hexane 2:1.

[0126] ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85-1.10 (m, 12H), 1.60-2.65 (m, 12H), 3.40 (s, 3H), 3.60 (t, 2H), 3.55-3.70 (m, 1H), 3.85 (s, 3H), 4.15 (t, 2H), 4.25 (m, 1H), 6.70-6.85 (m, 3H) ppm.

EXAMPLE C2

Preparation from Carbonic Ester B1 in the Presence of Water

[0127] A solution of 0.449 g B 1, 3.3 ml tetrahydrofuran and 1.7 ml water is cooled to 0° C. 0.205 g N-bromosuccinimide is added to the solution and the mixture stirred for 30 minutes at 0° C. and for 15 hours at 70° C. The reaction mixture is cooled to 0° C. and added to 30 ml of 40% aqueous sodium hydrogen sulfite solution that has been cooled to 0° C. The mixture is extracted with ethyl acetate (3×50 ml). The organic phases are washed consecutively with water (1×30 ml) and concentrated aqueous NaCl solution (1×30 ml), dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/hexane 1:1) 0.42 g title compound D1 is obtained from the residue (content of title compound= approx. 80%); TLC R_f=0.34 (cis-lactone) and 0.38 (trans-lactone) with diethyl ether/hexane 2:1.

[0128] ^{1}H-NME (300 MHz, $CDCl_3$): δ 0.85-1.10 (m, 12H), 1.60-2.65 (m, 12H), 3.40 (s, 3H), 3.60 (t, 2H), 3.55-3.70 (m, 1H)), 3.85 (s, 3H), 4.15 (t, 2H), 4.25 (m, 1H), 6.70-6.85 (m, 3H) ppm.

EXAMPLE C3

Preparation from Cyclohexylamine Salt C2

[0129] A solution of 164.3 g C2 and dichloromethane is cooled to 0° C. 26.6 ml trifluoroacetic acid is added drop by drop and the mixture stirred for 1 hour. The reaction mixture is cooled to −20° C. Then 6×9.38 g N-bromosuccinimide is added in portions every 2 minutes. The reaction mixture is stirred for a further 2 hours at −15 to −20° C., and 160 ml 4% aqueous sodium hydrogen sulfite solution then added at 0° C. The mixture is extracted with water (1 l) and the organic phase separated off. The aqueous phase is extracted with dichloromethane (0.5 l) and the combined organic phases washed with water (1 l) and aqueous NaCl solution (0.5 l), then dried over sodium sulfate and concentrated on a rotary evaporator. The crude title compound DI obtained in

this way (161.4 g) (content of title compound approx. 90%) is further reacted in examples D2 and E2.

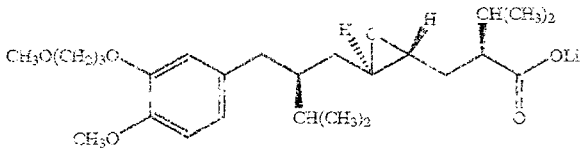
[0130] D) Preparation of Compounds of Formula VII

EXAMPLE D1

Preparation of

[0131]

(E1)



[0132] A solution of 16.65 g D1 and 150 ml isopropanol is cooled to 0° C., then 66.6 ml 2N LiOH is added over a period of 10 minutes and the mixture stirred for 1.5 hours (the intermediate E1 is immediately reacted further in the next step).

EXAMPLE D2

[0133] Compound E1 is obtained in an analogous manner using compound D1 prepared as described under example C3 and is used in example E2.

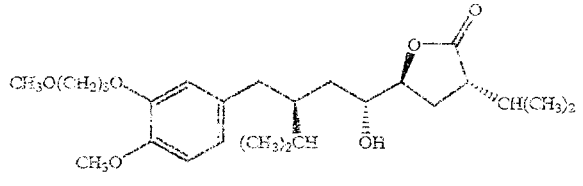
E) Preparation of Compounds of Formula VIII

EXAMPLE E1

Preparation of

[0134]

(F1)



[0135] To the reaction mixture of example D1, 100 ml 2N HCl is added drop by drop, and the reaction mixture is stirred for 1 hour at room temperature. The reaction mixture is diluted with water (500 ml) and extracted with tert-butyl methyl ether (3×250 ml). The organic phases are washed consecutively with water (2×500 ml) and concentrated aqueous NaCl solution (200 ml), dried over sodium sulfate and concentrated on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/hexane 2:1) 12.0 g title compound F1 is obtained from the residue (content of title compound=approx. 88%); TLC R_f=0.16 (diethyl ether/hexane 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80-1.05 (m, 12H), 1.10-2.25 (m, 10H), 2.35 (m, 1H), 2.50-2.75 (m, 2H), 3.40 (s, 3H), 3.60 (t, 2H), 3.90 (s, 3H), 3.80-3.90 (m, 1H), 4.15 (t, 2H), 4.25 (m, 1H), 6.70-6.85 (m, 3H) ppm.

EXAMPLE E2

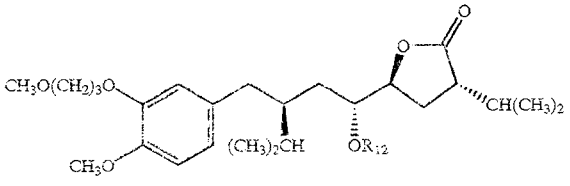
[0136] The stirred mixture of 161.4 g D1 (crude), 1.61 l tetrahydrofuran and 0.474 l water is stirred at room temperature for 20 h with 0.474 l 2N LiOH. Then 1.61 l water is added and the tetrahydrofuran (1.7 l) evaporated off on a rotary evaporator. The resulting mixture is washed with tert-butyl methyl ether (0.5 l) and the aqueous solution of the intermediate E1 is obtained and immediately reacted further. While stirring, tert-butyl methyl ether (1.0 l) and 4N HCl (0.316 l) are added. The organic phase is separated off and stirred for 2 hours under reflux (with a water separator). The solution is cooled, dried over sodium sulfate and concentrated on a rotary evaporator. The crude title compound F1 obtained in this way (136.1 g) (content of title compound approx. 90%) is further reacted in example F4.

[0137] F) Preparation of Compounds of Formula IX

EXAMPLE F1

Preparation of

[0138]



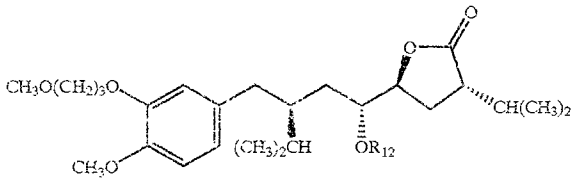
[0139] wherein R_{12} is CH_3—SO_2—(G1).

[0140] To a solution of 0.325 g F1 and 8 ml dichloromethane, 0.156 ml triethylamine is added and the mixture cooled to 0° C. 0.087 ml methanesulfonyl chloride is added drop by drop and the mixture then stirred for 1 hour at room temperature. The reaction mixture is poured onto water (10 ml) and extracted with tert-butyl methyl ether (2×10 ml). The organic phases are washed consecutively with 5% aqueous sodium hydrogencarbonate solution (10 ml) and concentrated aqueous NaCl solution (10 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/hexane 2:1), title compound G1 is obtained from the residue as a slightly yellowish oil (0.32 g, 82%) TLC R_f=0.18 (diethyl ether/hexane 2:1) ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85-1.05 (m, 12H), 1.55-2.25 (m, 9H), 2.40 (m, 1H), 2.60 (m, 1H), 2.75 (m, 1H), 2.95 (s, 3H), 3.40 (s, 3H), 3.60 (t, 2H), 3.85 (s, 3H), 4.15 (t, 2H), 4.45 (m, 1H), 4.80 (m, 1H), 6.70-6.85 (m, 3H) ppm.

EXAMPLE F2

Preparation of

[0141]



[0142] wherein R_{12} is 4-BrC_6H_5—SO_2— (G2)

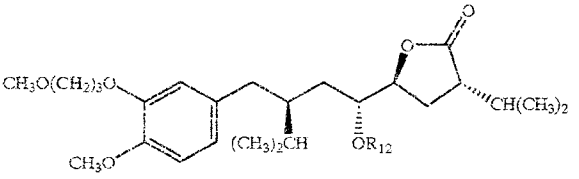
[0143] To a solution of 0.437 g F1 and 5 ml dichloromethane, 0.307 g 4-bromobenzenesulfochloride and 0.147 g 4-dimethylaminopyridine are consecutively added and the mixture then stirred for 24 hours at room temperature. The reaction mixture is poured onto iced water (30 ml) and extracted with diethyl ether (3×30 ml). The organic phases are washed consecutively with 5% aqueous sodium hydrogencarbonate solution (30 ml) and concentrated aqueous NaCl solution (30 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/hexane 1:1), title compound G2 is obtained from the residue as a slightly yellowish oil (0.304 g, 46%): TLC R_f=0.36 (diethyl ether-hexane 2:1).

[0144] ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80-1.0 (m, 12H), 1.55-2.20 (m, 9H), 2.25-2.45 (m, 2H), 2.70 (m, 1H), 3.40 (s, 3H), 3.60 (t, 2H), 3.90 (s, 3H), 4.15 (m, 2H), 4.35 (m, 1H), 4.65 (m, 1H), 6.60-6.85 (m, 3H), 7.60-7.75 (m, 4H) ppm.

EXAMPLE F3

Preparation of

[0145]



[0146] wherein R_{12} is 4-$CH_3C_6H_5$—SO_2— (G3).

[0147] To a solution of 0.437 g F1 and 5 ml dichloromethane, 0.229 g 4-methylbenzenesulfochloride and 0.147 g 4-dimethylaminopyridine are added and the mixture then stirred for 24 hours at room temperature. The reaction mixture is poured onto iced water (30 ml) and extracted with diethyl ether (3×30 ml). The organic phases are washed consecutively with 5% aqueous sodium hydrogencarbonate solution (30 ml) and concentrated, aqueous NaCl solution (30 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation on a rotary evaporator. By means of flash chromatography (SiO_2 60F/diethyl ether/hexane 1:1), title compound G3 is obtained from the residue as a slightly yellowish oil (0.40 g, 68%) TLC R_f=0.26 (diethyl ether-hexane 2:1).

[0148] ^{1}H-NMR (300 MHz, $CDCl_3$): (0.80-1.0 (m, 12H), 1.55-2.20 (m, 9H), 2.30-2.50 (m, 2H), 2.45 (s, 3H), 2.65 (m, 1H), 3.40 (s, 3H), 3.60 (t, 2H), 3.90 (s, 3H), 4.15 (m, 2H), 4.35 (m, 1H), 4.70 (m, 1H), 6.60-6.85 (m, 3H), 7.35 (d, 2H), 7.70 (d, 2H) ppm.

EXAMPLE F4

Preparation of G1

[0149] To a solution of 136.1 g F 1 (crude), prepared as described in example E2, and 0.86 l toluene, 52.8 ml triethylamine is added and the mixture cooled to 0° C. 29.45 ml methanesulfonyl chloride is added drop by drop and the mixture then stirred for 1 hour at 15° C. The reaction mixture is cooled to 0° C., 7.88 ml 3-dimethylamino-1-propylamine is added (the excess of methanesulfonylchloride is destroyed) and the mixture stirred for 15 minutes. The reaction mixture is washed with water (1 l), the organic phase separated off and the aqueous phase extracted again with toluene (0.6 l). The organic phases are washed consecutively with water/saturated NaCl solution (5:1; 0.6 l) and saturated aqueous NaCl solution (0.6 l), dried over sodium sulfate and concentrated on a rotary evaporator. The crude title compound F1 obtained in this way (165 g) (content of title compound approx. 90%) is further reacted in example G2.

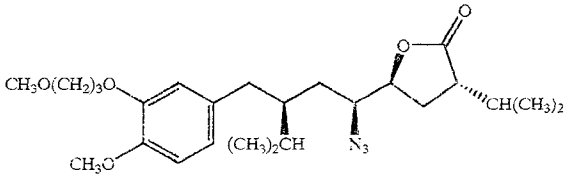
[0150] G) Preparation of Compounds of Formula II

EXAMPLE G1

Preparation of

[0151]

(H1)



[0152] A mixture of 9.5 g G1, 2.35 g sodium azide and 100 ml 1.3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone is stirred for 20 hours at 60° C. The reaction mixture is poured onto 500 ml water and extracted with tert-butyl methyl ether (3×200 ml). The organic phases are washed consecutively with water (3×500 ml), 5% aqueous sodium hydrogencarbonate solution (200 ml) and concentrated aqueous NaCl solution (200 ml). The combined organic phases are dried

over sodium sulfate and concentrated on a rotary evaporator. By means of crystallization from 150 ml diisopropylether-hexane (1:2) at 0° C., title compound H1 is obtained from the residue as white crystals (5.62 g, 67%); m.p. 61-620 C; TLC R_f=0.41 (ethyl acetate-hexane 1:1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85-1.10 (m, 12H), 1.40 (m, 1H), 1.60-2.25 (m, 8H), 2.45 (m, 1H), 2.60 (m, 2H), 2,95 (m, 1H), 3,40 (s, 3H), 3.60 (t, 2H), 3.85 (s, 3H), 4.15 (t, 2H), 4.30 (m, 1H)), 6.70-6.85 (m, 3H) ppm.

[0153] Derivative H1 can be prepared by reaction of G2 or G3 by analogy with example G1.

EXAMPLE G2

Preparation of H1

[0154] A mixture of 165 g G1 (crude), 41.1 g sodium azide and 0.8 l 1.3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone is stirred for 20 hours at 60° C. The reaction mixture is cooled, poured onto 1.5 l water and extracted with methylcyclohexane (2×750 ml). The organic phases are washed consecutively with water (4×750 ml) and concentrated aqueous NaCl solution (750 ml). The combined organic phases are dried over sodium sulfate and concentrated to a volume of 900 ml on a rotary evaporator. The resulting solution is inoculated with 10 mg of title compound and stirred for 20 hours at ambient temperature. The resulting suspension is cooled to 0° C., and title compound H1 is obtained by filtration in the form of white crystals (104 g, 71%)

EXAMPLE G3

Preparation of H1

[0155] A mixture of 10.3 g G1 (crude), 50 ml methylcyclohexane, 40 ml 2N sodium azide (aqueous solution) and 0.4 g Aliquat® is stirred for 20 h at 80° C. The reaction mixture is cooled to 40° C., the aqueous phase is separated off and the organic phase washed at 40° C. with (2×40 ml). The organic phase is dried over sodium sulfate and filtered. The filtrate is inoculated with 5 mg of title compound and stirred for 20 hours at ambient temperature. The resulting suspension is cooled to 0° C., and title compound H1 is obtained by filtration in the form of white crystals (6.60 g, 71%)

[0156] H) Preparation of Compounds of Formula III

EXAMPLE H1

Preparation of

[0157]

[0158] A mixture of 59.1 g H1, 41.82 g 3-amino-2,2-dimethyl-propionamide, 2.28 g 2-hydroxypyridine in 59.1 ml triethylamine is stirred over a period of 16 hours at 90° C. Then 33 ml triethylamine is distilled off over a period of 0.5 hours, and the residue is agitated for a further 8.5 hours at 90° C. The cooled reaction mixture is extracted between ethyl acetate (3×500 ml), saturated aqueous sodium hydrogencarbonate solution (1×500 ml) and saturated sodium chloride solution (1×500 ml). The combined organic phases are dried with 100 g sodium sulfate, filtered and concentrated on the rotary evaporator. The residue is dried and crude title compound F1 is obtained as an oil (78.4 g, quantitative) (HPLC assay: 88.5%): TLC R_f=0.13 (ethyl acetate-hexane 4:1); chromatographed sample: TLC R_f=0.13 (ethyl acetate/hexane 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 0.85-0.96 (m, 12H), 1.23 (s, 6H), 1.30-1.40 (m, 1H), 1.53-1.80 (m, 5H), 1.82-1.93 (m, 1H), 2.06-2.14 (m, 3H), 2.45-2.57 (m, 2H), 2.87-2.92 (m, 1H), 3.13 (d, 1H), 3.32-3.52 (m, 3H), 3.36 (s, 3H), 3.59 (t, 2H), 3.84 (s, 3H), 4.12 (t, 2H), 5.51 (bs, 1H), 6.01 (bs, 1H), 6.43 (t, 1H), 6.72 (dd, 1H), 6.75 (d, 1H), 6.81 (d, 1H) ppm.

EXAMPLE H2

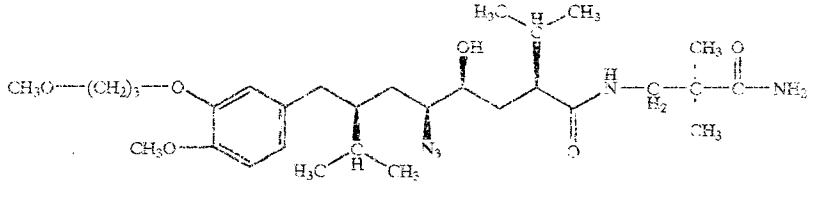
Preparation of J1

[0159] A mixture of 9.23 q H1, 6.97 g 3-amino-2,2-dimethylpropionamide, 1.90 g 2-hydroxypyridine and 5.0 ml triethylamine is stirred over a period of 24 hours at 65° C. The cooled reaction mixture is extracted between tert-butyl methyl ether (2×150 ml) and water (2×150 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated on a rotary evaporator. The residue is dried and crude title compound F1 is obtained as an oil (11.65 g, quantitative) (HPLC assay: >95%).

EXAMPLE H3

Preparation of J1

[0160] A mixture of 4.62 g H1, 3.48 g 3-amino-2,2-dimethylpropionamide and 0.95 g 2-hydroxypyridine is stirred over a period of 24 hours at 65° C. The cooled reaction mixture is extracted between tert-butyl methyl ether (2×100 ml) and water (2×100 ml). The combined organic phases are dried over sodium sulfate, filtered and concentrated on a rotary evaporator. The residue is dried and crude



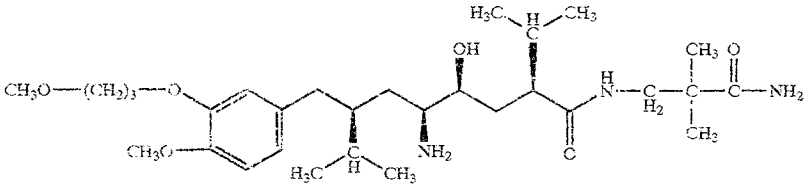
title compound J1 is obtained. as an oil (5.75 g, quantitative) (HPLC assay: >95%).

[0161] J) Hydrogenation of the Azide Group to Form Compounds of Formula I

EXAMPLE J1

Preparation of

[0162]

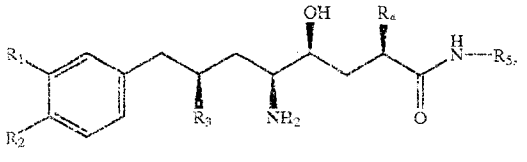


(K1)

[0163] 78.4 g (HPLC assay: 88.5%) J1 (crude) is hydrogenated for 3 hours in the presence of 3.92 g Pd/C 5% and 7.2 ml ethanolamine in 700 ml tert-butyl methyl ether at ambient temperature and 3.0 bar. The reaction mixture is filtered and the catalyst washed with 300 ml tert-butyl methyl ether. The filtrate is washed consecutively with 400 ml 2N NaOH and 400 ml brine. The aqueous phases are then extracted with tert-butyl methyl ether (2×400 ml). The combined organic phases are dried with 100 g sodium sulfate and concentrated by evaporation. The residue is mixed with 7.31 g fumaric acid and dissolved in 200 ml ethanol and filtered until clear. The filtrate is concentrated by evaporation to a total weight of 104 g and dissolved in 1.7 l acetonitrile at 35° C. The resulting solution is inoculated with 10 mg of title compound (nemifumarate) and stirred for 17 hours at ambient temperature. The suspension is cooled to 0° C. and filtered off by suction after 2 hours. The residue is washed with acetonitrile (3×200 ml) and then dried in a vacuum at 35° C. The title compound K1 (hemifumarate) is obtained as white crystals (59.5 g, 81% in relation to J1): 1H NMR (360 MHz, DMSO-d_6); δ 0.7-0.9 (m, 12H), 1.04 (s, 6H), 1.27 (m, 3H), 1.4-1.8 (m, 4H), 1.94 (m, 2H), 2.23 (m, 1H), 2.35 (dd, J 8.4, 8.0 Hz, 1H), 2.45 (m, 1H), 3.08 (m, 2H), 3.2-3.5 (m, 2H), 3.24 (s, 3H), 3.47 (t, J=6.4 Hz, 2H), 3.74 (s, 3H), 3.97 (t, J=6.4 Hz, 2H), 6.37 (s, 1H), 6.68 (dd, J=8.0, 2.0 Hz, 1H), 6.77 (d, J=6 Hz, 1H), 6.80 (bs, 1H), 6.83 (d, J=8 Hz, 1H), 7.13 (bs, 1H), 7.49 (t, J=6 Hz. 1H).

What is claimed is:

1. Process for preparation of compounds of formula I,

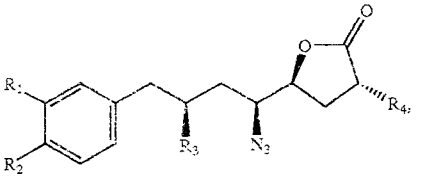


(I)

wherein

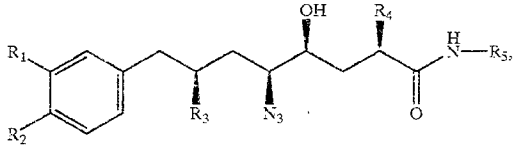
R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_5 is C_1-C_6alkyl, C_1-C_6hydroxyalkyl, C_1-C_6alkoxy-C_1-C_6-alkyl, C_1-C_6alkanoyloxy-C_1-C_6alkyl, C_1-C_6aminoalkyl, C_1-C_6alkylamino-C_1-C_6alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, alkanoylamido-C_1-C_6-alkyl, HO(O)C—C_1-C_6-alkyl, C_1-C_5alkyl-O—(O)C—C_1-C_6alkyl, H_2N—C(O)—C_1-C_6alkyl, C_1-C_6alkyl-HN—C(C)—C_1-C_6alkyl or (C_1-C_6alky!)$_2$N—C(O)—C_1-C_6-alkyl,

a) by reacting a compound of formula II,



(II)

with an amine of formula R_5—NH_2 to form a compound of formula III,

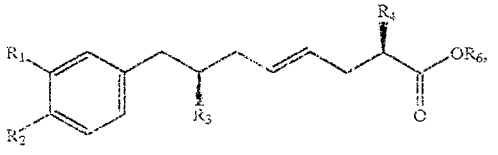


(III)

and

b) by reducing the azide group of the compound of formula III to the amine group and isolating the compounds of formula I, if necessary with the addition of a salt-forming acid, comprising the preparation of compounds of formula II by

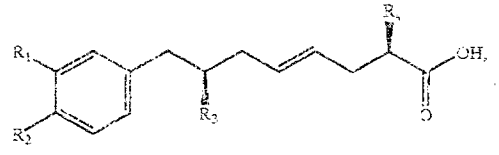
c1) reacting a compound of formula IV,



(IV)

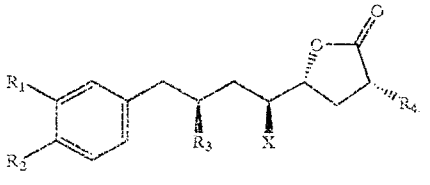
wherein R_6 is C_1-C_{20}alkyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkyl-C_1-C_6alkyl, C_6-C_{10}aryl or C_6-C_{10}-aryl-C_1-C_6alkyl, with a halogenation agent to form a compound of formula VI, or

c2) reacting a carboxylic acid of formula V, or a salt of this carboxylic acid,



(V)

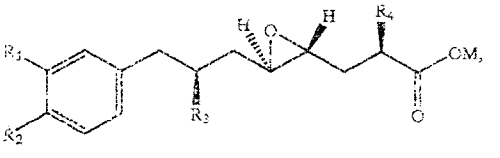
with a halogenation agent to form a compound of formula VI,



(VI)

wherein X is Cl, Br or I,

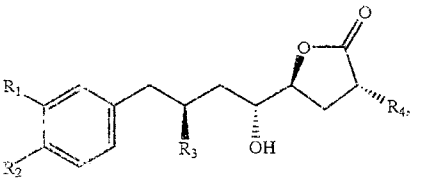
d) reacting the compound of formula VI in the presence of an alkali metal or alkaline earth metal hydroxide or an alcohol to form a compound of formula VII,



(VII)

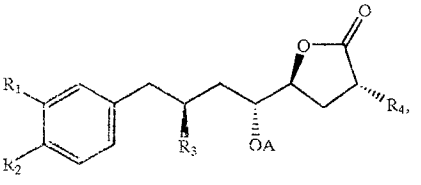
wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group,

e) hydrolysing the compound of formula VII in the presence of an acid to form a compound of formula VIII,



(VIII)

f) substituting the hydrogen atom of the hydroxyl group in the compound of formula VIII and converting it to a leaving group AO to form compounds of formula IX,



(IX)

g) and then reacting the compound of formula IX with an azidation agent to form a compound of formula II, or

h) reacting the compound of formula VIII directly with a zinc azide/-bis-pyridine complex in the presence of a tertiary phosphine and an azodicarboxylate, if necessary in an organic solvent, to form a compound of formula II.

2. A process according to claim 1 comprising an embodiment wherein R_1 is C_1-C_4alkoxy or C_1-C_4alkoxy-C_1-C_4alkyloxy, R_2 is C_1-C_4alkoxy, R_3 is C_2-C_4alkyl, R_4 is C_1-C_4alkyl and R_5 is $H_2NC(O)$—C_1-C_6alkyl which if necessary is N-monosubstituted or N-di-C_1-C_4alkyl substituted.

3. A process according to claim 2 comprising an embodiment wherein R_1 is 1-methoxyprop-3-yloxy and R_2 is methoxy.

4. A process according to claim 2 comprising an embodiment wherein R_3 and R_4 are in each case isopropyl.

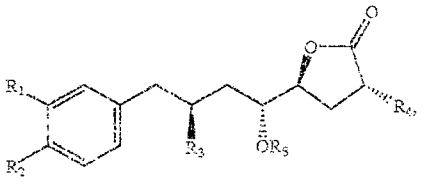
5. A process according to claim 2 comprising an embodiment wherein R_5 is $H_2NC(O)$—C_1-C_6alkyl.

6. A process according to claim 1 comprising an embodiment wherein R_1 is methoxy-C_2-C_4alkyloxy, R_2 is methoxy or ethoxy, R_3 is C_2-C_4alkyl, R_4 is C_2-C_4alkyl and R_5 is $H_2NC(O)$—C_1-C_6alkyl

7. A process according to claim 1 comprising an embodiment wherein R_1 is 3-methoxy-prop-3-yloxy, R_2 is methoxy, R_3 and R_4 are each 1-methyleth-1-yl, and R_5 is $H_2NC(O)$—$[C(CH_3)_2]$—CH_2—.

8. Compounds of formula X,

(X)

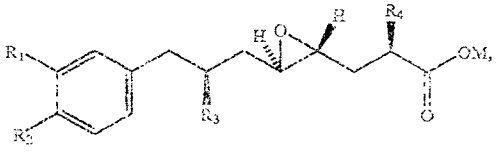


wherein

R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, R_4 is C_1-C_6alkyl, and R_8 is hydrogen or R_8O is a leaving group.

9. Compounds of formula VII,

(VII)

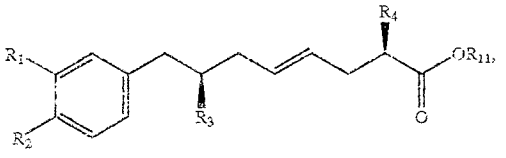


wherein M is an alkali metal, an equivalent alkaline earth metal or the residue of an alcohol minus a hydroxyl group, and

R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, and R_4 is C_1-C_6alkyl.

10. Compounds of formula XIII,

(XIII)



wherein R_{11} is an alkali metal, an equivalent alkaline earth metal, hydrogen or the residue of an alcohol minus a hydroxyl group, and

R_1 and R_2 are, independently of one another, H, C_1-C_6alkyl, C_1-C_6halogenalkyl, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkyl, or C_1-C_6alkoxy-C_1-C_6alkyloxy, R_3 is C_1-C_6alkyl, and R_4 is C_1-C_6alkyl.

* * * * *

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 09 057907

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **618** DE

FECHA **19 DE JULIO 2010** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **13 DE OCTUBRE DE 2010**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____X____ NO _____

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Carlos R. Olarte
Apoderado

Oficio N°: 00329

ASUNTO:	Radicación	N°	09-57907
	Trámite		011
	Evento		378
	Actuación		440
	Folios		009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Ghynopharm S.A.S, reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

JOSÉ LUÍS SALAZAR LÓPEZ
Director de Nuevas Creaciones (E).

El anterior oficio fue notificado por fijación en lista de fecha, 07 ENE. 2011.

202088