

Industria y Comercio

SUPERINTENDENCIA

13 008135 00

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

SOLICITUD DE:

☒

Patente de invención

☐

Patente de Modelo de Unidad

☐

Capítulo I

☒

Capítulo II

2

SOLICITANTE
(71)Nombre: **NOVARTIS AG**

Dirección: Lichtstrasse 35

Nacionalidad o Domicilio: CH-4056 Basilea,
Suiza

Lugar de Constitución: Suiza

Teléfono: 41613241111 Fax: 41613227532

E-mail

IDENTIFICACIÓN

C.C. ☐NIT ☐C.E. ☐Otro ☐

Número

3

REPRESENTANTE
O APODERADO
(74)

Nombre: JIMENA ESCOBAR URIBE

Dirección: Cra. 11A No. 94-76 (Of. 305)

Teléfono: 6 162051/61 Fax: 6 161889

E-mail: escobaru@elsitio.net.co

IDENTIFICACIÓN

C.C. ☒NIT ☐C.E. ☐Otro ☐

Número 39 779 452.T.P 88228

4

INVENTOR (ES)
(72)Nombre: **FREDERICK RAY KINDER**

Dirección: 37 Olyphant Drive

Nacionalidad o domicilio: Morristown, New Jersey 07960, Estados Unidos

5

PCT (86)

Solicitud Internacional No. PCT/EP01/09068Fecha Agosto 6, 2001Publicación Internacional No. WO 02/12220 AZFecha Febrero 14, 20026 TÍTULO (84) PROCESO PARA LA PREPARACIÓN DE DISCODERMOLIDA Y SUS ANALÓGOS

6

Clasificación Internacional (51)

C 07 D 309/30 // ALIX 31/351

7

Prioridad

(33) País de Origen
Estados Unidos

(32) Fecha

Agosto 7, 2000

(31) Número de Solicitud

09/633753SI ☒ NO ☐

9

Comprobante de pago No.

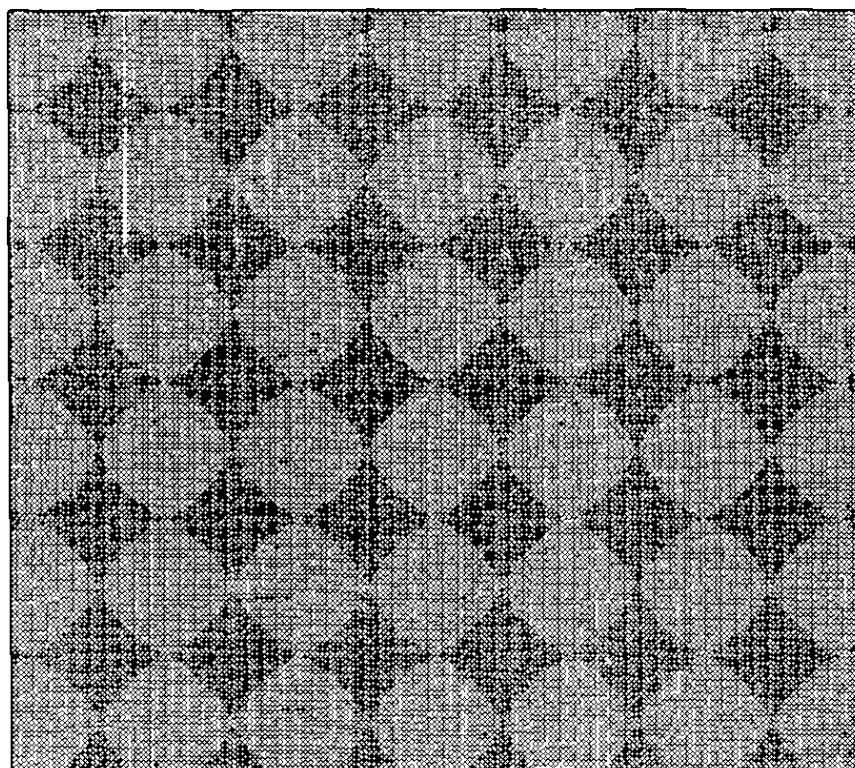
03-843

Fecha

Enero 7, 2003

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica Prot. 17.398
- ☒ Poderes si fuere el caso Protocolo No. 17.398
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☒ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso copia de contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 X 12 .
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
- ☐ Otros

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE: JIMENA ESCOBAR URIBE

FIRMA:

[Handwritten signature]

C.C. 38.779.452 DE Usaquén T.P. 168.228

As. 2528/PCT

2

Solicito expresamente a nombre de la sociedad
NOVARTIS AG, sociedad constituida de
conformidad con las leyes de Suiza, domiciliada en
Lichtstrasse 35, CH-4056 Basilea, Suiza, el
otorgamiento de Patente para la invención titulada
**"PROCESO PARA LA PREPARACIÓN DE
DISCODERMOLIDA Y SUS ANALOGOS"**.

Clase: C 07


JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquen
T.P . 68.228

9.523



3

SUPERINDUSTRIA Y COMERCIO

Radicación : 83006135 00000000
Fecha (IMP) : 2003-02-04 16:03:13
Trámite : 011 PCT-PATENT 379 FASE NUCI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 200176989-2

RECIBO OFICIAL DE CAJA : 03 - 843
FECHA : ENERO 7 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
ESCEPAR UNIDE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00113-6	9022091	07/01/2003	6,426,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE N.º. _____

Carrera 13 No. 27-00 Pisos 5 y 10
Conmutador: 334 12 21
Fax: 281 31 25
Santa Fe de Bogotá, D.C., Colombia

PATENT C OPERATI N TREATY

PCT 10
P + TM Dept.

22 Okt. 2001

PCT	day	FILE	M/D	F/L	PS/TS
Kopier:					

From the RECEIVING OFFICE

To:

Backer, Konrad
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

19.10.01

Applicant's or agent's file reference
4-31532A/USN

IMPORTANT NOTIFICATION

International application No.
PCT/EP 01/09068 ✓

International filing date (day/month/year)
06/08/2001 ✓

Priority date (day/month/year)
07/08/2000 ✓

Applicant
NOVARTIS AG

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.

3. ☐ Other:

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the Receiving Office



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

A. HENNINGSEN
Tel.: (070) 340 2956

PCT

REQUEST

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

For receiving Office use only

PCT/EP 01/09068

International Application No.

06 AUG 2001

(06.08.01)

International Filing Date

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 4-31532A/USN

Box No. I TITLE OF INVENTION

PROCESS FOR PREPARING DISCODERMOLIDE AND ANALOGUES THEREOF

Box No. II APPLICANT

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

Novartis AG
Lichtstrasse 35
4056 Basel
CH

☐ This person is also inventor

Telephone No. +41 61 324 11 11

Facsimile No. +41 61 322 75 32

Teleprinter No.

State (that is, country) of nationality: CH

State (that is, country) of residence: CH

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

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

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

Novartis-Erfindungen
Verwaltungsgesellschaft m.b.H.
Brunner Strasse 59
1230 Vienna
AT

This person is:

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

State (that is, country) of nationality: AT

State (that is, country) of residence: AT

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

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

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

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

☒ agent☐ common representative

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

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CH

Telephone No. +41 61 324 11 11

Facsimile No. +41 61 322 75 32

Teleprinter No.

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

Continuation of Box No. III

FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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

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

KINDER, ^{ad}Frederick Ray
37 Olyphant Drive
Morristown, NJ 07960
US

This person is:

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

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

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

This person is:

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

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☐

the United States of America only

☐

the States indicated in the Supplemental Box

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

This person is:

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

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☐

the United States of America only

☐

the States indicated in the Supplemental Box

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

This person is:

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

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☐

the United States of America only

☐

the States indicated in the Supplemental Box

☐

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

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line) CC

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

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

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

Supplemental Box --- If the Supplemental Box is not used, this sheet should not be included in the request:

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [Indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
 - (vii) If, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. II

Novartis AG is applicant for all designated States with the exception of: AT (Austria)
US (USA)

Continuation of Box No. III

Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. is applicant for AT (Austria) only.

Box No. VI PRIORITY CLAIM					☐ Further priority claims are indicated in the Supplemental Box				
Filing Date of earlier application (day/month/year)		Number of earlier application		Where earlier application is:					
				national application: country	regional application: regional Office		international application: receiving Office		
item (1) 07 August 2000 (07.08.00)		08/633753		US					
item (2)									
item (3)									

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

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA/	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)
---	---

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets: request : 5 description (excluding sequence listing part) : 14 claims : 7 abstract : 1 drawings : 0 sequence listing part of description : 0 Total number of sheets : 27	This international application is accompanied by the item(s) marked below: 1. ☒ fee calculation sheet 2. ☒ separate signed power of attorney 3. ☒ copy of general power of attorney; reference number, if any: AV 36671 + 37586 4. ☐ statement explaining lack of signature 5. ☒ priority document(s) identified in Box No VI as item(s): (1) 6. ☐ translation of international application into (language): 7. ☐ separate indications concerning deposited microorganism or other biological material 8. ☐ nucleotide and/or amino acid sequence listing in computer readable form 9. ☒ other (specify): Copy letter re Change of Address
---	--

Figure of the drawings which should accompany the abstract: —	Language of filing of the international application: English
--	---

Box No. IX SIGNATURE OF APPLICANT OR AGENT

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

In the name of the applicants
The representative

H. Becker

BECKER, Konrad, AV 36671 + 37586

26.06.2001

For receiving Office use only		2. Drawings: ☐ received ☐ not received:
1. Date of actual receipt of the purported international application:	(06.08.01) 06 AUG 2001	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid	

Date of receipt of the record copy by the International Bureau:	For International Bureau use only
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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 February 2002 (14.02.2002)

PCT

(10) International Publication Number
WO 02/12220 A2

(51) International Patent Classification: C07D 309/30, C07C 271/22

(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).

(21) International Application Number: PCT/EP01/09068

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

(22) International Filing Date: 6 August 2001 (06.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 09/633,753 7 August 2000 (07.08.2000) US

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

(71) Applicant (for all designated States except AT, US): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4002 Basel (CH).

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

(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventor; and

(75) Inventor/Applicant (for US only): KINDER, Frederick, Ray [US/US]; 37 Olyphant Drive, Morristown, NJ 07960 (US).

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

WO 02/12220 A2

(54) Title: PROCESS FOR PREPARING DISCODERMOLIDE AND ANALOGUES THEREOF

(57) Abstract: A more practical synthesis for preparing discodermolide and structurally related analogues, novel compounds useful in the process and novel compounds prepared by the process.

25.05.2002
4 -31532A/USN
Peter Roth

VT
PCT
EP01/09068

ATY
Jey

P + TM Dept.

25. März 2002

APPL M/D F/L PS/TS

Kopen:

From the INTERNATIONAL SEARCHING AUTHORITY

To:

NOVARTIS AG
Corporate Intellectual Property
Attn. Becker, Konrad
Patent & Trademark Department
CH-4002 Base
SWITZERLAND

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

25/03/2002

Applicant's or agent's file reference

4-31532A/USN

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 01/09068

International filing date
(day/month/year)

06/08/2001

Applicant

NOVARTIS AG

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 551 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Margarita Tzelepi

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-31532A/USN	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/EP 01/09068	International filing date (day/month/year) 06/08/2001	(Earliest) Priority Date (day/month/year) 07/08/2000
Applicant NOVARTIS AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09068

15

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D309/30 C07C271/22 C07F7/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07F C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 01982 A (HARBOR BRANCH OCEANOGRAPHIC INSTIT.) 21 February 1991 (1991-02-21) the whole document	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 March 2002

Date of mailing of the international search report

25/03/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 851 apo nl,
Fax (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/EP 01/09068

16

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9101982	A	21-02-1991	US 4939168 A	03-07-1990
			AT 121739 T	15-05-1995
			CA 2056412 A1	12-02-1991
			DE 69018991 D1	01-06-1995
			DE 69018991 T2	24-08-1995
			DK 486565 T3	02-10-1995
			EP 0486565 A1	27-05-1992
			ES 2071826 T3	01-07-1995
			JP 3008985 B2	14-02-2000
			JP 4507245 T	17-12-1992
			WO 9101982 A1	21-02-1991
			US 5010099 A	23-04-1991

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND
------------------------	---------------------------

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 4-31532A/USN	
International application No. PCT/EP 01/09068	International filing date (day/month/year) 06 August 2001 (06.08.01)	(Earliest) Priority date (day/month/year) 07 August 2000 (07.08.00)	
Title of invention PROCESS FOR PREPARING DISCODERMOLIDE AND ANALOGUES THEREOF			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis AG Lichtstrasse 35 4056 Basel CH		Telephone No.: +4161 324 11 11	
		Facsimile No.: +4161 322 75 32	
		Teleprinter No.:	
State (that is, country) of nationality: CH		State (that is, country) of residence: CH	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1230 Vienna AT			
State (that is, country) of nationality: AT		State (that is, country) of residence: AT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) KINDER, JR., Frederick Ray 37 Lyphand Drive Morristown, NJ 07860 US			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☐ Further applicants are indicated on a continuation sheet.			

Box No. III AGENT & COMMON REPRESENTATIVE; & ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CH

Telephone No.:

+4161 324 11 11

Facsimile No.:

+4161 322 75 32

Teleprinter No.:

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

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This checkbox may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☒ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | | |
|----|---|---|--------|
| 1. | translation of international application | : | sheets |
| 2. | amendments under Article 34 | : | sheets |
| 3. | copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. | copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. | letter | : | sheets |
| 6. | other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 4. ☐ statement explaining lack of signature |
| 2. ☐ separate signed power of attorney | 5. ☐ nucleotide and/or amino acid sequence listing in computer readable form |
| 3. ☐ copy of general power of attorney; reference number, if any: | 6. ☐ other (specify): |

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

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

In the name of the applicants
The representative

11. Becker

11.02.2002

BECKER, Konrad, AV 36671 + 37588

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

<table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="width: 50%;">International application No. PCT/EP 01/09068</td><td style="width: 50%;">For International Preliminary Examining Authority use only</td></tr><tr><td>Applicant's or agent's file reference 4-31532A/USN</td><td>Date stamp of the IPEA</td></tr></table>	International application No. PCT/EP 01/09068	For International Preliminary Examining Authority use only	Applicant's or agent's file reference 4-31532A/USN	Date stamp of the IPEA	
International application No. PCT/EP 01/09068	For International Preliminary Examining Authority use only				
Applicant's or agent's file reference 4-31532A/USN	Date stamp of the IPEA				
Applicant Novartis AG et al.					
Calculation of prescribed fees					
1. Preliminary examination fee	EUR 1633.- P				
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered as H is 25% of the handling fee.)	EUR 147.- H				
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1680.- TOTAL				
Mode of Payment					
☒ authorization to charge deposit account with the IPEA (see below) ☐ cash ☐ cheque ☐ revenue stamps ☐ postal money order ☐ coupons ☐ bank draft ☐ other (specify):					
Deposit Account Authorization (this mode of payment may not be available at all IPEAs)					
The IPEA / EP ☒ is hereby authorized to charge the total fees indicated above to my deposit account.					
☒ (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permits) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.					
Novartis AG					
 Ella Rutschmann Patent and Trademark Administrators  Hans-Rudolf Haus Patent and Trademark Administrators					
2811 0031	11.02.2002				
Deposit Account Number	Date (day/month/year)				
Signature					

Form PCT/IPEA/401 (Annex) (July 1998; reprint January 2001)

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

P + TM Dept.

PCT 12 April 2002

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BECKER, Konrad
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

APPL M/O F/L PS/TB

Kopien:

Date of mailing
(day/month/year)

10/04/2002

Applicant's or agent's file reference
4-31532A/USN

IMPORTANT NOTIFICATION

International application No.

PCT/EP 01/09068

International filing date (day/month/year)

06/08/2001

Priority date (day/month/year)

07/08/2000

Applicant

NOVARTIS AG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

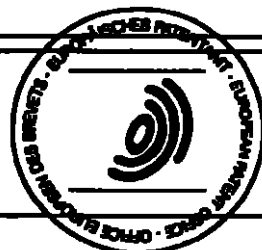


European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

FERRO VASCONCELOS M

Tel. (+49-89) 2399 2828



Form PCT/IPEA/16 (July 1992) P20473

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-31532A/USN	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 01/ 09068	International filing date (day/month/year) 06/08/2001	Priority date (day/month/year) 07/08/2000
International Patent Classification (IPC) or national classification and IPC C07D309/30		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 12/02/2002	Date of completion of this report 05/04/2002
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+ 49-89) 2399-0, Tx: 523656 epmu d Fax: (+ 49-89) 2399-4465	Authorized officer VERHULST W Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/ EP 01/ 09068

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, Inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.

24

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

INFORME EXAMEN PRELIMINAR INTERNACIONAL (PCT artículo 36 y regla 70)

Referencia del solicitante o agente 4-31532A/USN	Ver notificación de la transmisión del examen preliminar internacional (formato PCT/IPEA/416) PARA PROSEGUIR	
No. Solicitud Internacional PCT/EP 01/09068	Fecha de presentación internacional (día/mes/año) 06/08/2001	Fecha de prioridad (día/mes/año) 07/08/2000
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D308/30		
Solicitante NOVARTIS AG et al.		

1. Este examen preliminar internacional ha sido preparado por esta Autoridad encargada del Examen Preliminar Internacional y es transmitida al solicitante de acuerdo con el artículo 36. 2. Este INFORME consiste de un total de 2 páginas, incluyendo esta hoja. ___ Este Informe también está acompañado por ANEXOS, esto es hojas de la descripción, reivindicaciones y/o dibujos, los cuales han sido modificados y son la base para este Informe y/o hojas que contienen rectificaciones presentadas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT). Estos anexos consisten en un total de ___ hojas.
3. Este informe contiene indicaciones que se relacionan con los siguientes puntos: I. ☒ Base del Informe II. ☐ Prioridad III. ☐ El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial IV. ☐ Falta de unidad de invención V. ☒ Declaración motivada bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración VI. ☐ Ciertos documentos citados VII. ☐ Ciertos defectos en la solicitud internacional VIII. ☐ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 12/02/2002	Fecha en que se completó este informe 05/04/2002
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**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

Solicitud internacional No. PCT/EP 01/09068

I. BASE DEL INFORME

La base de este informe del examen preliminar internacional es la solicitud como fue presentada originalmente.

V. Declaración motivada bajo la Regla 66.2 (a) (II) con relación a la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que sustentan dicha declaración

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención como es definida en las reivindicaciones cumple con los criterios mencionados en el Artículo 33 (1) PCT, esto es, aparenta ser novedosa, tener nivel inventivo y ser aplicable industrialmente..

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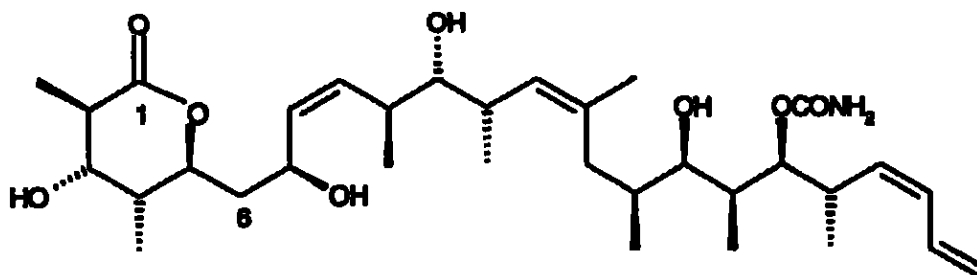
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PROCESO PARA LA PREPARACION DE DISCODERMOLIDA
Y SUS ANALOGOS

La invención se refiere a un proceso para la preparación de discodermolida y sus análogos, a compuestos novedosos utilizados en el proceso, y a compuestos novedosos preparados mediante el proceso.

ANTECEDENTES DE LA INVENCION



(+)-DISCODERMOLIDA

La (+)-discodermolida es un producto natural de policétido novedoso que fue aislado a partir de los extractos de la esponja marina *Discodermolide dissoluta* por los investigadores en la Harbor Branch Oceanographic Institution (HBOI) (Gunasekera M, Longley RE, Schulte GK. Discodermolide: a new bioactive polyhydroxylated lactone from the marine sponge *Discodermia dissoluta*. [la fe de erratas publicada aparece en J. Org. Chem. 1991; 56:1346]. J. Org. Chem. 1990;55:4912-15). La discodermolida carece de un parecido estructural obvio con el paclitaxel, y no obstante, comparte con el paclitaxel (la sustancia activa

del fármaco Taxol) la capacidad para estabilizar los microtúbulos. En los ensayos basados en el mecanismo, la discodermolida es más efectiva que el paclitaxel. De hecho, de la mano de los compuestos conocidos para inducir la polimerización de tubulina purificada, la discodermolida es la más potente. Sin embargo, los microtúbulos, un componente estructural importante en las células, no son simples polímeros en equilibrio de la tubulina. Existen como ensambles dinámicos regulados impulsados por GTP de los heterodímeros de tubulina α y β . Aunque la dinámica es relativamente lenta en las células inter-fases, al entrar a la mitosis, la velocidad de crecimiento y acortamiento se incrementa de 20 a 100 veces - el microtúbulo promedio se dobla sobre la mitad de las subunidades de tubulina cada 10 segundos. Este cambio en la velocidad permite que la red citoesquelética de microtúbulos se desmantele, y se ensamble un conjunto en forma de huso bipolar de microtúbulos. El huso se une a los cromosomas y los separa. La respuesta a la supresión completa de la dinámica de los microtúbulos en las células es la muerte. Sin embargo, las células mitóticas son más sensibles y el umbral de tolerancia parece ser específicos del tipo de célula. Las moléculas como paclitaxel que se fijan con una alta afinidad a los microtúbulos, interrumpen el proceso dinámico en las células tumorales con resultados letales, inclusive cuando la proporción del fármaco fijado a la tubulina sea muy baja.

La discodermolida se fija a la tubulina de una manera

competitiva con el paclitaxel. Debido a que el paclitaxel ha probado ser útil en el tratamiento de algunos cánceres, otros compuestos de la misma clase mecánica pueden tener utilidad contra los desórdenes hiperproliferativos.

5 El desarrollo futuro de la discodermolida o de análogos estructuralmente relacionados es impedido por la falta de una fuente natural confiable del compuesto o de una ruta sintética factible. La discodermolida que se presenta naturalmente es escasa, y la cosecha del organismo producto presenta problemas
10 logísticos. De acuerdo con lo anterior, existe una necesidad siempre creciente de mejores síntesis que hagan posible la preparación de cantidades comercialmente aceptables de discodermolida y análogos estructuralmente relacionados.

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COMPENDIO DE LA INVENCION

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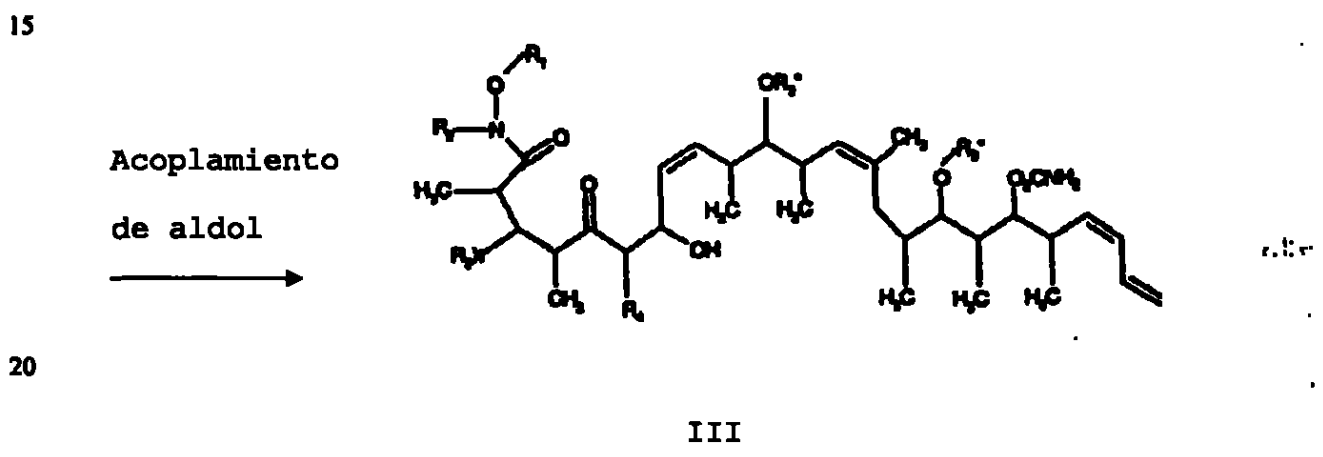
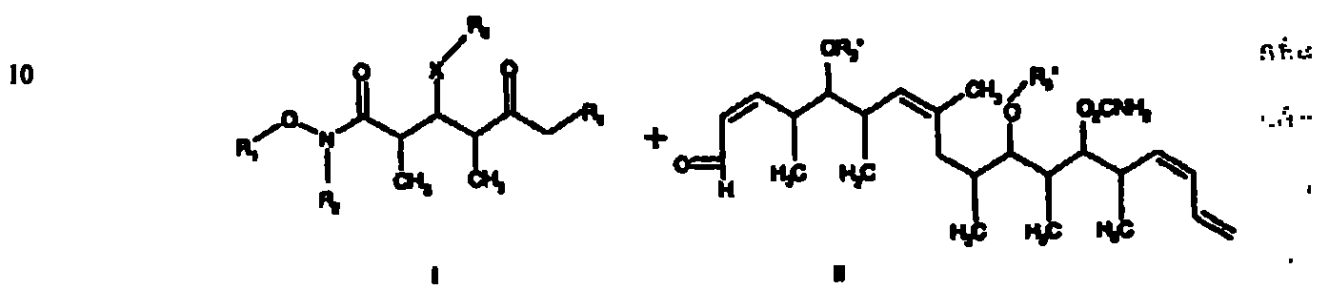
La presente invención se refiere a una síntesis más práctica de discodermolida y sus análogos. En otra modalidad, la presente invención se refiere a novedosos compuestos útiles en la preparación de discodermolida y sus análogos. En una modalidad adicional, la presente invención se refiere a compuestos
20 novedosos que se preparan mediante el proceso de la presente invención.

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DESCRIPCION DETALLADA DE LA INVENCION

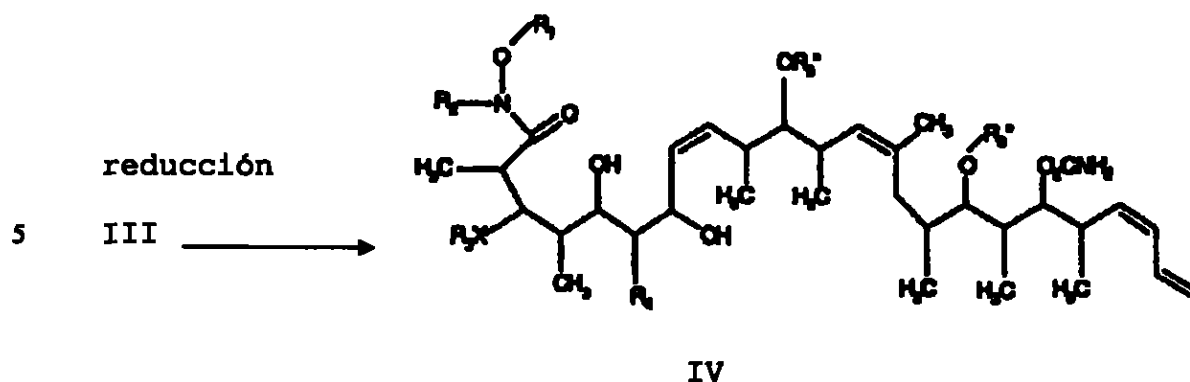
La esencia de la presente invención es el descubrimiento de una síntesis más práctica para la discodermolida y sus análogos. De una manera más particular, se ha descubierto que la discodermolida y sus análogos se pueden preparar mediante una reacción de tres pasos como sigue:

PASO 1



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PASO 2



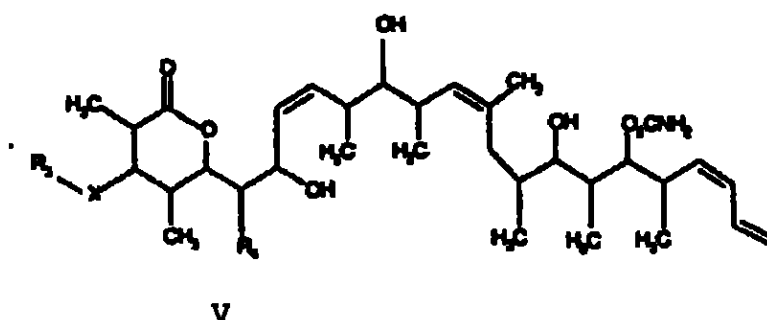
PASO 3

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Lactonización promo-
vida por ácido y
desprotección

IV $\longrightarrow$

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En donde R_1 es alquilo (de 1 a 6 átomos de carbono), bencilo, o un grupo protector de hidroxilo lábil al ácido. R_2 es alquilo (de 1 a 6 átomos de carbono), o bencilo; R_3 es hidrógeno, alquilo (de 1 a 6 átomos de carbono), bencilo, C(O)-alquilo (de 1 a 12 átomos de carbono), C(O)Ph, C(O)O-alquilo (de 1 a 12 átomos de carbono), C(O)OPh, C(O)NH-alquilo (de 1 a 12 átomos de carbono), C(O)NHPh, o un grupo protector de hidroxilo lábil al ácido; R_3'' es un grupo protector de hidroxilo lábil al ácido; R_4 es hidrógeno o metilo; y X es O, NH, NCH₃, S, ó CH₂, con

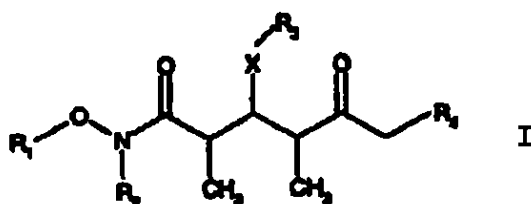
la condición de que cuando X es O y R₃ es un grupo protector de hidroxilo lábil al ácido en el compuesto de la fórmula I, la fracción "-X-R₃" en el compuesto de la fórmula V es -OH.

Con respecto a los pasos individuales, el Paso 1 involucra el acoplamiento de un compuesto de cetona de la fórmula I con un compuesto de aldehído de la fórmula II mediante una reacción de aldol, para obtener un compuesto de β-hidroxicetona de la fórmula III. El acoplamiento convenientemente se realiza con entre 1 y 20, de preferencia entre 5 y 15 equivalentes del compuesto de cetona de la fórmula I en relación con el compuesto de aldehído de la fórmula II. El acoplamiento se conduce en la presencia de: 1) un haluro o triflato de dialquilboro, de preferencia un cloruro o triflato de boro quirral, más preferiblemente β-clorodi-isopinocanfenilborano; 2) una base, de preferencia una amina, más preferiblemente trietilamina; y 3) un solvente orgánico polar, de preferencia un éter, más preferiblemente dietiléter, a una temperatura de entre -100°C y 20°C, de preferencia entre -78°C y -20°C, durante un período de entre 2 y 72 horas, de preferencia durante 16 horas.

El Paso 2 se refiere a la reducción del compuesto de β-hidroxicetona de la fórmula III, y más particularmente, el grupo cetona común a estos compuestos, para obtener un compuesto de 1,3-diol de la fórmula IV. La reducción se conduce en la presencia de: 1) un agente reductor de cetona, de preferencia un borohidruro, tal como triacetoxiborohidruro de tetrametila-

monio; 2) un solvente orgánico polar, de preferencia acetoni-
trilo; y 3) un solvente prótico, de preferencia un ácido car-
boxílico, tal como ácido acético, a una temperatura de entre
78°C y 20°C, de preferencia entre -40°C y -10°C, durante un pe-
ríodo de entre 2 y 72 horas, de preferencia durante 16 horas.
Con respecto al Paso 3, involucra la lactonización y desprotec-
ción de los grupos protectores de hidroxilo lábiles al ácido de
un compuesto de la fórmula IV para obtener un compuesto de la
fórmula V. La reacción de lactonización y desprotección se
conduce en la presencia de: 1) un ácido prótico, de preferencia
una solución acuosa de ácido prótico, de preferencia una solu-
ción acuosa de haluro de hidrógeno, tal como cloruro de hidró-
geno acuoso; y 2) un solvente orgánico polar, de preferencia
una mezcla de solventes orgánicos polares, más preferiblemente
una mezcla de un alcohol alifático y un éter, tal como metanol
y tetrahidrofurano, a una temperatura de entre -20°C y 40°C, de
preferencia entre 20°C y 25°C, durante un período de 8 horas y
7 días, de preferencia entre 16 y 72 horas, más preferiblemente
entre 24 y 48 horas.

En otra modalidad, la presente invención se refiere a los
compuestos de cetona novedosos de la fórmula I:



en donde:

R_1 es alquilo (de 1 a 6 átomos de carbono), bencilo, o un grupo protector de hidroxilo lábil al ácido;

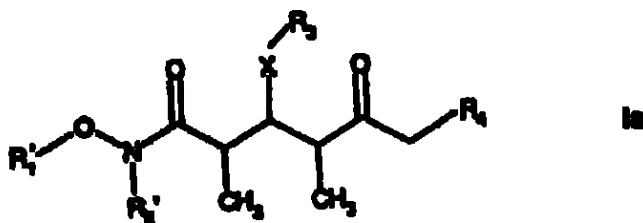
R_2 es alquilo es alquilo (de 1 a 6 átomos de carbono), o bencilo;

R_3 es hidrógeno, alquilo (de 1 a 6 átomos de carbono), bencilo, C(O)alquilo (de 1 a 12 átomos de carbono), C(O)Ph, C(O)O-alquilo (de 1 a 12 átomos de carbono), C(O)OPh, C(O)NH-alquilo (de 1 a 12 átomos de carbono), C(O)NHPh, o un grupo protector de hidroxilo lábil al ácido;

R_4 es hidrógeno o metilo; y

X es O, NH, NCH₃, S, ó CH₂.

Los compuestos preferidos son aquéllos de la fórmula Ia:



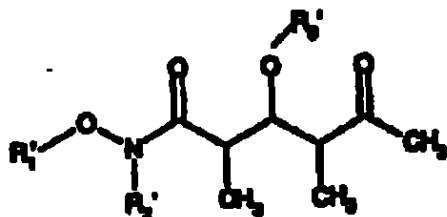
en donde:

cada uno de R_1' y R_2' es alquilo (de 1 a 6 átomos de carbono);

X es O, ó CH₂; y

R_3 y R_4 son como se definen anteriormente.

Los compuestos más preferidos son aquéllos de la fórmula Ib:

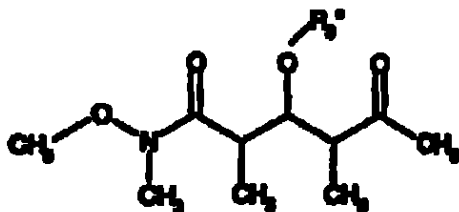


en donde:

R_3' es alquilo (de 1 a 6 átomos de carbono), C(O)-alquilo (de 1 a 12 átomos de carbono), bencilo, C(O)O-alquilo (de 1 a 12 átomos de carbono), o un grupo protector de hidroxilo lábil al ácido; y

R_1' y R_2' son como se definen anteriormente.

Los compuestos todavía más preferidos son aquéllos de la fórmula Ic:



en donde:

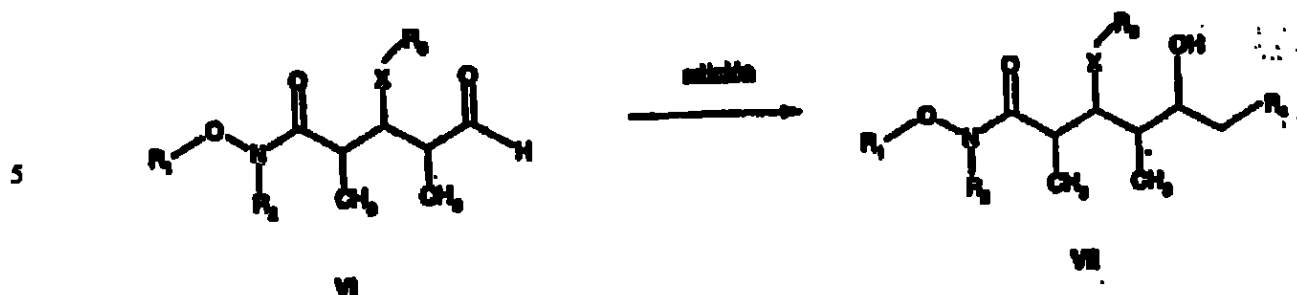
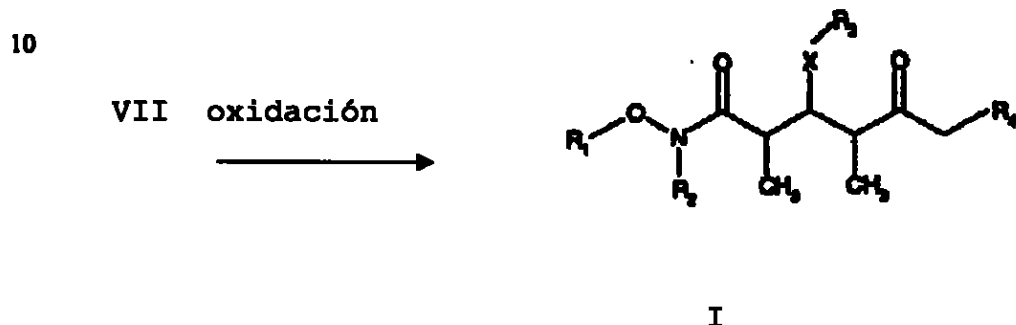
R_3'' es un grupo protector de hidroxilo lábil al ácido.

En las definiciones anteriores: el término "alquilo (de 1 a 6 átomos de carbono)", como se utiliza en la presente, se refiere a un grupo de cadena recta o ramificada que consiste ex-

clusivamente en carbono e hidrógeno, y que tiene de 1 a 6 átomos de carbono, mientras que el término "alquilo (de 1 a 12 átomos de carbono)", como se utiliza en la presente, se refiere a un grupo de cadena recta o ramificada que consiste exclusivamente en carbono e hidrógeno, y que tiene de 1 a 12 átomos de carbono. Los ejemplos de los grupos "alquilo" incluyen metilo, etilo, propilo, butilo, pentilo, 3-metilpentilo, etcétera.

El término "grupos protectores de hidroxilo lábiles al ácido" como se utiliza en la presente, se refiere a cualquier grupo enlazado con oxígeno que se pueda remover al exponerse a un ácido. Los expertos en la materia conocen numerosos ejemplos de estos grupos, y se pueden encontrar en Greene y Wuts, Protective Groups in Organic Synthesis, 2ª edición, John Wiley & Sons, Nueva York, 1991. Los ejemplos específicos incluyen, pero no se limitan a, *t*-butildimetilsililo, trietilsililo, *t*-butildifenilsililo, tri-isopropilsililo, metoximetilo, y tetrahidropiranilo.

En una modalidad adicional, la presente invención se refiere a un proceso para la preparación de los compuestos novedosos de la fórmula I. De una manera más particular, los compuestos de la fórmula I se pueden preparar como se ilustra en seguida:

PASO APASO B

15 en donde R_1 , R_2 , R_3 , y X son como se definen anteriormente.

Con respecto a los pasos individuales, el Paso A involucra la adición de un grupo metilo o etilo a un compuesto de aldehído de la fórmula VI para obtener un compuesto de alcohol de la fórmula VII. La adición se realiza en la presencia de: 1) un

20 reactivo organometálico, de preferencia un haluro de alquil-litio o de alquilmagnesio, tal como bromuro de metilmagnesio; y 2) un solvente orgánico polar, de preferencia un éter, tal como dietiléter, a una temperatura de entre -78°C y 40°C , de preferencia entre -78°C y 0°C , más preferiblemente a aproximadamente

25 -40°C , durante un periodo de entre 5 minutos y 24 horas, de

preferencia entre 30 minutos y 2 horas, más preferiblemente durante aproximadamente 1 hora.

El Paso B involucra la oxidación de un compuesto de alcohol de la fórmula VI para obtener el compuesto de cetona deseado de la fórmula I. La oxidación se realiza en la presencia de:

5 1) un oxidante, de preferencia una combinación de sulfóxido de dimetilo y un agente activador, más preferiblemente una combinación de sulfóxido de dimetilo y un complejo de trióxido de azufre con piridina; 2) una base, de preferencia una base orgánica, más preferiblemente una trialkilamina, tal como trietilamina; y 3) un solvente orgánico polar, de preferencia un hidrocarburo clorado tal como diclorometano. La oxidación adecuadamente se realiza a una temperatura de entre -78°C y 40°C , de preferencia entre 5°C y 20°C , durante un período de entre 10 minutos y 24 horas, de preferencia entre 1 hora y 12 horas, más preferiblemente entre 4 y 6 horas.

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Los compuestos de aldehído de las fórmulas II y VI son conocidos o se pueden preparar de una manera análoga a los procesos estipulados en la literatura para otros aldehídos estructuralmente similares.

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En todavía otra modalidad, la presente invención se refiere a los novedosos compuestos de β -hidroxi-cetona de la fórmula III, y a los compuestos novedosos de 1,3-diol de la fórmula IV.

Aunque el producto de cada reacción descrito anteriormente, si se desea, se puede purificar mediante técnicas convencionales.

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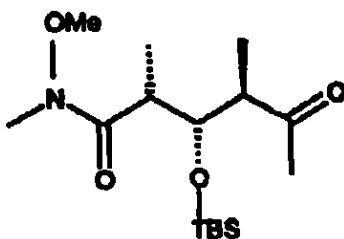
cionales, tales como cromatografía o recristalización (si es un sólido), el producto crudo de una reacción convenientemente se emplea en la siguiente reacción sin purificación.

Como es evidente para los expertos en este campo, los compuestos de las fórmulas I y III-V contienen átomos de carbono asimétricos, y por consiguiente, se debe entender que se contemplan los estereoisómeros individuales como incluidos dentro del alcance de esta invención.

Los siguientes ejemplos son para propósitos de ilustración solamente, y no pretenden limitar de ninguna manera el alcance de la presente invención.

EJEMPLO 1

(2R,3S,4R)-3-[[(1,1-dimetiletil)dimetilsilil]oxi]-N-metoxi-N,2,4-trimetil-5-oxo-hexanamida.



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A una solución de 13.1 gramos (39.5 milimoles) de la mezcla diaestereomérica preparada en la Etapa 1.1 en una mezcla que comprende 150 mililitros de cloruro de metileno, 50 mililitros de sulfóxido de dimetilo, y 25 mililitros de trietilamina, se agregan por goteo, mediante un embudo de adición, 19.0 gra-

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mos, (120 milimoles) del complejo de trióxido de azufre-piridina en 150 mililitros de sulfóxido de dimetilo a 0°C. Luego la solución resultante se agita durante 1-1/2 horas a 0°C. Después de cuyo tiempo, la mezcla de reacción se concentra mediante un evaporador giratorio en un baño de enfriamiento a <10°C. Entonces la solución se diluye con 200 mililitros de éter, y luego se extrae sucesivamente con 200 mililitros de una solución de sulfato ácido de sodio 1M y 200 mililitros de salmuera. Luego se seca la capa orgánica sobre sulfato de sodio, y la mezcla del producto crudo se purifica mediante cromatografía por evaporación empleando hexano como el eluyente inicialmente, y luego una mezcla eluyente de acetato de etilo al 5 por ciento en hexano, para dar el compuesto deseado como un aceite transparente.

¹H RMN (300 MHz, CDCl₃) δ 4.23 (dd, J = 7.5, 4.2 Hz, 2H), 3.61 (s, 3H), 3.01 (s, 3H), 2.92 (m, 2H), 2.64 (m, 2H), 2.08 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H), 0.81 (s, 9H), 0.00 (s, 6H).

Etapas 1.1 (2R,3S,4S)-3-[[[(1,1-dietiletil)dimetilsilil]oxi]-5-hidroxi-N-metoxi-N,2,4-trimetil-hexanamida

A una solución de 6.9 gramos (21.8 milimoles) de (2R,3S,4S)-3-[[[(1,1-dietiletil)dimetilsilil]oxi]-N-metoxi-N,2,4-trimetil-5-oxo-pentanamida en 50 mililitros de éter, se agregan 10.2 mililitros (30.5 milimoles) de una solución 3 M de

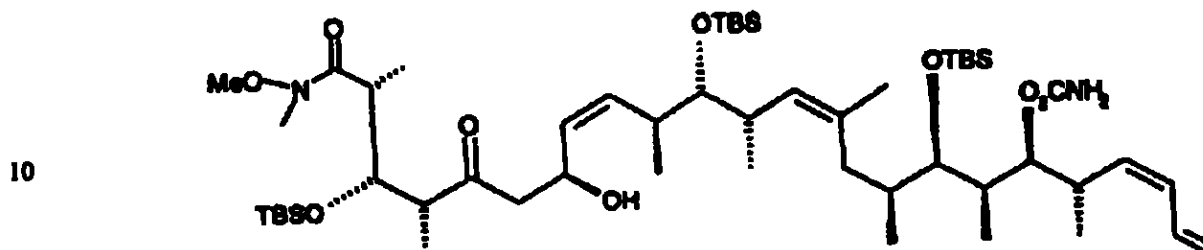
bromuro de metilmagnesio en éter, por goteo, a -40°C , después de lo cual, la mezcla se agita a -20°C durante 1 hora. Luego la mezcla de reacción se diluye con 200 mililitros de éter, y la reacción se apaga mediante la adición de la mezcla de reacción a 20 gramos de hielo triturado a 0°C . Entonces la mezcla se lava con 100 mililitros de una solución de sulfato ácido de sodio 1M, y se divide con 2 porciones de 150 mililitros de éter. Luego se combinan las capas orgánicas y se secan sobre sulfato de sodio. Entonces la mezcla del producto crudo se pasa por cromatografía empleando una mezcla eluyente de acetato de etilo al 20 por ciento en hexano inicialmente, y luego una mezcla eluyente de acetato de etilo al 40 por ciento en hexano, para dar dos diaestereómeros como aceites amarillos claros, los cuales se utilizan en el siguiente paso sin mayor purificación.

15 Diaestereómero 1: ^1H RMN (300 MHz CDCl_3): δ 4.08 (dd, $J = 9.8$, 6.8 Hz, 2H), 3.64 (s, 3H), 3.54 (d, $J = 2.6$ Hz, 2H), 3.08 (s, 3H), 3.00 (m, 2H), 1.48 (m, 2H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 6.4$ Hz, 3H), 0.81 (s, 9H), 0.76 (d, $J = 7.2$ Hz, 2H), 0.01 (d, $J = 3.8$ Hz, 6H).

20 Diaestereómero 2: ^1H RMN (300 MHz, CDCl_3): δ 4.19 (dd, $J = 12.1$, 6.0 Hz, 2H), 3.86 (dd, $J = 9.0$, 1.51 Hz, 2H), 3.56 (s, 3H), 3.18 (m, 2H), 3.01 (s, 3H), 1.28 (m, 2H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.94 (d, 6.4 Hz, 3H), 0.88 (d, 7.2 Hz, 3H), 0.78 (s, 9H), 0.01 (d, 1.3Hz, 6H).

EJEMPLO 2

(2R,3S,4R,7S,8Z,10S,11S,12S,13Z,16S,17R,18R,19S,20S,21E) -
 19-[(aminocarbonil)oxil]-3,11,17-tris[[(1,1-dietiletil)dime-
 5 tilsilil]oxi]-7-hidroxi-N-metoxi-N,2,4,10,12,14,16,18,20-no-
 nametil-5-oxo-8,13,21,23-tetracosatetraenamida.



A una solución agitada de 2.18 gramos (6.79 milimoles, 10
 equivalentes) de (+)-β-clorodi-isopinocanfenilborano en 4 mili-
 15 litros de dietiléter a 0°C, se le agregan 1.04 mililitros (11
 equivalentes, destilada sobre hidruro de calcio) de trietilamí-
 na, y luego una solución de 2.25 gramos (6.79 milimoles, 10
 equivalentes) del compuesto del Ejemplo 1 en 3 mililitros de
 dietiléter. Después de agitar durante 2 horas a 0°C, la mezcla
 20 se enfría a -78°C, después de cuyo tiempo se agrega una solu-
 ción previamente enfriada (-78°C) de 450 miligramos (0.679 mi-
 limoles) de (2Z,4S,5S,6S, 7Z,10S,11R,12R,13S,14S,15E)-13-[(ami-
 nocarbonil)oxil]-5,11-bis[[(1,1-dietiletil)dimetilsilil]-
 oxi]-4,6,8,10,12,14-hexametil-2,7,15,17-octadecatetraenal en 4
 25 mililitros de dietiléter por medio una cánula. Después de que

10

30

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se mantiene la mezcla resultante a una temperatura de -78°C durante 3 horas, se transfiere a un congelador (-27°C) durante 16 horas. Luego la reacción se apaga con 8 mililitros de metanol (cuyo pH se ajusta a 7 con 12 mililitros de una solución reguladora del pH) y 4 mililitros de una solución de peróxido de hidrógeno al 50 por ciento a 0°C . Después de agitar durante 2 horas 25°C , se separan las capas orgánicas. Entonces se extrae la capa orgánica 5 veces con porciones de 25 mililitros de diclorometano. Luego se secan las capas orgánicas combinadas sobre sulfato de magnesio, se concentran utilizando un evaporador giratorio, y se pasan por cromatografía (Biotage, gel de sílice, gradiente del 10 al 30 por ciento de acetato de etilo/hexano) para dar el compuesto deseado como un aceite incoloro altamente viscoso.

$[\alpha]_{\text{D}} + 12.56^{\circ}$ ($c = 1.0$, CH_2Cl_2); IR (CH_2Cl_2) 3547 (m, OH), 3359 (m, CONH₂), 2958 (vs), 2990 (vs), 1729 (vs, C=O), 1664 (m), 1462 (s), 1385 (s), 1254 (s), 1037 (s), 1037 (s), 1004 (s), 835 (vs); ^1H RMN (500MHz, CDCl_3) δ 6.61 (1H, ddd, $J = 17.1, 10.5, 10.5\text{Hz}$, H₂₃), 6.03 (1H, dd, $J = 11.0, 11.0\text{Hz}$, H₂₂), 5.50 (1H, dd, $J = 10.6, 10.6\text{Hz}$, H₉), 5.37 (1H, dd, $J = 10.6, 10.5\text{Hz}$, H₂₁), 5.35 (1H, dd, $J = 10.8, 8.5\text{Hz}$, H₈), 5.23 (1H, dd, $J = 15.3, 2.1\text{Hz}$, H_{24A}), 5.13 (1H, d, $J = 10.2\text{Hz}$, H_{24B}), 5.05 (1H, d, $J = 10.0\text{Hz}$, H₁₃), 4.79 (1H, t, $J = 8.0\text{Hz}$, H₇), 4.72 (1H, t, $J = 5.9\text{Hz}$, H₁₉), 4.60-4.50 (2H, br, CONH₂), 4.33 (1H, dd, $J = 6.9, 4.3\text{Hz}$, H₃), 3.74 (3H, s, NOCH₃), 3.43 (1H, dd, $J = 5.0, 4.1\text{Hz}$, H₁₇), 3.31

(1H, dd, $J = 5.2, 5.1$ Hz, H_{11}), 3.13 (3H, s, NCH_3), 3.08 (1H, br, OH), 3.00 (1H, m, H_{20}), 2.78-2.69 (2H, m, $H_4 + H_{6A}$), 2.70-2.62 (1H, m, H_{10}), 2.66-2.54 (2H, m, $H_2 + H_{6B}$), 2.49-2.45 (1H, m, H_{12}), 2.12 (1H, dd, $J = 12.4, 12.3$ Hz, H_{15A}), 1.93-1.86 (2H, m, $H_{16} + H_{18}$), 1.76-1.65 (1H, m, H_{15B}), 1.62 (3H, s, Me_{14}), 1.14 (3H, d, $J = 7.0$ Hz, Me_2), 1.11 (3H, d, $J = 7.0$ Hz, Me_4), 1.00 (3H, d, $J = 3.1$ Hz, Me_{20}), 0.99 (3H, d, $J = 3.3$ Hz, Me_{10}), 0.96-0.90 (21H, m, $Me_{18} + 2 \times Si(CH_3)_3$), 0.88 (3H, d, $J = 6.6$ Hz, Me_{12}), 0.83 (9H, s, $Si(CH_3)_3$), 0.73 (3H, d, $J = 6.7$ Hz, Me_{16}), 0.10 & 0.08 & 0.04 & 0.03 & 0.03 & 0.01 (6x3H, 3xSi(CH₃)₂);

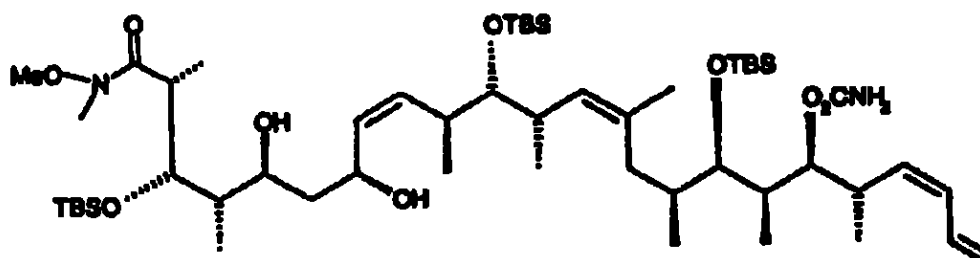
^{13}C RMN (100.6 MHz, $CDCl_3$) δ 212.9, 175.9, 156.9, 136.0, 133.7, 132.1, 131.9, 131.3, 129.8, 129.6, 117.9, 80.6, 78.7, 76.8, 73.6, 64.9, 62.1, 61.3, 54.7, 53.1, 51.7, 49.0, 45.1, 44.9, 37.9, 37.1, 36.2, 35.9, 35.0, 34.4, 30.0, 29.1, 26.26, 26.24, 25.97, 23.0, 18.51, 18.5, 18.43, 18.14, 17.43, 16.44, 13.5, 10.99, 10.1, -3.29, -3.4, -3.5, -3.9, -4.1, -4.4; m/z (ESI⁺) 1017 (100 (MNa^+)).

EJEMPLO 3

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(2R,3S,4S,5S,7S,8Z,10S,11S,12S,13Z,16S,17R,18R,19S,20S,21E)-19-
[(aminocarbonil)oxil]-3,11,17-tris[[(1,1-dimetiletil)dimetil-
silil]oxi]-5,7-hidroxi-N-metoxi-N,2,4,10,12,14,16,18,20-no-
nametil-8,13,21,23-tetracosatetraenamida.

25



5

A una solución de 1.02 gramos (3.9 milimoles) de triacetoxiborohidruro de tetrametilamonio en 2.2 mililitros de acetonitrilo anhidro se le agregan 2.2 mililitros de ácido acético anhidro, y la mezcla se agita a temperatura ambiente durante 30 minutos. Luego la mezcla se enfría a -29°C , y a la mezcla enfriada se le agrega una solución de 450 miligramos (0.453 milimoles) del compuesto del Ejemplo 2 en un 1 mililitro de acetonitrilo anhidro. Entonces la mezcla resultante se agita a -29°C durante 18 horas, después de cuyo tiempo la reacción se apaga con 2 mililitros de tartrato de sodio y potasio acuoso 0.5N. Luego la mezcla se deja calentar lentamente a temperatura ambiente, después de lo cual se diluye con cloruro de metileno, y se lava con bicarbonato de sodio saturado. Entonces la capa orgánica se extrae cuatro veces con cloruro de metileno. Las capas orgánicas combinadas se lavan luego con salmuera, se secan con sulfato de sodio, y se concentran al vacío. Entonces se purifica el residuo resultante mediante cromatografía por evaporación (Biotage, gel de sílice, gradiente del 10 al 30 por ciento de acetato de etilo/hexano) para dar el compuesto deseado como un sólido blanco.

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$[\alpha] + 29.75$ grados ($c = 0.87$, CH_2Cl_2); ^1H RMN (499.87 MHz, CDCl_3)
 δ 6.60 (1H, ddd, $J = 16.8, 10.5, 10.5$ Hz, H_{23}), 6.02 (1H, t, $J = 11.0$, H_{22}), 5.48 (1H, dd, $J = 10.0, 9.8$ Hz, H_9), 5.37 (1H, dd, $J = 10.6, 11.2$ Hz, H_{21}), 5.35 (1H, dd, $J = 10.8, 8.5$ Hz, H_8),
5 5.22 (1H, d, $J = 15.8$ Hz, H_{24A}), 5.12 (1H, d, $J = 10.2$ Hz, H_{24B}),
4.98 (1H, d, $J = 10.1$ Hz, H_{13}), 4.79 (1H, t, $J = 6.3$ Hz, H_7),
4.65 (1H, t, $J = 5.9$ Hz, H_{19}), 4.60–4.50 (2H, br, CONH_2), 4.20
(1H, dd, $J = 7.7, 2.3$ Hz, H_3), 3.92 (1H, m, H_5), 3.73 (3H, s, NOCH_3),
10 3.45 (1H, br, OH-5), 3.41 (1H, dd, $J = 10.9, 4.7$ Hz, H_{17}), 3.31 (1H, dd, $J = 5.2, 5.1$ Hz, H_{11}), 3.18 (3H, s, NCH_3),
3.08 (1H, br, OH), 2.99 (1H, m, H_{20}), 2.67 (1H, m, H_{10}), 2.43–
2.41 (2H, m), 2.11 (1H, t, $J = 12.3$ Hz), 1.90–1.87 (2H, m),
1.76–1.58 (10H, m), 1.25 (3H, t, Me), 1.7 (3H, d, $J = 7.1$ Hz, Me),
0.99 (3H, d, $J = 6.4$ Hz, Me), 0.97 (3H, d, $J = 6.5$ Hz, Me),
15 0.93–0.83 (30H, m, Me + $3 \times \text{Si}(\text{CH}_3)_3$), 0.71 (3H, d, $J = 6.8$
Hz, Me), 0.10 & 0.08 & 0.04 & 0.03 & 0.03 & 0.01 (6x3H,
 $3 \times \text{Si}(\text{CH}_3)_2$). ^{13}C RMN (100.6 MHz, CDCl_3) δ 156.88, 140.02, 134.19,
133.66, 132.10, 131.88, 131.40, 131.30, 131.11, 130.06, 129.79,
117.91, 115.44, 80.79, 80.69, 78.61, 78.32, 74.31, 70.68,
20 65.55, 61.66, 45.69, 40.38, 38.36, 37.92, 37.83, 37.29, 36.29,
35.07, 34.91, 34.45, 32.36, 29.68, 26.21, 26.12, 26.03, 25.95,
22.95, 18.52, 18.43, 18.12, 17.41, 17.07, 16.57, 13.44, 12.29,
10.32, 10.14, -3.20, -3.43, -3.96, -4.16, -4.48 m/z (ESI+) 1019
(100 (MNa⁺)).

EJEMPLO 4**Preparación de (+)-discodermolida**

A una solución de 450 miligramos (0.452 milimoles) del compuesto del Ejemplo 3 en 56 mililitros de tetrahidrofurano, se le agregan 56 mililitros de una solución acuosa de ácido clorhídrico 4N. Luego la solución resultante se agita a temperatura ambiente durante 24, entonces se agrega 10 mililitros de metanol, y después esta solución se agita durante 24 horas adicionales a temperatura ambiente. A la solución se le agregan entonces 50 mililitros de acetato de etilo, seguidos por la adición de bicarbonato de sodio a 0°C hasta un pH de 8. Luego la solución orgánica se lava con salmuera. Entonces se extrae la capa orgánica tres veces con porciones de 30 mililitros de acetato de etilo, y los extractos combinados se secan sobre sulfato de sodio. La filtración y la concentración, seguidas por cromatografía por evaporación empleando una mezcla eluyente de cloruro de metileno al 50 por ciento en acetato de etilo inicialmente, y luego acetato de etilo al 100 por ciento, produce la (+)-discodermolida.

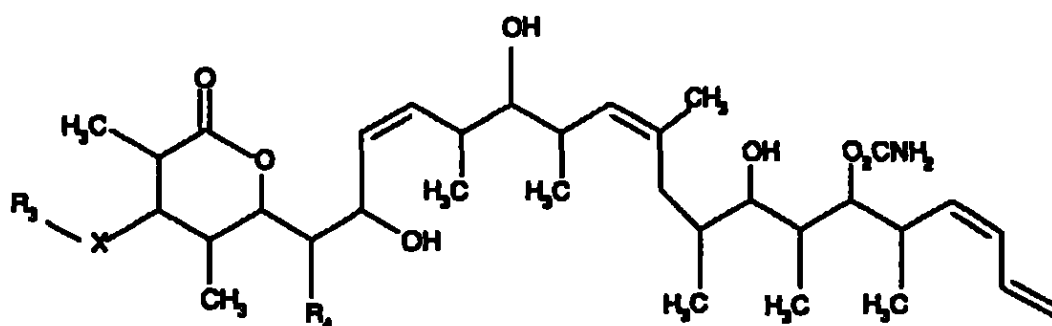
[α]_D+22.0° (c=1.41, MeOH); p.f. 122-124°C; ¹³C RMN (100.6MHz, CDCl₃) δ 176.8, 160.33, 134.17, 133.92, 133.88, 133.59, 133.28, 131.59, 131.00, 118.80, 80.66, 80.22, 78.48, 76.48, 73.66, 63.70, 44.56, 42.60, 38.79, 37.71, 36.92, 36.77, 36.69, 34.97, 34.62, 23.45, 19.73, 18.25, 18.11, 16.05, 15.84, 13.27, 9.44 m/z (ESI+) 594 (100 (M+1⁺)).

REIVINDICACIONES

1. Un proceso para la preparación de un compuesto de la fórmula V:

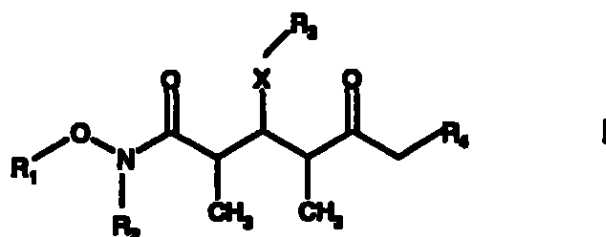
5'

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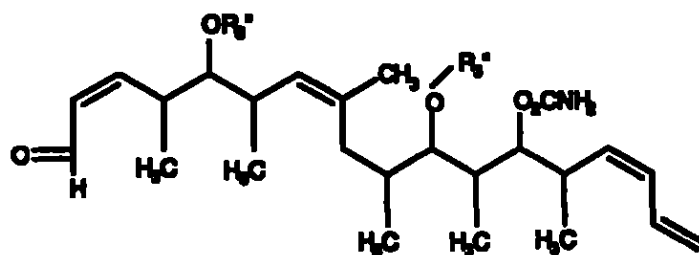
el cual comprende, en un primer paso, acoplar un compuesto de cetona de la fórmula I:

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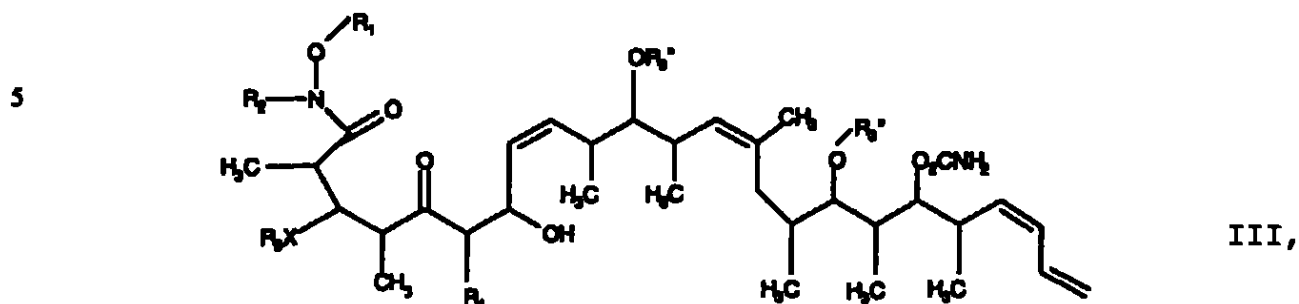
con un compuesto de aldehído de la fórmula II:

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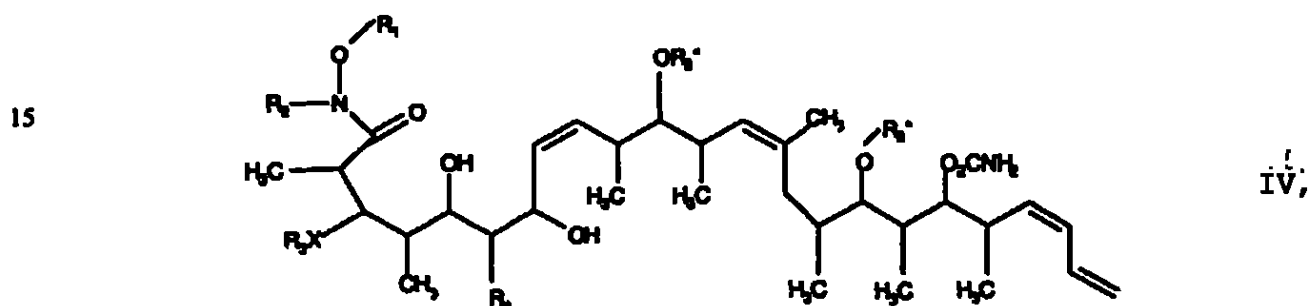


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en la presencia de un haluro o triflato de dialquilboro, una base de amina, y un solvente orgánico polar, para obtener una β -hidroxicetona de la fórmula III:



10 en un segundo paso, reducir el compuesto de cetona obtenido en el primer paso mediante su tratamiento con un reactivo de borohidruro en un solvente orgánico polar y en un solvente prótico, para obtener un 1,3-diol de la fórmula IV:



20 y en un tercer paso, lactonizar y desproteger los grupos protectores de hidroxilo lábiles al ácido del 1,3-diol obtenido en el segundo paso, mediante su tratamiento con un haluro de hidrógeno disuelto en un solvente polar o una mezcla de solventes, para obtener el compuesto deseado de la fórmula V, en donde R_1 es alquilo (de 1 a 6 átomos de carbono), bencilo, o un

25 grupo protector de hidroxilo lábil al ácido; R_2 es alquilo (de

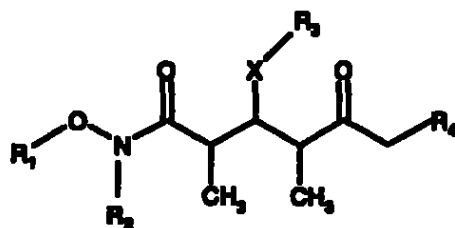
1 a 6 átomos de carbono), o bencilo; R_3 es hidrógeno, alquilo (de 1 a 6 átomos de carbono), bencilo, $C(O)$ -alquilo (de 1 a 12 átomos de carbono), $C(O)Ph$, $C(O)O$ -alquilo (de 1 a 12 átomos de carbono), $C(O)OPh$, $C(O)NH$ -alquilo (de 1 a 12 átomos de carbono), $C(O)NHPh$, o un grupo protector de hidroxilo lábil al ácido; R_3'' es un grupo protector de hidroxilo lábil al ácido; R_4 es hidrógeno o metilo; y X es O , NH , NCH_3 , S , ó CH_2 , con la condición de que cuando X es O y R_3 es un grupo protector de hidroxilo lábil al ácido en el compuesto de la fórmula I, la fracción " $-X-R_3$ " en el compuesto de la fórmula V es $-OH$.

2. Un proceso de acuerdo con la reivindicación 1, en donde el paso de acoplamiento se realiza en la presencia de β -clorodi-isopinocanfenilborano, trietilamina, y dietiléter, a una temperatura de entre $-78^\circ C$ y $-20^\circ C$.

3. Un proceso de acuerdo con la reivindicación 1, en donde el paso de reducción se realiza en la presencia de triacetoxiborohidruro de tetrametilamonio, acetonitrilo, y ácido acético, a una temperatura de entre $-40^\circ C$ y $-10^\circ C$.

4. Un proceso de acuerdo con la reivindicación 1, en donde la lactonización y desprotección de los grupos protectores de hidroxilo lábiles al ácido se realizan en la presencia de cloruro de hidrógeno acuoso, metanol, y tetrahidrofurano, a una temperatura de entre $-20^\circ C$ y $40^\circ C$.

5. Un compuesto de la fórmula I:



5

en donde:

R_1 es alquilo (de 1 a 6 átomos de carbono), bencilo, o un grupo protector de hidroxilo lábil al ácido;

R_2 es alquilo es alquilo (de 1 a 6 átomos de carbono), o
10 bencilo;

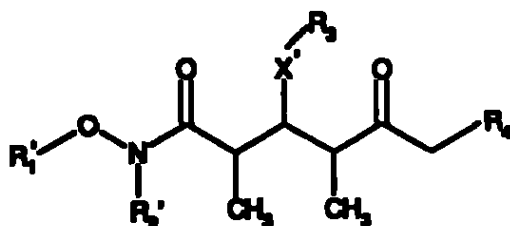
R_3 es hidrógeno, alquilo (de 1 a 6 átomos de carbono), bencilo, C(O)alquilo (de 1 a 12 átomos de carbono), C(O)Ph, C(O)O-alquilo (de 1 a 12 átomos de carbono), C(O)OPh, C(O)NH-alquilo (de 1 a 12 átomos de carbono), C(O)NHPh, o un grupo
15 protector de hidroxilo lábil al ácido;

R_4 es hidrógeno o metilo; y

X es O, NH, NCH₃, S, ó CH₂.

6. Un compuesto de acuerdo con la reivindicación 5, de la fórmula Ia:

20



25

en donde:

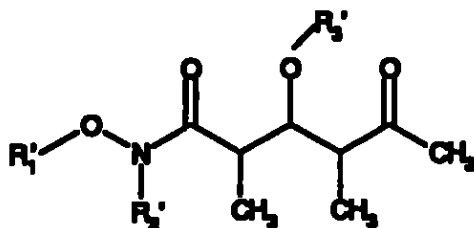
cada uno de R_1' y R_2' es alquilo (de 1 a 6 átomos de carbono);

X es O, ó CH_2 ; y

5 R_3 y R_4 son como se definen en la reivindicación 5.

7. Un compuesto de acuerdo con la reivindicación 6, de la fórmula Ib:

10



Ib

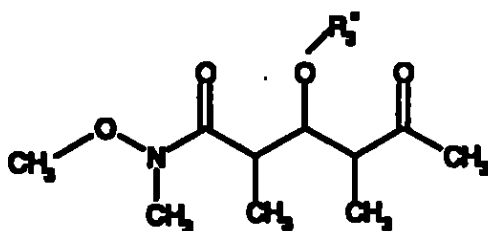
en donde:

15 R_3' es alquilo (de 1 a 6 átomos de carbono), C(O)-alquilo (de 1 a 12 átomos de carbono), bencilo, C(O)O-alquilo (de 1 a 12 átomos de carbono), o un grupo protector de hidroxilo lábil al ácido; y

R_1' y R_2' son como se definen en la reivindicación 6.

20 8. Un compuesto de acuerdo con la reivindicación 7, de la fórmula Ic:

25

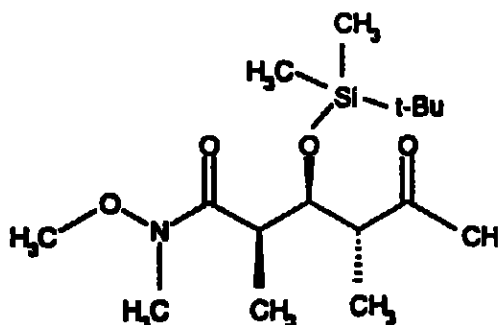


Ic

en donde:

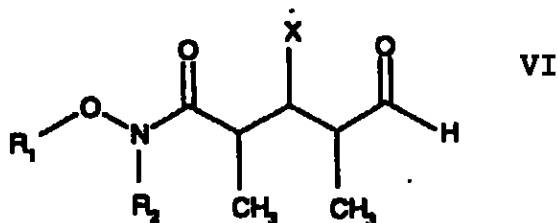
R_3'' es un grupo protector de hidroxilo lábil al ácido.

9. Un compuesto de acuerdo con la reivindicación 8, el cual es (2*R*,3*S*,4*R*)-3-[[[1,1-dimetiletil)dimetilsilil]oxi]-*N*-metoxi-*N*,2,4-trimetil-5-oxo-hexanamida que tiene la fórmula:



10

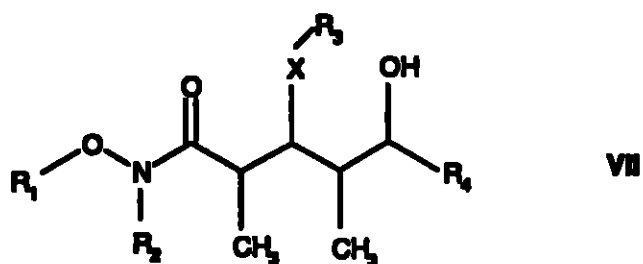
10. Un proceso para la preparación de un compuesto de la fórmula I de acuerdo con la reivindicación 5, el cual comprende, en un primer paso, la adición de un reactivo organometálico de metilo o etilo a un aldehído de la fórmula VI:



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en la presencia de un solvente orgánico polar, para obtener un alcohol de la fórmula VII:

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y en un segundo paso, oxidar el compuesto de alcohol preparado en el primer paso, mediante su tratamiento con un oxidante y una base en un solvente orgánico polar, para obtener el compuesto deseado de la fórmula I, en donde R_1 , R_2 , R_3 , R_4 , y X son como se definen en la reivindicación 5.

10

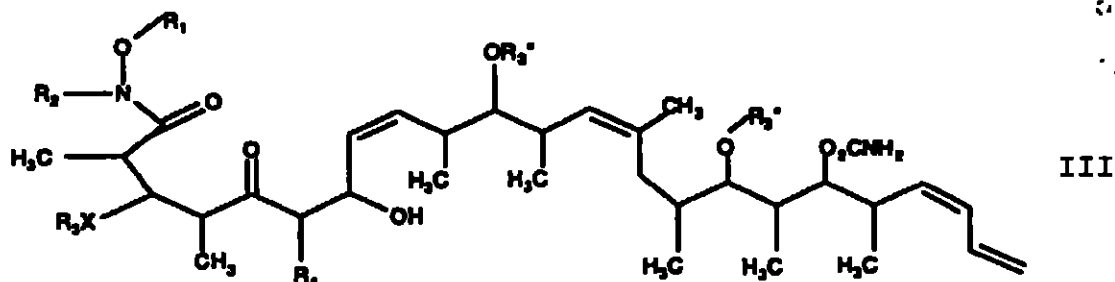
11. Un proceso de acuerdo con la reivindicación 10, en donde el paso de adición se realiza en la presencia de bromuro de metilmagnesio y dietiléter, a una temperatura de entre -78°C y 40°C .

15

12. Un proceso de acuerdo con la reivindicación 10, en donde el paso de oxidación se realiza en la presencia de un complejo de trióxido de azufre-piridina, trietilamina, y diclorometano, a una temperatura de entre -78°C y 40°C .

20

13. Un compuesto de la fórmula III:



25

en donde:

R_1 es alquilo (de 1 a 6 átomos de carbono), bencilo, o un grupo protector de hidroxilo lábil al ácido;

R_2 es alquilo es alquilo (de 1 a 6 átomos de carbono), o
5 bencilo;

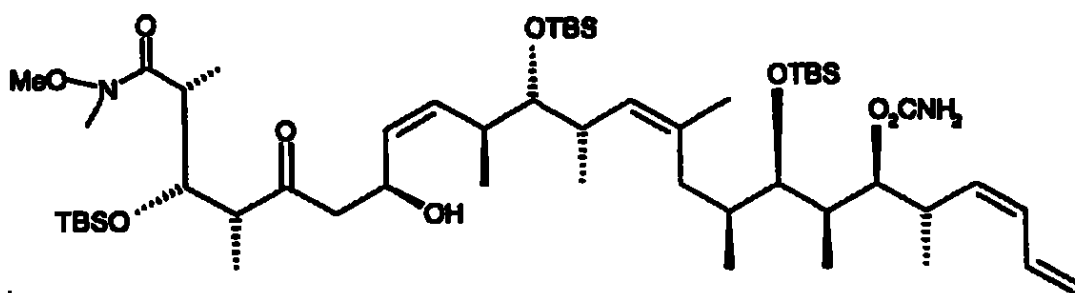
R_3 es hidrógeno, alquilo (de 1 a 6 átomos de carbono), bencilo, $C(O)$ alquilo (de 1 a 12 átomos de carbono), $C(O)Ph$, $C(O)O$ -alquilo (de 1 a 12 átomos de carbono), $C(O)OPh$, $C(O)NH$ -alquilo (de 1 a 12 átomos de carbono), $C(O)NHPh$, o un grupo
10 protector de hidroxilo lábil al ácido;

R_4 es hidrógeno o metilo; y

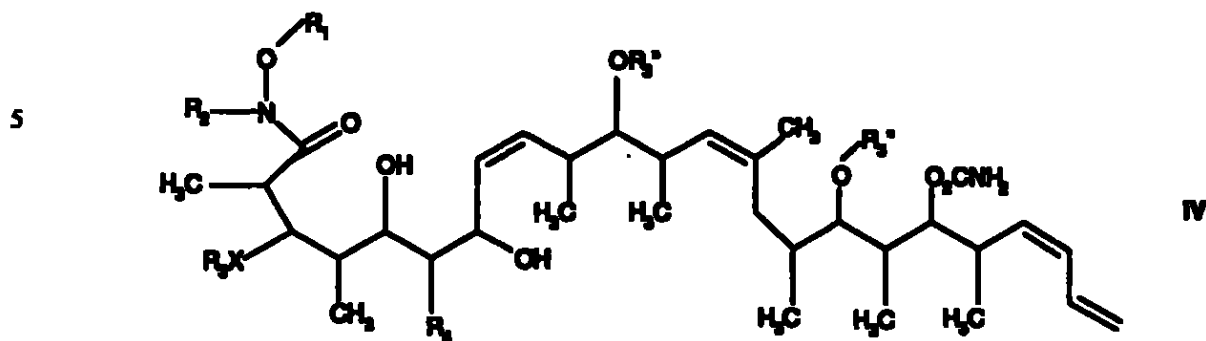
X es O , NH , NCH_3 , S , ó CH_2 ; y

cada uno de R_3 es un grupo protector de hidroxilo lábil al ácido.

15 14. Un compuesto de acuerdo con la reivindicación 13, el cual es (2*R*,3*S*,4*R*,7*S*,8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,18*R*,19*S*,20*S*, - 21*E*)-19-[(aminocarbonil)oxil]-3,11,17-*tris*[(1,1-dimetiletil)-dimetilsilil]oxil]-7-hidroxi-*N*-metoxi-*N*,2,4,10,12,14,16,18,20-
nonametil-5-oxo-8,13,21,23-tetracosatetraenamida, que tiene la
20 fórmula:



15. Un compuesto de la fórmula IV:



en donde:

R_1 es alquilo (de 1 a 6 átomos de carbono), bencilo, o un grupo protector de hidroxilo lábil al ácido;

15 R_2 es alquilo es alquilo (de 1 a 6 átomos de carbono), o bencilo;

R_3 es hidrógeno, alquilo (de 1 a 6 átomos de carbono), bencilo, C(O)alquilo (de 1 a 12 átomos de carbono), C(O)Ph, C(O)O-alquilo (de 1 a 12 átomos de carbono), C(O)OPh, C(O)NH-alquilo (de 1 a 12 átomos de carbono), C(O)NHPh, o un grupo protector de hidroxilo lábil al ácido;

20

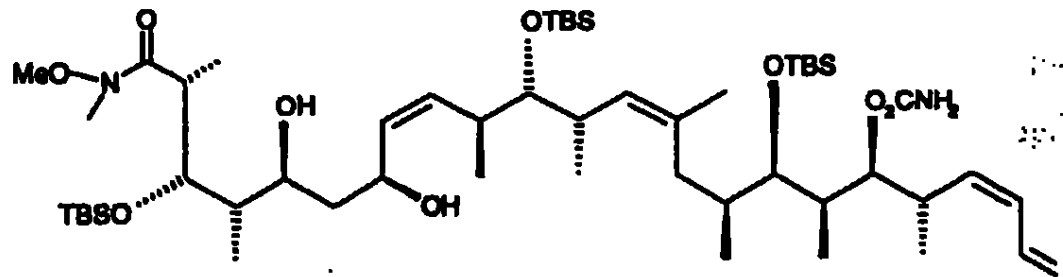
R_4 es hidrógeno o metilo; y un

X es O, NH, NCH₃, S, ó CH₂; y

cada uno de R_3'' es un grupo protector de hidroxilo lábil al ácido.

25 16. Un compuesto de acuerdo con la reivindicación 15, el

cual es: (2*R*,3*S*,4*S*,5*S*,7*S*,8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*,18*R*,19*S*, -
 20*S*,21*E*)-19-[(aminocarbonil)oxil]-3,11,17-tris[[(1,1-dimetil-
 etil)dimetilsilil]oxi]-5,7-hidroxi-*N*-metoxi-*N*,2,4,10,12,14,16,-
 18,20-no-nametil-8,13,21,23-tetracosatetraenamida que tiene la
 fórmula:



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RESUMEN

Una síntesis más práctica para la preparación de discoder-
10 molida y análogos estructuralmente relacionados, compuestos no-
vedosos útiles en el proceso, y compuestos novedosos preparados
mediante el proceso.

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