

Clarke, Modet & C^o
COLOMBIA

ESCOBAR - URIBE ASOCIADOS
Intellectual Property

131
137

As. 2798/PCT.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-025149- -00005-0000

Ref.: Expediente No. 05-025.149
Solicitud de Patente a nombre de
Novartis AG.

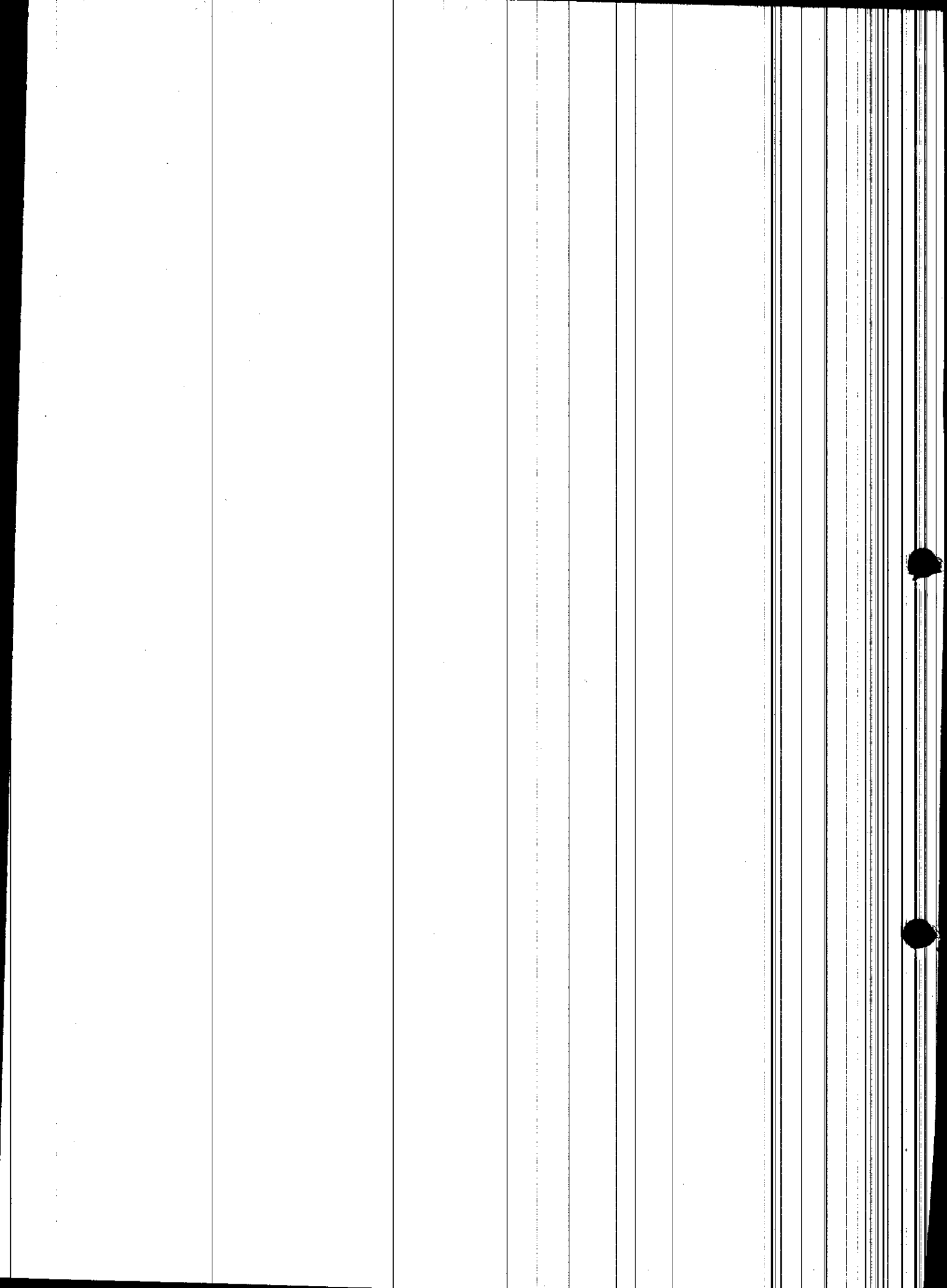
Fecha: 2007-08-14 16:19:28 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad Novartis AG., con domicilio en Basilea, Suiza, solicitantes de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 07 - 49,132 de 20 de junio de 2007, por la suma de \$404.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


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



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-025149- -00005-0000

Fecha: 2007-08-14 16:19:28 Dep. 2020 NUECREACION
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

BO OFICIAL DE CAJA : 07 - 49,132
A : JUNIO 20 DE 2007

***** CONSIGNACION *****

POSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
MARKET MODEY Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	66415407	19/06/2007	2,662,000.00

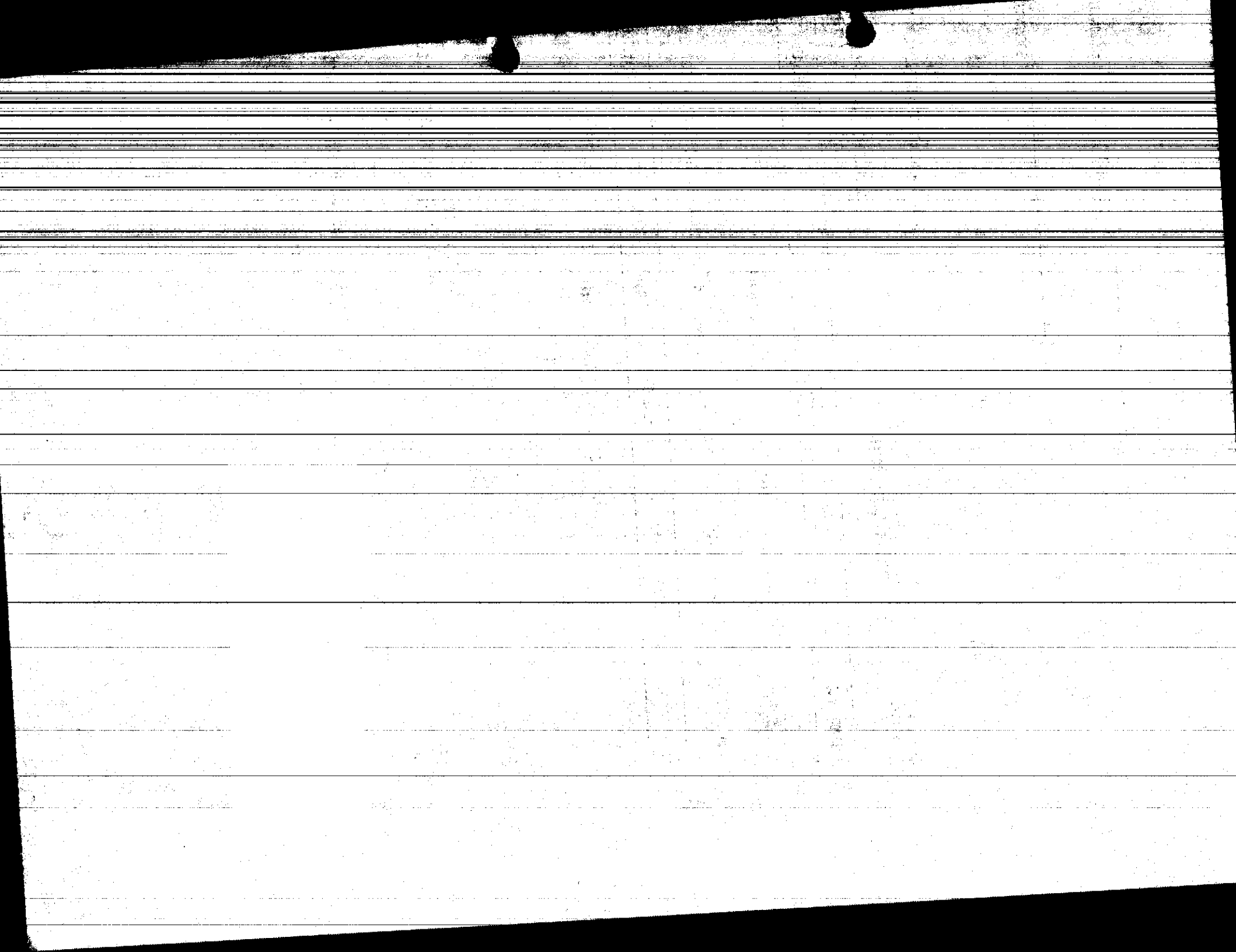
***** CONCEPTO *****

T. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
0005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	404,000.00
	TOTAL :	\$ 404,000.00

CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE : _____

BO DE CAJA APLICADO AL EXPEDIENTE No. _____



DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-25149

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 573 DE

FECHA 28 DE FEBRERO DE 2007 EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL 30 DE MAYO DE 2007

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 April 2002 (18.04.2002)

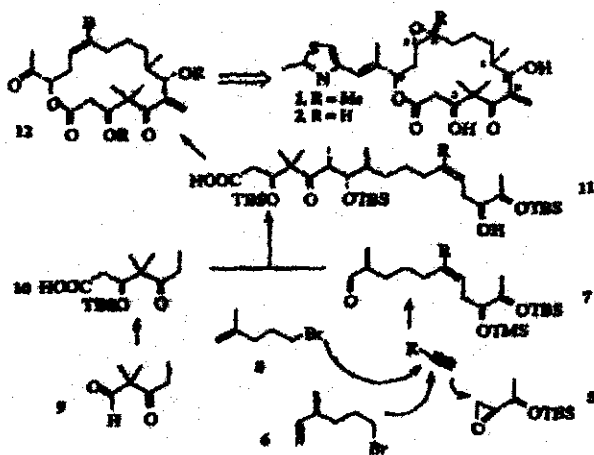
PCT

(10) International Publication Number
WO 02/30356 A2

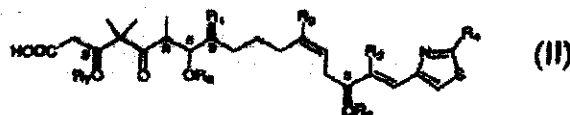
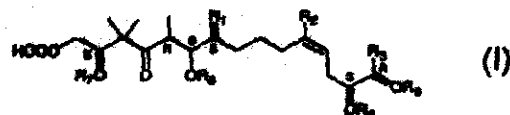
- (51) International Patent Classification: A61K (74) Agents: MARTIN, Timothy, J. et al.; Timothy J. Martin, P.C., Suite 200, 9250 W 5th Avenue, Lakewood, CO 80226 (US).
- (21) International Application Number: PCT/US01/32225
- (22) International Filing Date: 15 October 2001 (15.10.2001) (51) Designated 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, UZ, VN, YU, ZA, ZW.
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/240,488 13 October 2000 (13.10.2000) US (54) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, 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: THE UNIVERSITY OF MISSISSIPPI [US/US]; 1009 NCNPR, University, MS 38677 (US).
- (72) Inventor: AVERY, Mitchell, A.; 303 Woodland Hills Drive, Oxford, MS 38655 (US).

[Continued on next page]

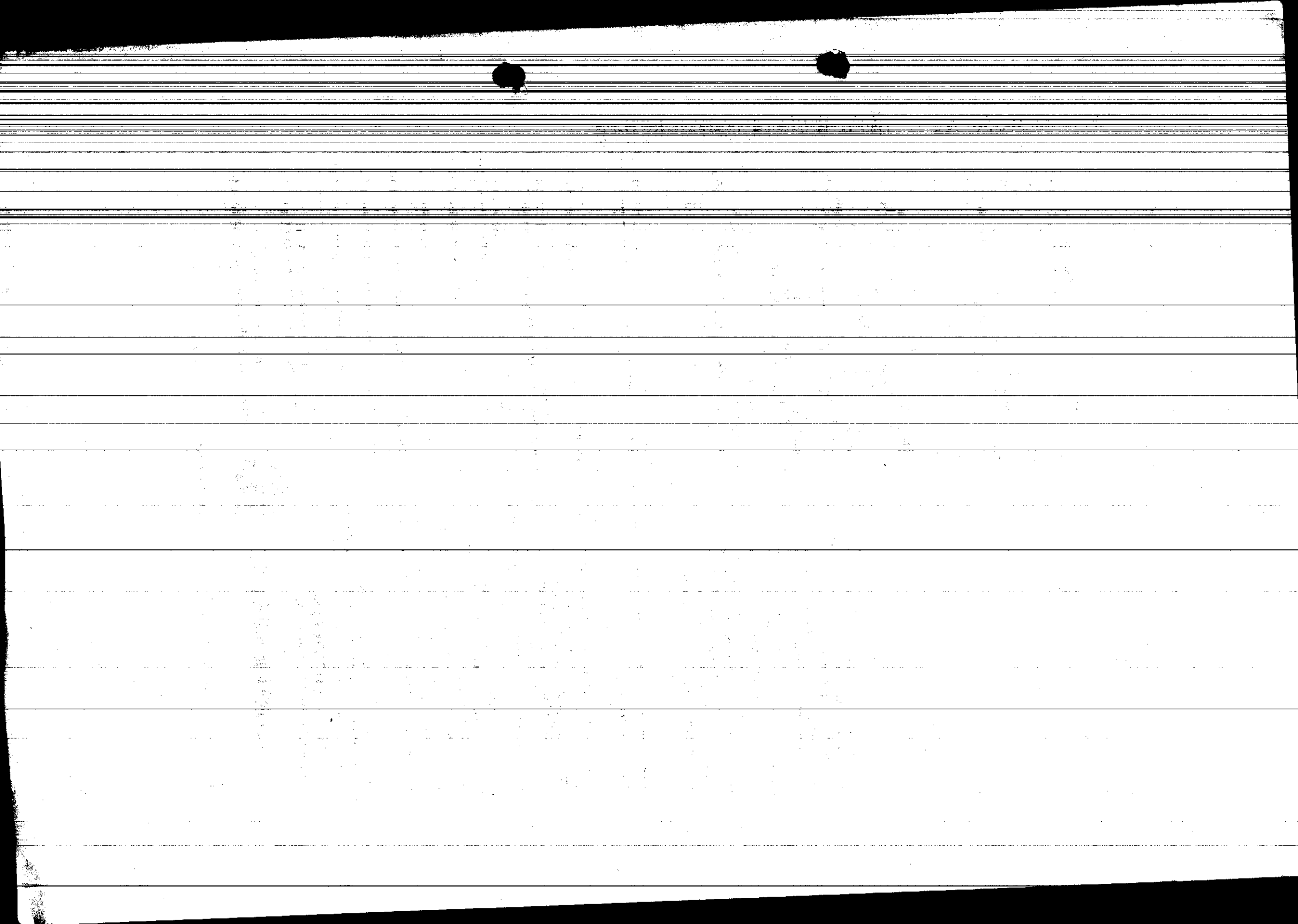
(54) Title: SYNTHESIS OF EPOTHILONES AND RELATES ANALOGS



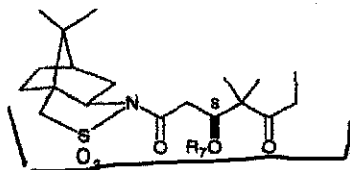
(57) Abstract: The present invention relates to methods for use in producing epothilones and analogs and derivatives thereof. A general method according to the present invention broadly comprises performing an aldol condensation of a first compound with a second compound thereby to form a third compound selected from the formulas (I) and (II) and stereoisomers thereof, and performing a macrolactonization of the third compound. The present invention also provides chemical compounds, and methods for producing such chemical compounds, that are useful in producing epothilones and analogs and derivatives thereof.



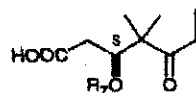
WO 02/30356 A2



63. A chemical compound according to claim 62 wherein M is Li.
64. A chemical compound according to claim 62 wherein R_7 is selected from H and TBS.
65. A process for producing a chemical compound useful in producing epothilones and analogs and derivatives thereof, comprising
- (a) converting a first compound of a formula:

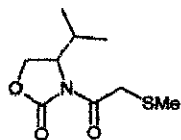


to a second compound of a formula:

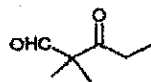


wherein R_7 is selected from H and a protecting group.

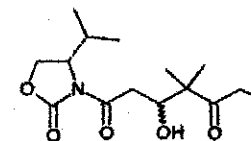
66. A method according to claim 65 wherein R_7 is TBS.
67. A process for producing a chemical compound useful in producing epothilones and analogs and derivatives thereof, comprising
- (a) reacting a first compound of a formula:



with a second compound of a formula:

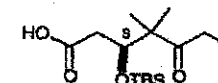


thereby to form a third compound of a formula:



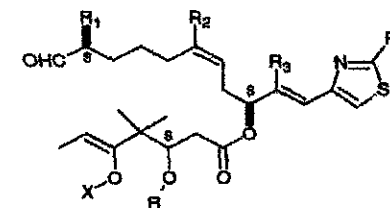
and

- (b) converting said third compound to a fourth compound of a formula:

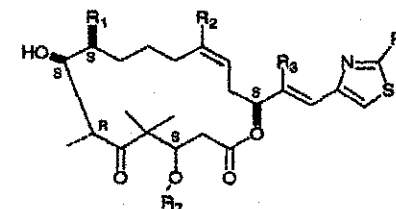


68. A process for use in producing epothilones and analogs and derivatives thereof, comprising:

- (a) converting a first compound of a formula selected from:

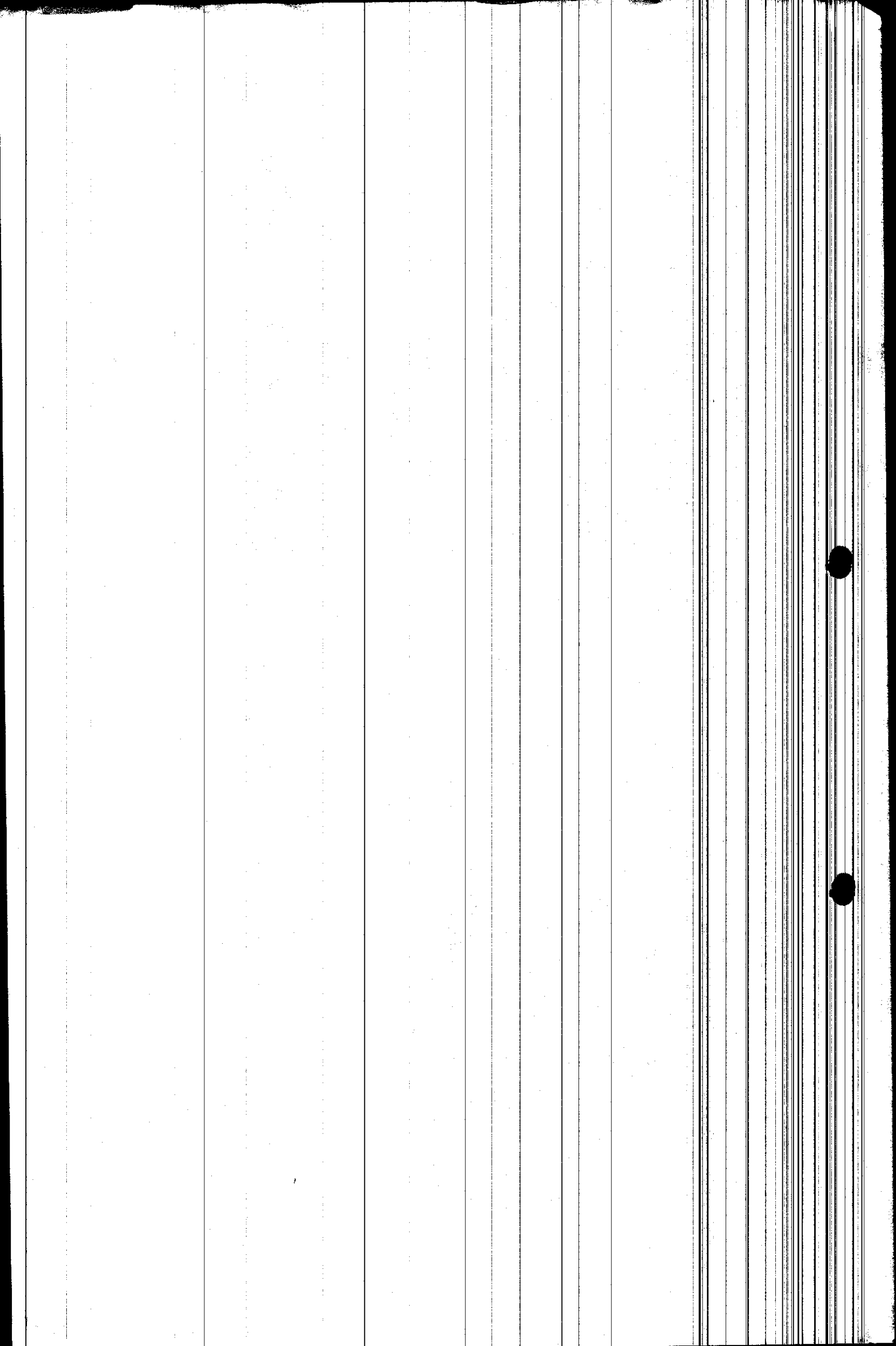


and stereoisomers thereof to a second compound of a formula selected from:



and stereoisomers thereof, wherein R_1 , R_2 , R_3 and R_4 are each selected from H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclo, and substitutions thereof; and wherein R_7 is selected from H and a protecting group.

69. A chemical compound having a formula selected from:



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

(19) World Intellectual Property Organization
International Bureau



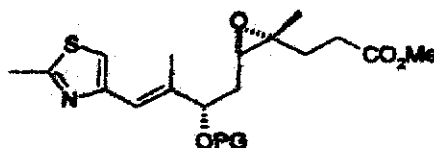
(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07439 A2

- (51) International Patent Classification⁷: C07D 417/06, 493/04, 275/06, 417/14 // (C07D 493/04, 313:00, 303:00)
- (21) International Application Number: PCT/US00/20064
- (22) International Filing Date: 24 July 2000 (24.07.2000)
- (25) Filing Language: English
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60/145,005 22 July 1999 (22.07.1999) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/145,005 (CIP)
Filed on 22 July 1999 (22.07.1999)
- (71) Applicant (for all designated States except US): SCHERING AKTIENGESELLSCHAFT [DE/US]; D-13342 Berlin (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): MULZER, Johann [DE/DE]; Friedrichshagen Weg 20, D-13467 Berlin (DE). MARTIN, Harry [DE/AT]; Westbahnstrasse 56/2/8, A-1070 Wien (AT).
- (74) Agents: SHUBIN, Harry, B. et al.; Millen, White, Zeleno & Branigan, P.C., Arlington Courthouse Plaza 1, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PRODUCTION OF EPOTHIOLONE B AND DERIVATIVES AS WELL AS INTERMEDIATE PRODUCTS FOR THIS PROCESS



(57) Abstract: The present invention is directed to a process for the production of epothiolone compounds, the improvement comprising preparing said compounds by cyclization of a compound produced from an intermediate of formula (II) wherein PG is a protecting group.

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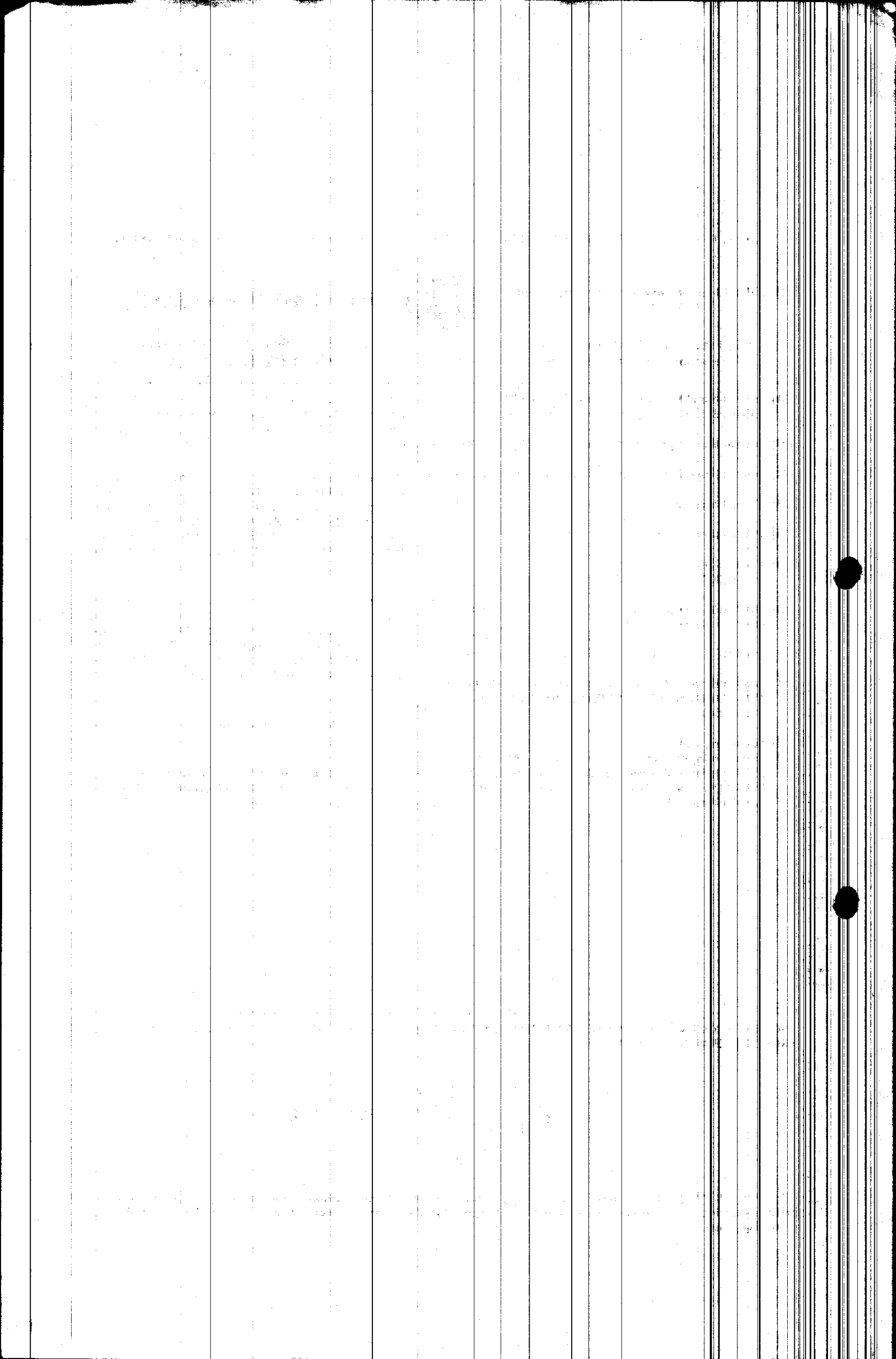
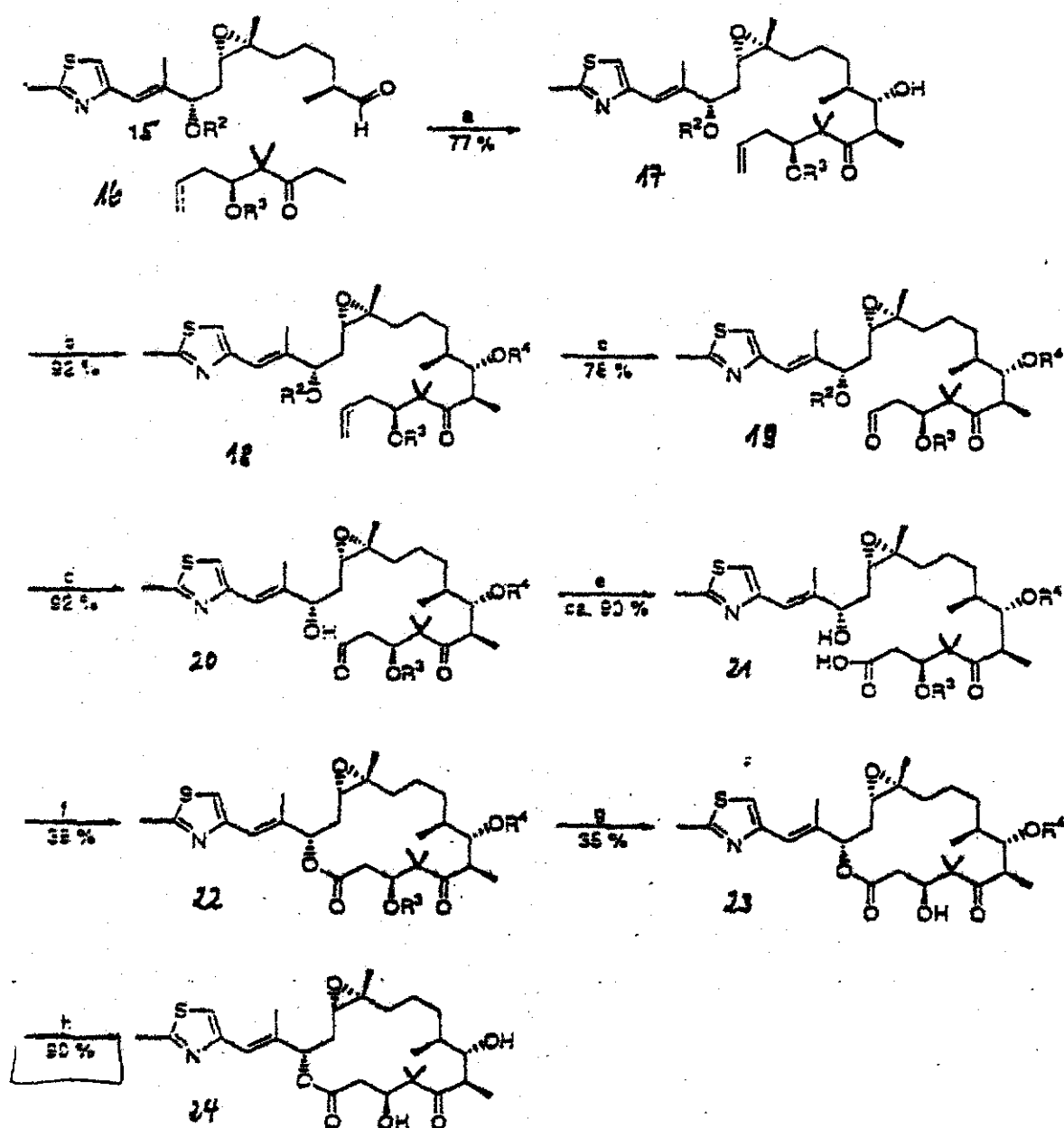


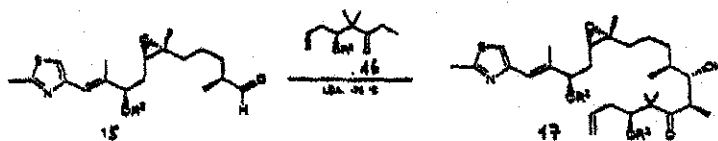
Diagram 2

Total Synthesis of Epothilone B (Epoxide Path)



^{13}C NMR (100.6 MHz, CDCl_3): δ 205.2, 164.9, 153.4, 142.5, 119.2, 115.8, 76.7, 62.4, 61.1, 46.7, 36.4, 33.6, 31.0, 26.2, 23.3, 22.7, 19.6, 18.6, 14.4, 13.7, -4.2, -4.7.

Aldol Reaction



Example: $\text{R}^2 = \text{TES}$, $\text{R}^3 = \text{TBS}$

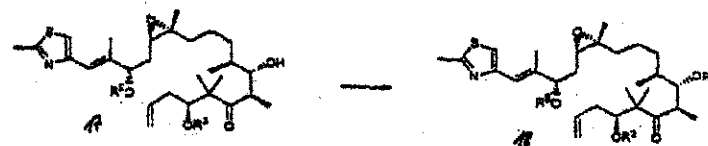
1.75 ml (1.23 mmol) of isopropylamine is dissolved in 4 ml of absolute THF and mixed at -45°C with 0.78 ml of $n\text{BuLi}$ (1.6 M in hexane; 1.20 mmol), heated to 0°C after 5 minutes and stirred for 20 minutes at 0°C . After cooling to -78°C , 345 mg (1.21 mmol) of ketone 16 (dissolved in 1 ml of THF) is added in drops within 2 minutes, and the reaction mixture is heated to -40°C within 10 minutes. It is again cooled to -78°C , and 532 mg (1.18 mmol) of aldehyde 15 (dissolved in 1.5 ml of THF) is added in drops within 2-3 minutes. After 15 minutes at -78°C , it is quenched with 4 ml of saturated NH_4Cl solution while being stirred vigorously (initially slowly then quickly added), 6 ml of ether is added, and the cooling bath is replaced by a water bath. After thawing, some water is added, and the phases are separated after shaking out. Extraction with ether, drying (MgSO_4),

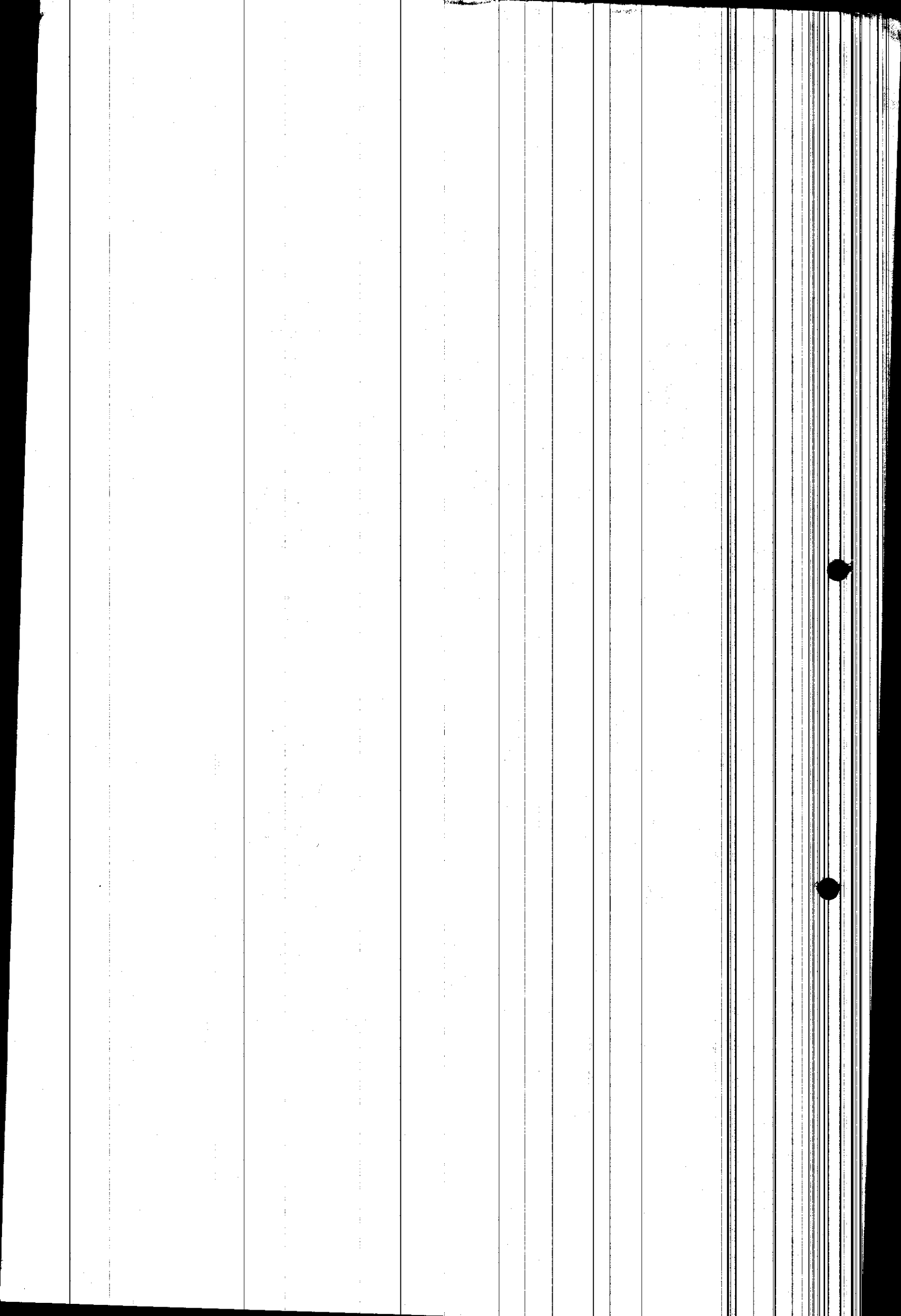
removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 10:1 - 5:1) yield 668 mg (77%) of desired main isomer 17 as a colorless, viscous liquid.

Compound 17 ($\text{R}^2 = \text{TES}$, $\text{R}^3 = \text{TBS}$)

^1H NMR (400 MHz, CDCl_3): δ = 6.93 (s, 1H), 6.51 (s, 1H), 5.72 (ddt, J = 17.1, 10.0, 7.0 Hz, 1H), 4.99 (m, 2H), 4.33 (dd, J = 9.0, 3.5 Hz, 1H), 3.92 (d, J = 6.3, 4.3 Hz, 1H), 3.49 (s, 1H), 3.31 (d, J = 9.0 Hz, 1H), 3.25 (d, J = 7.0 Hz, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 3H), 2.24-2.06 (m, 2H), 2.01 (d, J = 1.0 Hz, 3H), 1.95-1.87 (m, 1H), 1.82-1.72 (m, 1H), 1.63-1.45 (m, 5H), 1.41-1.30 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.20-1.05 (m, 1H), 1.12 (s, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl_3): δ = 222.5, 164.4, 153.1, 142.2, 136.3, 118.8, 116.7, 115.3, 76.5, 76.4, 74.9, 62.1, 61.1, 54.3, 41.1, 39.6, 36.0, 35.6, 33.4, 33.1, 26.05, 25.9, 23.4, 22.7, 22.4, 19.4, 19.2, 18.24, 18.21, 15.3, 14.0, 9.7, -3.5, -4.90, -4.6, -5.1.

7-OH Protection





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Example: $R^1 = \text{TES}$, $R^2 = \text{TBS}$, $R^3 = \text{Troc}$

200 mg (0.27 mmol) of aldol 17 is dissolved in 10 ml of methylene chloride and 5 ml of pyridine and mixed at 20°C (water bath) with 0.5 ml (2.4 mmol) of chloroformic acid-2,2,2-trichloroethyl ester and stirred for 30-45 minutes at room temperature. For working-up, the reaction mixture is shaken out with 80 ml of saturated NaHCO_3 solution and 40 ml of methylene chloride. Extraction with methylene chloride, drying (MgSO_4), removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 10:1) yield 251 mg (94%) of desired product 18 as a colorless oil.

Compound 18 ($R^1 = \text{TES}$, $R^2 = \text{TBS}$, $R^3 = \text{Troc}$)

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 6.92 (m, 1H), 6.51 (s, 1H), 5.79 (ddt, J = 16.6, 10.8, 7.0 Hz, 1H), 5.05-4.97 (m, 2H), 4.83 (d, J = 12.1 Hz, 1H), 4.81 (dd, J = 7.0, 4.5 Hz, 1H), 4.69 (d, J = 12.1 Hz, 1H), 4.33 (dd, J = 9.0, 3.5 Hz, 1H), 3.75 (dd, J = 6.5, 4.0 Hz, 1H), 3.44 (m, 1H), 2.88 (dd, J = 7.8, 4.0 Hz, 1H), 2.70 (s, 3H), 2.28-2.19 (m, 1H), 2.06-1.98 (m, 1H), 2.02 (s, 1H), 1.82-1.84 (m, 1H), 1.75-1.65 (m, 1H), 1.57-1.41 (m, 5H), 1.33-1.11 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H), 1.21-1.12 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 1.04 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.81 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H). $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ = 215.6, 164.4, 154.2, 153.1, 142.1, 136.4, 118.8, 116.6, 115.4, 94.8, 82.9, 78.1, 76.6, 76.4, 62.1, 50.8, 54.0, 42.1, 39.4, 36.0, 35.0, 31.3, 31.8, 26.1, 25.9, 24.0, 22.7, 22.3, 20.0, 19.2, 18.23, 18.21.

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16.1, 14.0, 11.5, -3.6, -3.9, -4.6, -5.1. IR (film) $\bar{\nu}_{\text{max}}$ = 2956, 2930, 2898, 1750, 1699, 1472, 1384, 1251, 1081, 992, 928, 816, 777, 732. Rotation: $[\alpha]_D^{25} = -30$ (c = 1.4, CH_2Cl_2). Analysis Calcd. for $\text{C}_{23}\text{H}_{26}\text{Cl}_2\text{NO}_7\text{Si}_2$ (511.45): C 56.69, H 5.18, N 1.54, Fnd.: C 56.54, H 5.18, N 1.47.

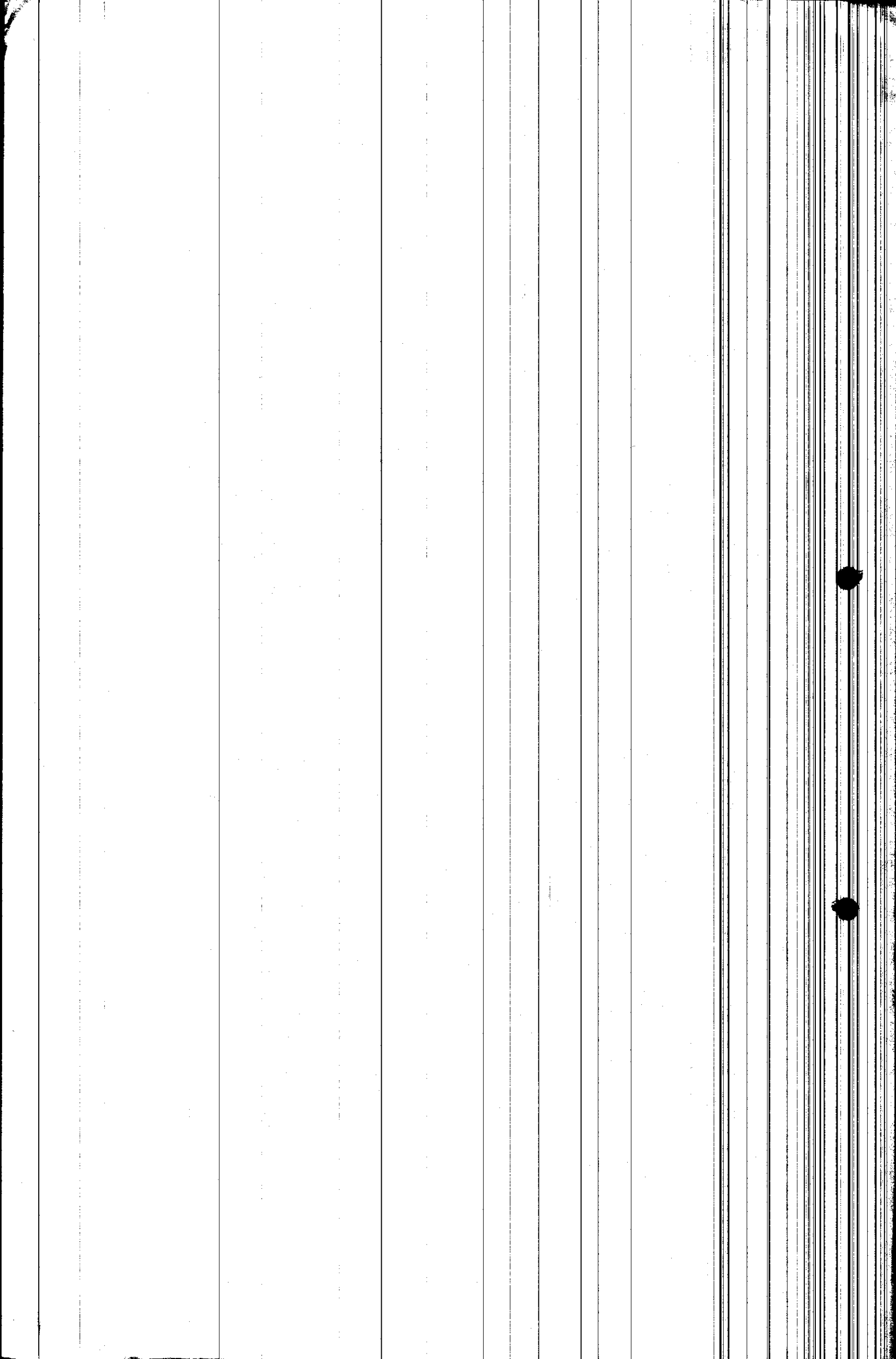
Dihydroxylation/Glycol Cleavage



Example: $R^1 = \text{TES}$, $R^2 = \text{TBS}$, $R^3 = \text{Troc}$

148 mg (0.162 mmol) of alkene 18 is dissolved in 5 ml of THF-tBuOH (1:1) and mixed with 2 mg of OsO_4 (5 mol%) and 0.89 ml of NMO (0.2 M in H_2O , 0.178 mmol). After 16 hours of stirring at 25°C, it is shaken out vigorously and for a long time with 10 ml of $\text{Na}_2\text{S}_2\text{O}_5$ (10% in H_2O) and 15 ml of methylene chloride. The phases are separated, and the aqueous phase is extracted three more times with methylene chloride. Drying (MgSO_4), removal of the solvent and filtration via a short silica gel column (hexane/ethyl acetate 1:1) yields 131 mg (86%) of diol as an isomer mixture, which is further used without additional purification.

131 mg (0.139 mmol) of diol is dissolved in 15 ml of ethanol and 3 ml of H_2O and mixed with 90 mg (0.420 mmol) of NaIO_4 .



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After three hours of stirring at 25°C, it is shaken out with 30 ml of semi-saturated NaHCO₃ solution and 30 ml of ether, and the phases are separated. Extraction with ether, drying (MgSO₄), removal of the solvent and subsequent column chromatography (Hexane/ethyl acetate 10:1 - 5:1) yield 115 mg (78% in terms of alkene) of aldehyde 19 as a colorless oil.

Compound 19 (R' = TES, R'' = TES, R''' = TBOC)

¹H NMR (400 MHz, CDCl₃): δ = 9.73 (dd, J = 2.0, 1.0 Hz, 1H), 6.92 (s, 1H), 6.80 (s, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.74 (dd, J = 7.5, 4.0 Hz, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.36-4.29 (m, 2H), 3.49-3.38 (m, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 1H), 2.67 (dd, J = 17.5, 4.5, 1.0 Hz, 1H), 2.39 (ddd, J = 17.5, 5.5, 2.0 Hz, 1H), 2.38 (s, 1H), 1.88 (ddd, J = 13.8, 9.4, 4.0 Hz, 1H), 1.76-1.66 (m, 1H), 1.60-1.40 (m, 5H), 1.38-1.10 (m, 2H), 1.33 (s, 3H), 1.26 (s, 3H), 1.20 (d, J = 6.5 Hz, 1H), 1.02 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), ¹³C NMR (100.6 MHz, CDCl₃): δ = 215.4, 200.2, 164.3, 154.2, 150.0, 142.1, 118.9, 115.4, 94.7, 82.3, 76.65, 76.3, 72.3, 68.1, 60.8, 53.4, 49.3, 42.2, 35.9, 34.9, 3.33, 31.9, 25.87, 25.85, 23.0, 32.8, 22.3, 20.0, 19.2, 18.2, 16.1, 15.8, 14.0, 11.1, -4.4, -4.5, -4.6, -5.1. 2H (E1m) ϕ_{min} = 2956, 2930, 2883, 2857, 1759, 1736, 1659, 1472, 1384, 1361, 1282, 1082, 992, 937, 836, 777, 734. Recrystallization: [α]_D²⁰ = -62.7 (c = 1.2, CHCl₃).

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18-O-Pretection Removal

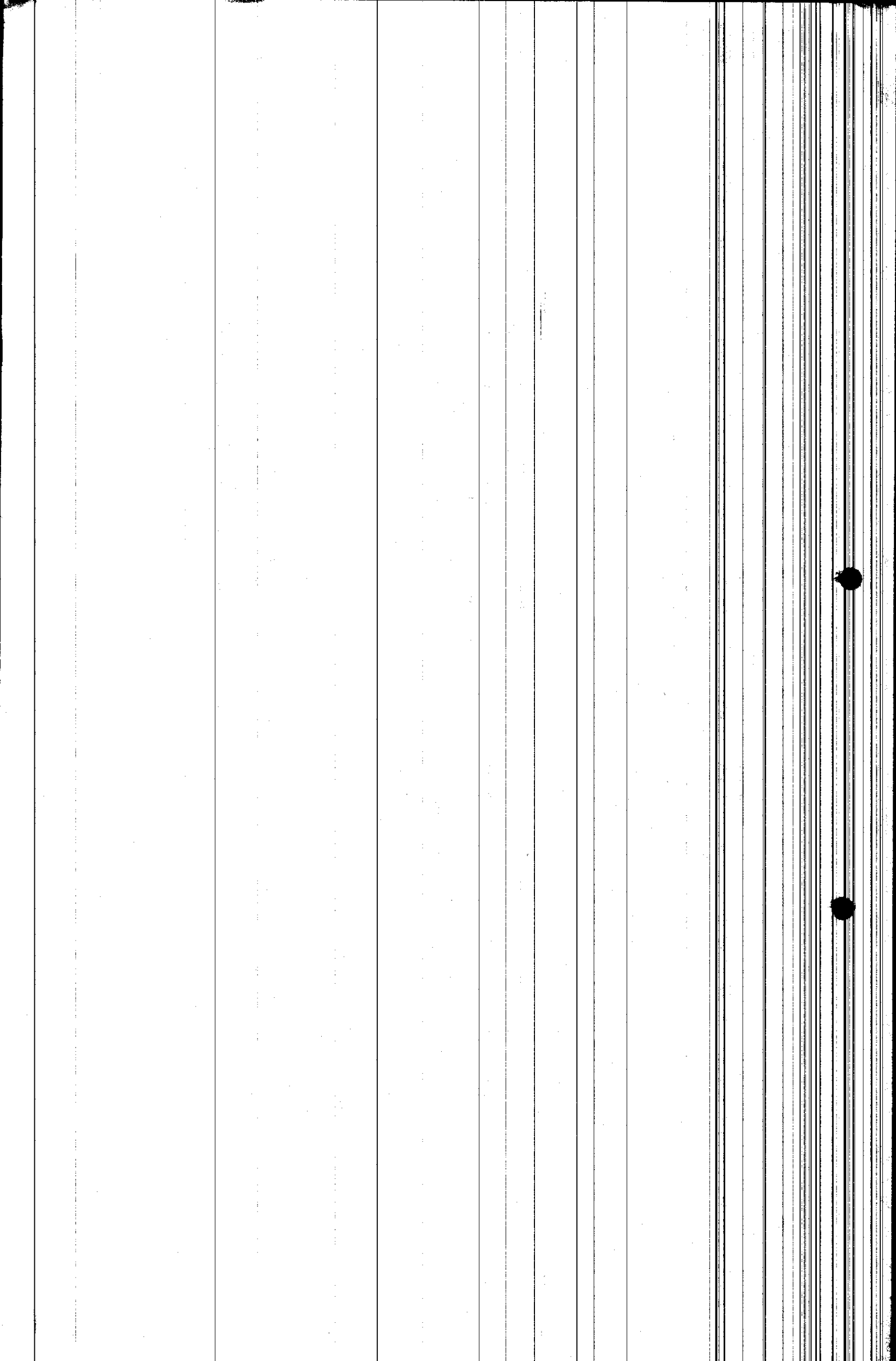


Example: R' = TES, R'' = TES, R''' = TBOC

68 mg (0.074 mmol) of 19 is dissolved in a polypropylene reaction vessel (with a cover) in 2.5 ml of absolute THF and mixed with 2.5 ml of a standard solution of HF-pyridine (prepared from 5 ml of HF-pyridine, 15 ml of pyridine and 30 ml of THF) that is buffered with pyridine. After 30 minutes, the reaction is completed. For working-up, 80 ml of saturated NaHCO₃ solution is introduced, and the reaction mixture is carefully added (plastic syringe) while being stirred vigorously. After extraction with ether (4 times 25 ml) and drying (MgSO₄), the solvent is removed in Rotavapor, whereby the pyridine is removed by repeated spinning-in with toluene. The residue is put on a column with deactivated silica gel (hexane/ethyl acetate 2:1 - 1:1), and 51 mg (93%) of product 20 is obtained as a pale yellow viscous oil.

Compound 20 (R' = TES, R'' = TES, R''' = TBOC)

¹H NMR (400 MHz, CDCl₃): δ = 9.74 (s, 1H), 6.98 (s, 1H), 6.60 (s, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.75 (dd, J = 7.8, 4.3 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.41-4.38 (m, 1H), 4.34 (t, 2



= 4.8 Hz, 1H); 3.49-3.41 (m, 1H), 3.96 (dd, $J = 8.0, 4.0$ Hz, 1H), 2.96 (s, 3H), 2.67 (dd, $J = 17.5$ Hz, 4.0 Hz, 1H), 2.40 (ddd, $J = 17.5, 8.5, 2.0$ Hz, 1H), 2.09 (d, $J = 2.5$ Hz, 1H), 2.06 (s, 3H), 1.94 (ddd, $J = 14.6, 8.5, 4.0$ Hz, 1H), 1.78-1.68 (m, 1H), 1.67 (ddd, $J = 14.0, 8.0, 4.0$ Hz, 1H), 1.58-1.41 (m, 4H), 1.35-1.25 (m, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.07 (d, $J = 6.5$ Hz, 3H), 1.04 (s, 3H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H), ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 218.4, 200.8, 184.6, 184.2, 182.7, 141.7, 118.9, 94.7, 82.3, 76.7, 75.4, 73.2, 61.8, 60.7, 59.4, 49.3, 42.2, 34.9, 34.1, 33.2, 32.0, 25.9, 23.0, 22.6, 22.1, 20.0, 19.2, 18.1, 18.9, 14.8, 11.2, -4.4, -4.5$.

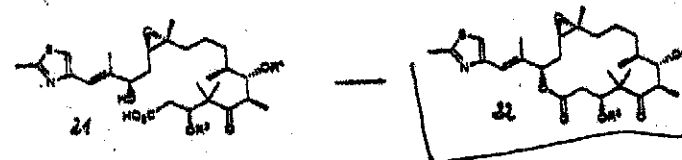
Pinnick-Oxidation/Macrolactonisation



Example: $R^1 = \text{TBS}$, $R^2 = \text{Troc}$

54 mg (0.068 mmol) of aldehyde 20 is dissolved in 2.5 ml of tBuOH and 2.5 ml of 2,3-dimethyl-2-butene and mixed with a solution of 30 mg of NaClO_2 and 30 mg of NaH_2PO_4 in 0.5 ml of H_2O and stirred for 45 minutes at room temperature. For working-up, the reaction mixture is mixed with 20 ml of semi-saturated NH_4Cl solution and extracted with methylene chloride (4 x 10 ml).

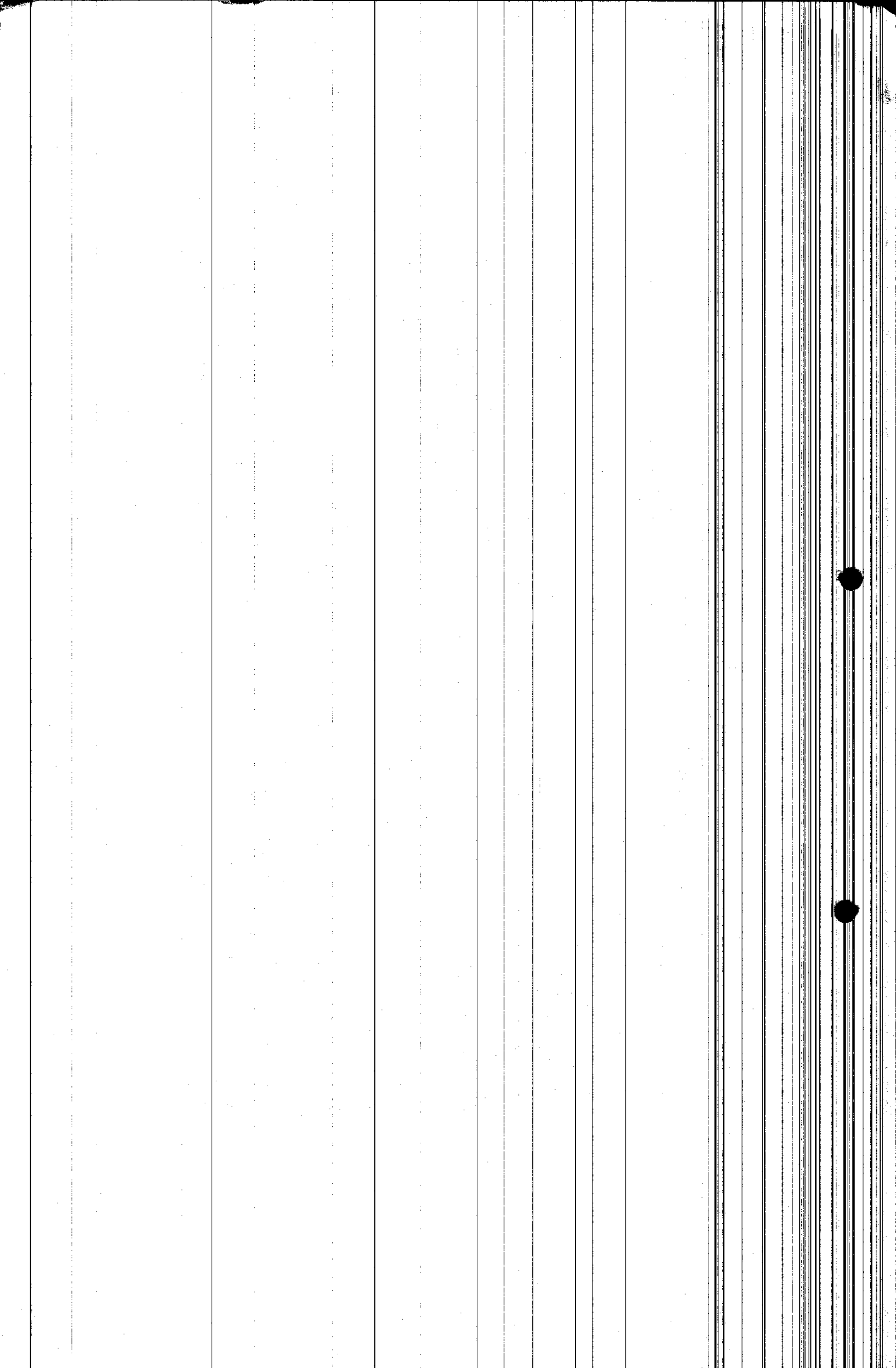
After drying, the solvent is removed, and crude acid 21 (51 mg) that is thus obtained is used directly in the next reaction.



51 mg (0.062 mmol) of crude acid 21 is dissolved in 1.5 ml of absolute THF and mixed at 0°C with 57 μl (0.36 mmol) of triethylamine and 45 μl (0.24 mmol) of 2,4,6-trichlorobenzoyl chloride and stirred for 20 minutes at room temperature. The active ester that is thus produced is slowly added in drops (15 minutes) to a solution of 80 mg (0.60 mmol) of DMAP in 35 ml of absolute toluene and stirred for 2 hours at room temperature (25°C). The reaction mixture is concentrated by evaporation to about 5 ml and filtered on a short silica gel column (rinsed with 30 ml of hexane/ethyl acetate). Removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 4:1) yields 18 mg (34%) of macro lactone 22 as a colorless oil.

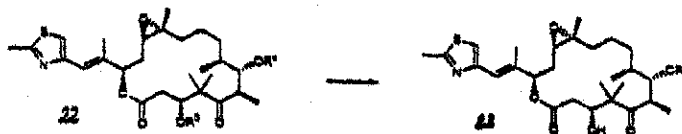
Compound 22 ($R^1 = \text{TBS}$, $R^2 = \text{Troc}$)

^1H NMR (600 MHz, CDCl_3): $\delta = 6.99$ (s, 1H), 6.86 (s, 1H), 5.21-5.14 (m, 2H), 4.97 (d, $J = 12.0$ Hz, 1H), 4.78 (d, $J = 12$ Hz, 1H), 4.05 (d, $J = 9.8$ Hz, 1H), 3.30 (dq, $J = 10.2, 6.3$ Hz, 1H), 2.82 (dd, $J = 10.3, 4.0$ Hz, 1H), 2.79 (dd, $J = 16.5, 1.5$ Hz, 1H).



2.71 (s, 3H), 2.64 (dd, $J = 16.5, 10.0$ Hz, 1H), 2.25-2.21 (m, 1H), 2.11 (s, 3H), 1.93-1.84 (m, 4H), 1.55-1.42 (m, 2H), 1.32-1.24 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.16-1.08 (m, 1H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.88 (s, 9H), 0.16 (s, 3H), -0.03 (s, 3H).

Protection Removal at 3-O



Example: $R^1 = \text{TBS}$, $R^2 = \text{Troc}$

18 mg (23 μmol) of macro lactone 22 is dissolved in 0.5 ml of THF and mixed with 2.5 ml of buffered HF-Py (see above) and stirred for 72 hours at room temperature, and then it is added carefully to 35 ml of a saturated NaHCO_3 solution and extracted with ether. Removal of the solvent (repeated spinning-in with toluene) and subsequent column chromatography (hexane/ethyl acetate 2:1 - 1:1) yield 5 mg (32%) of desired product 21 as a colorless oil. At the same time, 6 mg of starting material is recovered.

Compound 23 ($R^1 = \text{Troc}$)

$^1\text{H NMR}$ (350 MHz, CDCl_3): $\delta = 6.99$ (s, 1H), 6.63 (s, 1H), 5.52 (t, $J = 4.5$ Hz, 1H), 5.18 (dd, $J = 9.0, 2.0$ Hz, 1H), 4.84 (d, $J = 12$ Hz, 1H), 4.78 (d, $J = 12$ Hz, 1H), 4.15-4.05 (m, 1H), 3.79-3.70 (m, 2H), 3.54-3.52 (m, 1H), 2.87 (t, $J = 6.0$ Hz, 1H), 2.72 (s, 3H), 2.59 (dd, $J = 14.0, 10.0$ Hz, 1H), 2.46 (dd, $J = 14.0, 4.0$ Hz, 1H), 2.35 (t, $J = 7.5$ Hz, 2H), 2.12 (s, 3H), 2.00 (t, $J = 5.5$ Hz, 2H), 1.89-1.81 (m, 2H), 1.75-1.28 (m, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 1.19 (d, $J = 7.0$ Hz, 3H), 1.09 (s, 3H), 0.99 (d, $J = 7.0$ Hz, 3H).

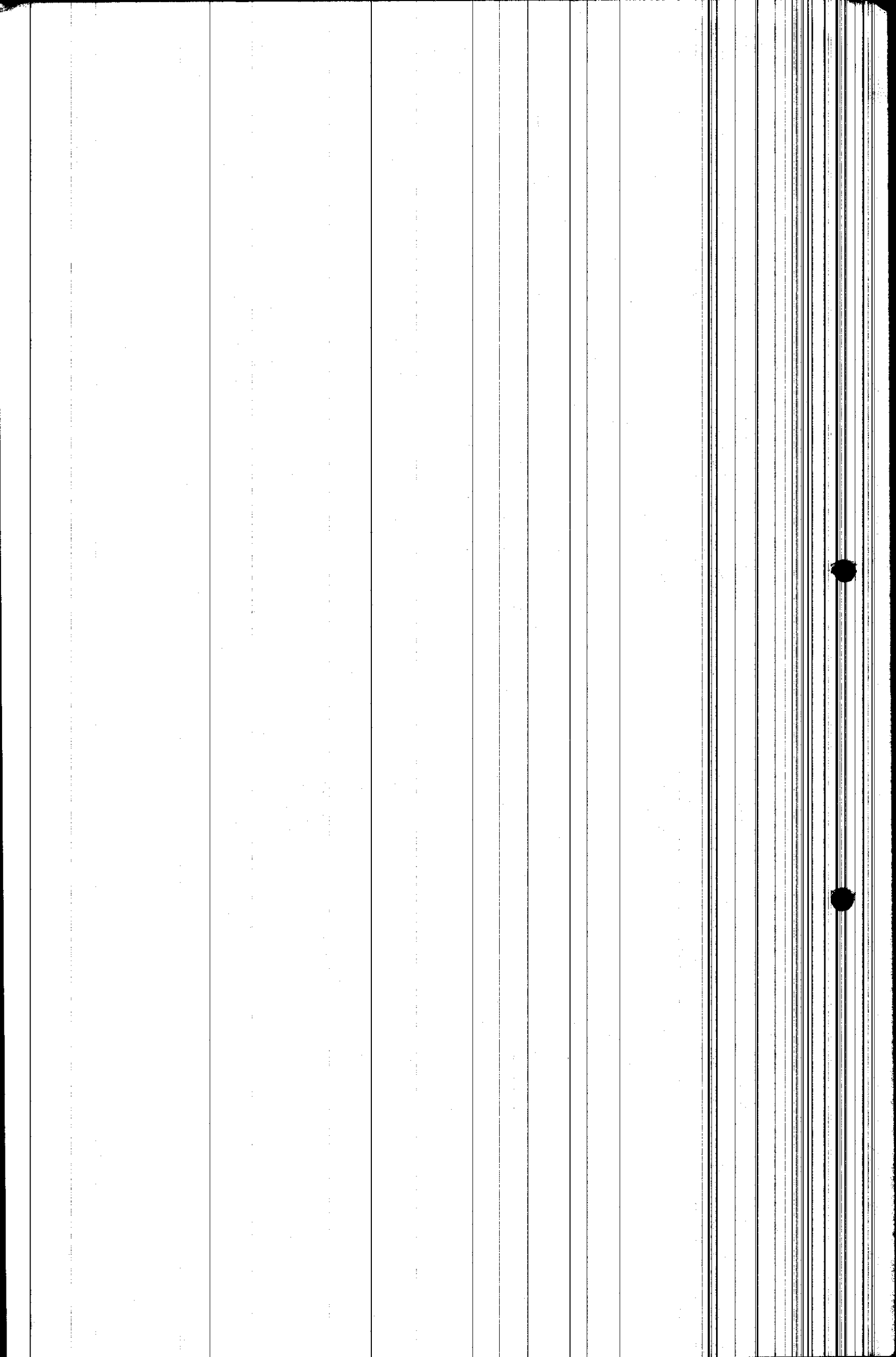
7-O-Protection Removal - Epothilone B



Example: $R^1 = \text{Troc}$

2.7 mg (4.4 μmol) of 23 is dissolved in 1.5 ml of ethanol, mixed with 25 mg of NH_4Cl and 25 mg of zinc (powder) and refluxed for 30 minutes. After cooling to room temperature, it is filtered on Celite, washed with ethyl acetate, and the solvent is removed in Rotavapor. Subsequent column chromatography (hexane/ethyl acetate 1:1) yields 1.4 mg (about 90%) of 24 (epothilone B).

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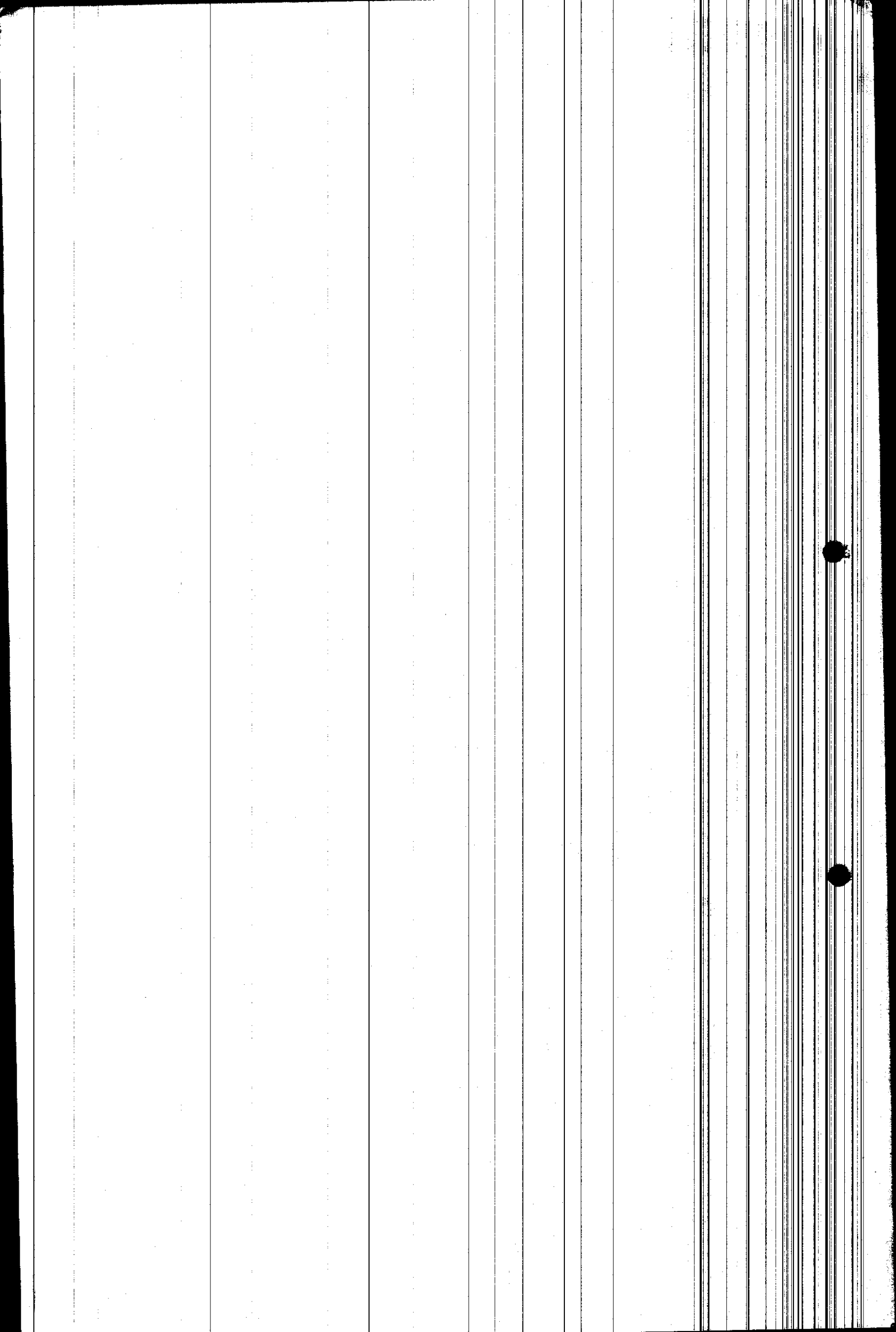
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Compound 24 (Exposition 2)
1H NMR (500 MHz, CDCl3): δ = 6.97 (m, 1H), 6.50 (m, 1H),
5.41 (d, t = 7.8, 2.4 Hz, 1H), 4.27-4.18 (m, 2H), 3.77 (m, 1H),
3.30 (m, 1H), 2.83 (dd, t = 7.8, 4.5 Hz, 1H), 2.70 (m, 1H), 2.68
(m, 1H), 2.54 (dd, t = 14.0, 10.2 Hz, 1H), 2.37 (dd, t = 14.0,
3.0 Hz, 1H), 2.13-2.05 (m, 1H), 2.05 (m, 1H), 1.92 (ddd, t =
15.1, 7.7, 7.7 Hz, 1H), 1.78-1.68 (m, 2H), 1.55-1.48 (m, 2H),
1.48-1.33 (m, 2H), 1.37 (m, 1H), 1.30-1.22 (m, 1H), 1.28 (m, 2H),
1.25 (s, 3H), 1.17 (d, t = 6.7 Hz, 3H), 1.08 (s, 3H), 1.01 (d, t =
7.0 Hz, 3H).
NMR data are identical to the data of K. C. Nicolaou and A.
Mantoulidis (Tet. Lett. 39 (1998) 8633-8636). HPLC analysis with
a comparison sample of A. Mantoulidis shows identical material.

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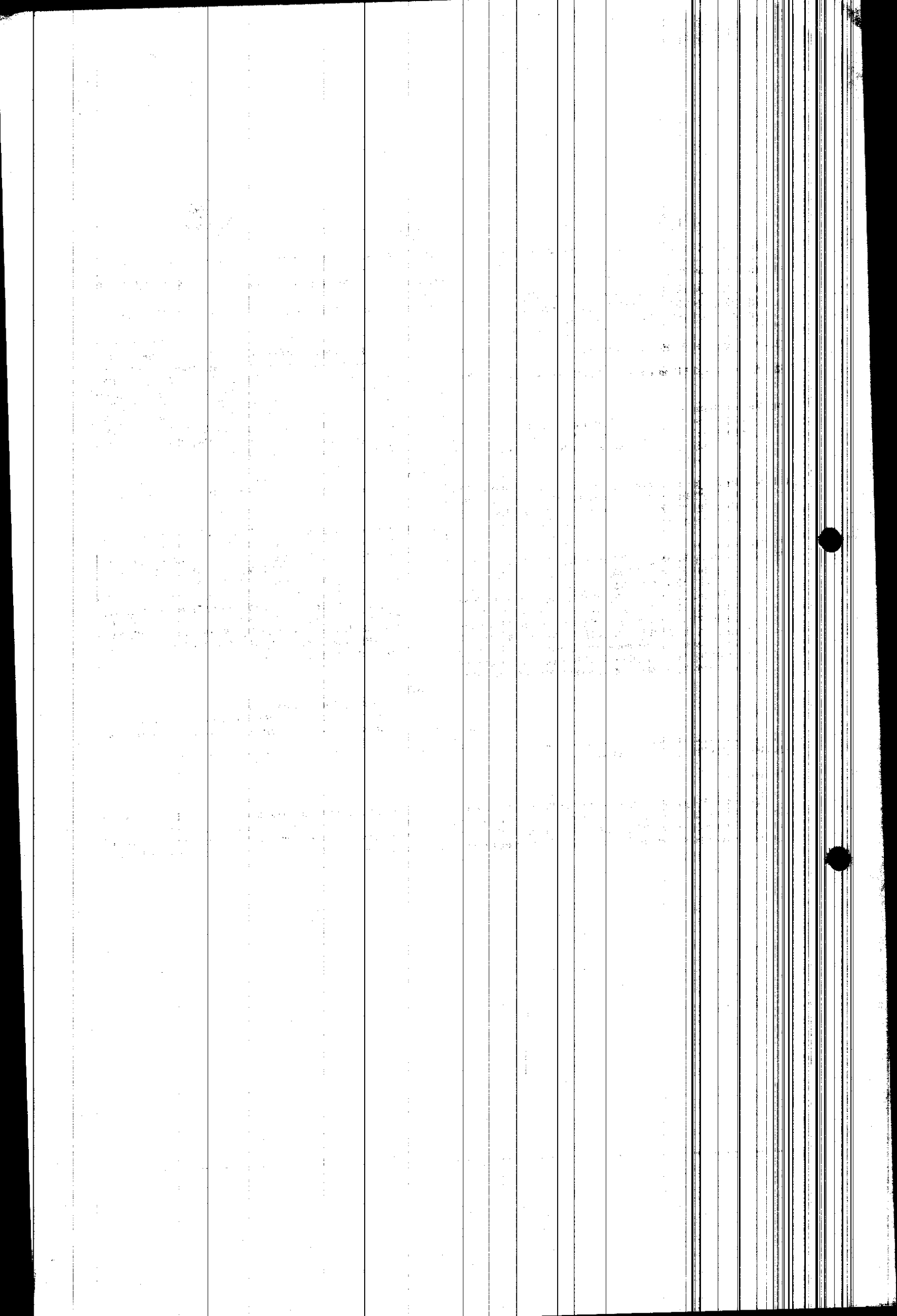
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(21) International Application Number: PCT/EP97/07011 (22) International Filing Date: 12 December 1997 (12.12.97) (30) Priority Data: 60/032,864 13 December 1996 (13.12.96) US 06/856,533 14 May 1997 (14.05.97) US 08/923,869 4 September 1997 (04.09.97) US (71) Applicants (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). THE SCRIPPS RESEARCH INSTITUTE [US/US]; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): NICOLAOU, Costa, Kyriacos [US/US]; 9625 Blackgird Road, La Jolla, CA 92037 (US). HIE, Yun [CN/US]; 9605 Genesee Avenue #12, San Diego, CA 92121 (US). NENKOVIC, Sacha [CA/US]; Apartment 2216, 3855 Nobel Drive, San Diego, CA 92122 (US). PASTOR, Joaquin [ES/US]; 4168 Camino Tierno, San Diego, CA 92122 (US). ROSCHANGAR, Frank [DE/US]; 9501 Genesee Avenue #604, San Diego, CA 92121 (US). SARABIA, Francisco [ES/ES]; Calle Héctor Villalobos, 11, bloq. 15 2-B, E-29014 Málaga (ES). VALLBERG, Hans		[SE/SE]; Mangledavägen 10, S-141 51 Huddinge (SE). VOURLOUMIS, Dionisios [GR/US]; Apartment 39, 4349 Nobel Drive, San Diego, CA 92122 (US). WINSSINGER, Nicolas [BE/US]; 643 Grovella Street, La Jolla, CA 92037 (US). YANG, Zhen [CN/US]; 4158 Decoro Street #2, San Diego, CA 92122 (US). KING, Nigel, Paul [GB/US]; 3550 Lebon Drive #6109, San Diego, CA 92122 (US). FINLAY, Maurice, Raymond, Verschoyle [GB/US]; 3530 Nobel Drive #6109, La Jolla, CA 92122 (US). (74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (OH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(54) Title: EPOTHILONE ANALOGS (57) Abstract Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. The analogs of epothilone are novel. Several of the analogs are demonstrated to have a superior cytotoxic activity as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymerization and stabilization of microtubules.		



diseases that are drug-resistant. The pharmacological usefulness of the compounds of formula I is especially demonstrated by the test systems mentioned above in the description of the figures; however, other test systems that are known to the man skilled in the art which have been used in the characterization of Taxol and Epirubicin A and B are appropriate as well. Especially, the compounds can be used for the treatment of solid cancers and leukemias, such as colon, breast, lung, prostate and epithelial carcinomas.

The present invention also relates to pharmaceutical compositions which comprise, as the active ingredient, one of the pharmacologically active compounds of the formula I as defined above or below, or a pharmaceutically acceptable salt thereof. Compositions for oral, in particular oral, and especially for parenteral administration are particularly preferred. The compositions comprise the active ingredient by itself or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends on the disease to be treated and on the species, age, weight, skin area and individual condition, as well as on the mode of administration.

The pharmaceutical compositions comprise about 5% to about 95% of the active ingredient, single-dose administration forms preferably containing about 20% to about 90% and administration forms which are not single-dosed preferably containing about 5% to about 20% of active ingredient. Dose unit forms, such as coated tablets, tablets or capsules, contain about 0.01 g to about 2 g, preferably about 0.02 g to about 1.0 g, of the active ingredient, in particular 0.02 to 0.6 g.

The present invention also relates to the use of compounds of the formula I for the preparation of pharmaceutical compositions for use against a proliferative disease, for example for the treatment of diseases which respond to enhancers of tubulin polymerization, in particular of the abovementioned diseases.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active ingredient with one or more solid carriers, granulating a resulting mixture, if appropriate, and processing the mixture or granules, if desired, to tablets or coated-tablet cores, if appropriate by addition of additional excipients.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and furthermore binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrants, such as the abovementioned starches, and furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginate acid or a salt thereof, such as sodium alginate.

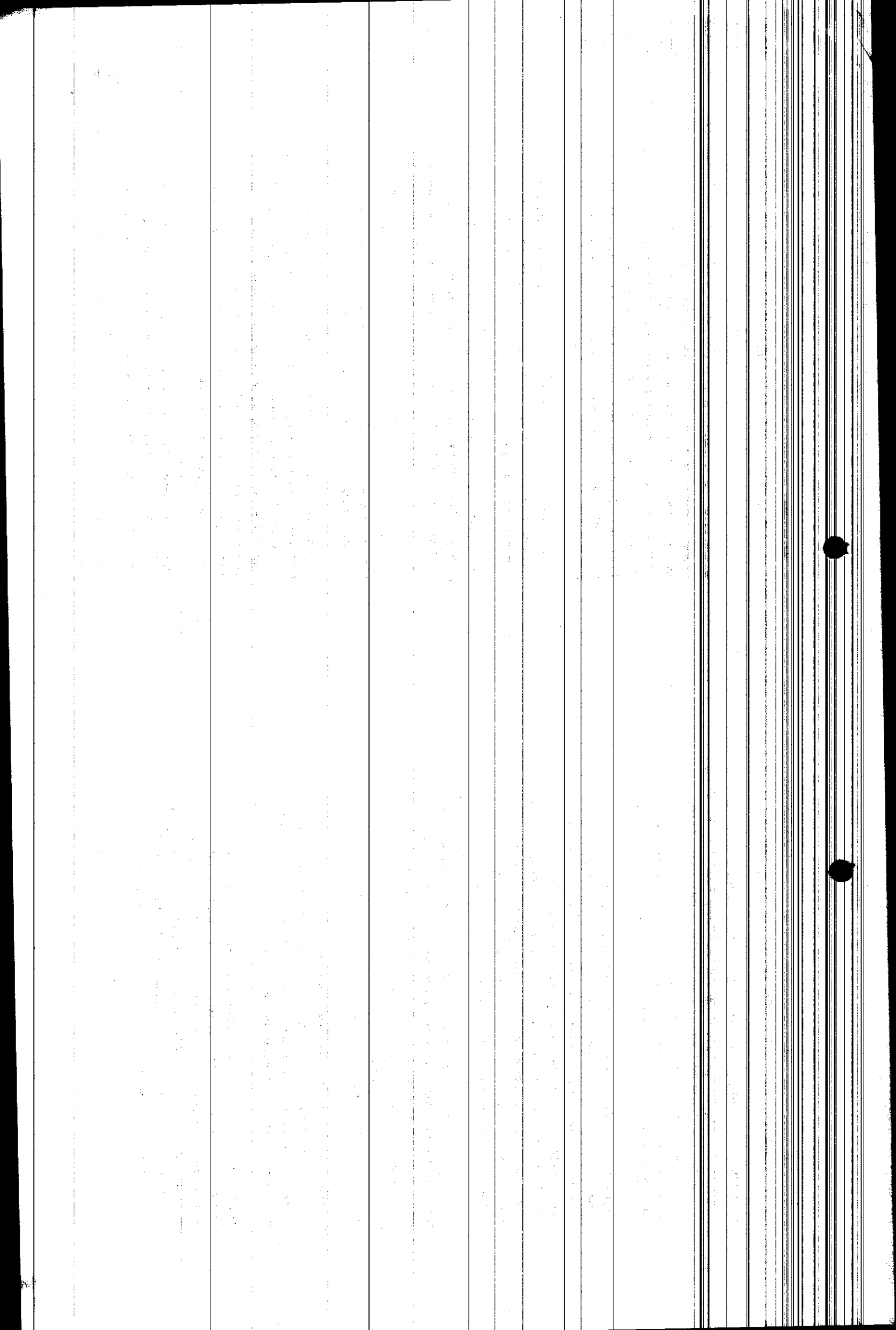
Additional excipients are, in particular, flow conditioners and lubricants, for example stearic acid, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, or derivatives thereof.

Coated-tablet cores can be provided with suitable coatings. If appropriate resistant to gastric juice, the substances used being, inter alia, concentrated sugar solutions, which contain gum arabic, talc, polyvinylpyrrolidone and/or titanium dioxide if appropriate, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of coatings which are resistant to gastric juice, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments can be admixed to the tablets or coated-tablet coatings, for example for identification or characterization of different active ingredient doses.

Pharmaceutical compositions which can be used orally are also dry-filled capsules of gelatin and soft, closed capsules of gelatin and a softener, such as glycerol or sorbitol. The dry-filled capsules can contain the active ingredient in the form of granules, for example mixed with fillers, such as corn starch, binders and/or lubricants, such as talc or magnesium stearate, and if appropriate stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils or paraffin oil, it also being possible to add stabilizers.

Further oral administration forms are, for example, syrups which are prepared in the customary manner and contain the active ingredient, for example, in suspended form and in a concentration of about 5% to 20%, preferably about 10%, or in a similar concentration

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which gives a suitable single dose, for example, when 5 or 10 ml are measured out. Further suitable forms are also, for example, pulverulent or liquid concentrates for preparation of shakes, for example in milk. Such concentrates can also be packed in single-dose amounts.

Compositions which are suitable for parenteral administration are, in particular, aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, or aqueous injection suspensions which contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and if appropriate stabilizers. The active ingredient can also be present here in the form of a lyophilisate, if appropriate together with excipients, and can be dissolved by addition of suitable solvents before parenteral administration.

Solutions such as are used, for example, for parenteral administration can also be used as infusion solutions.

The invention also relates to a method (process) for the treatment of the abovementioned disease states in warm-blooded animals, i.e. mammals, and in particular humans, preferably those warm-blooded animals which require such treatment. The compounds of the formula I of the present invention or their pharmaceutical salts, if salt-forming groups are present, are administered for this purpose for prophylaxis or treatment, and are preferably used in the form of pharmaceutical compositions, for example in an amount which is suitable for enhancing tubulin polymerization and is active prophylactically or especially therapeutically against one of the diseases mentioned which respond to such treatment, for example tumours. For a body weight of about 70 kg, a daily dose of about 0.1 g to about 15 g, preferably about 0.2 g to about 5 g, more preferably of about 0.5 to 3 g, of a compound of the formula I is administered here.

The pharmaceutical compositions are preferably those which are suitable for administration to a warm-blooded animal, for example a human, for treatment or prophylaxis of one of the abovementioned diseases and comprise an amount of a compound of the formula I or of a pharmaceutically acceptable salt thereof which is active against said diseases, together with an excipient.

Especially preferred are the final products and intermediates, as well as their salts, where salt-forming groups are present, and the reaction procedures or any parts thereof mentioned in the subsequent examples and in the figures:

The following examples illustrate methods for the total synthesis of epothilone A (1), epothilone B (2), designed analogs and the generation of epothilone libraries. The examples rely *inter alia* on the olefin metathesis reaction and macrocyclization as a means to form the macrocyclic ring. The disclosed methods promise the discovery of anticancer agents which will be superior to existing ones. The examples represent exemplary conditions which demonstrate the versatility of the methodology and are not meant to be restricted to the modes and compounds or intermediates disclosed.

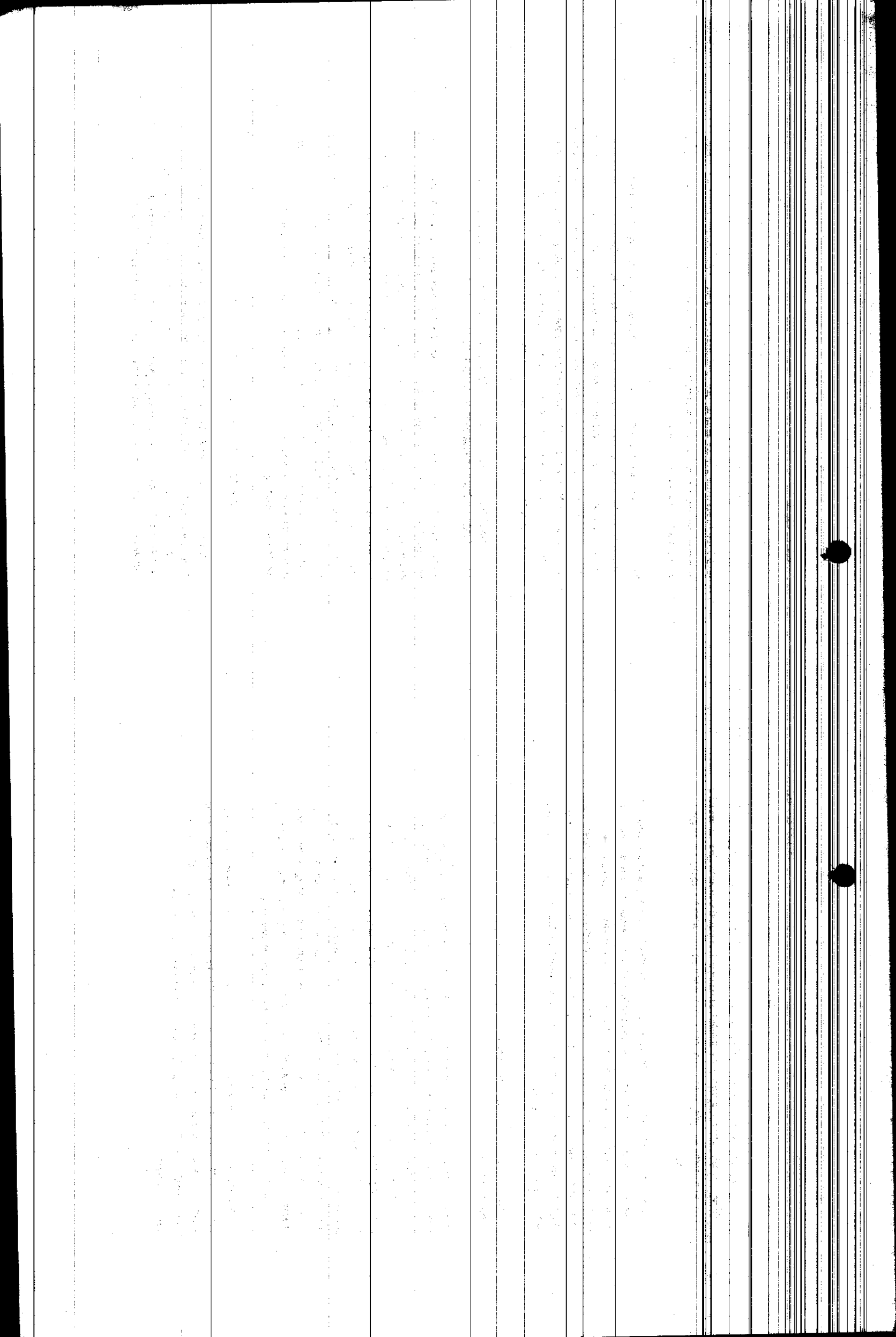
Example 1. Solution phase synthesis of epothilone A and B and analogs using an olefin metathesis approach (Figures 1-10)

A method using the olefin metathesis approach to synthesize epothilone A (1) and several analogs (38-41, 43-44, 51-57, 58-60, 64-65, and 67-69) is described (Figures 1-10). In this example, we describe the details of our olefin metathesis approach to epothilone A (1) and its application to the synthesis of several of its analogs. Key building blocks 6, 7 and 8 were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor 4 via an aldol reaction and an esterification coupling. Olefin metathesis of compound 4, under the catalytic influence of $\text{RuCl}_2(\text{-CHPh})(\text{PCy}_3)_2$ catalyst, furnished *cis*- and *trans*-cyclic olefins 3 and 48. Epoxidation of 48 gave epothilone A (1) and several analogs, whereas epoxidation of 30 resulted in additional epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

A. Retrosynthetic Analysis and Strategy (Figure 2)

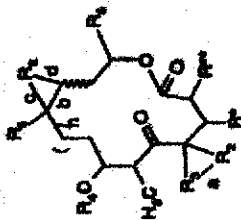
The structure of epothilone A (1) is characterized by a 18-membered macrocyclic lactone carrying a *cis*-epoxide moiety, two hydroxyl groups, two secondary methyl groups, and a gem dimethyl group, as well as a side-chain consisting of a trisubstituted double bond and a thiazole moiety (Figure 1). With its seven stereocenters and two geometrical elements, epothilone A (1) presents a considerable challenge as a synthetic target, particularly with re-

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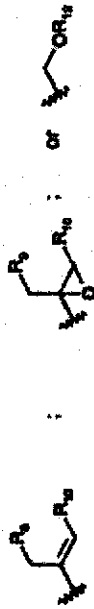


What is claimed is:

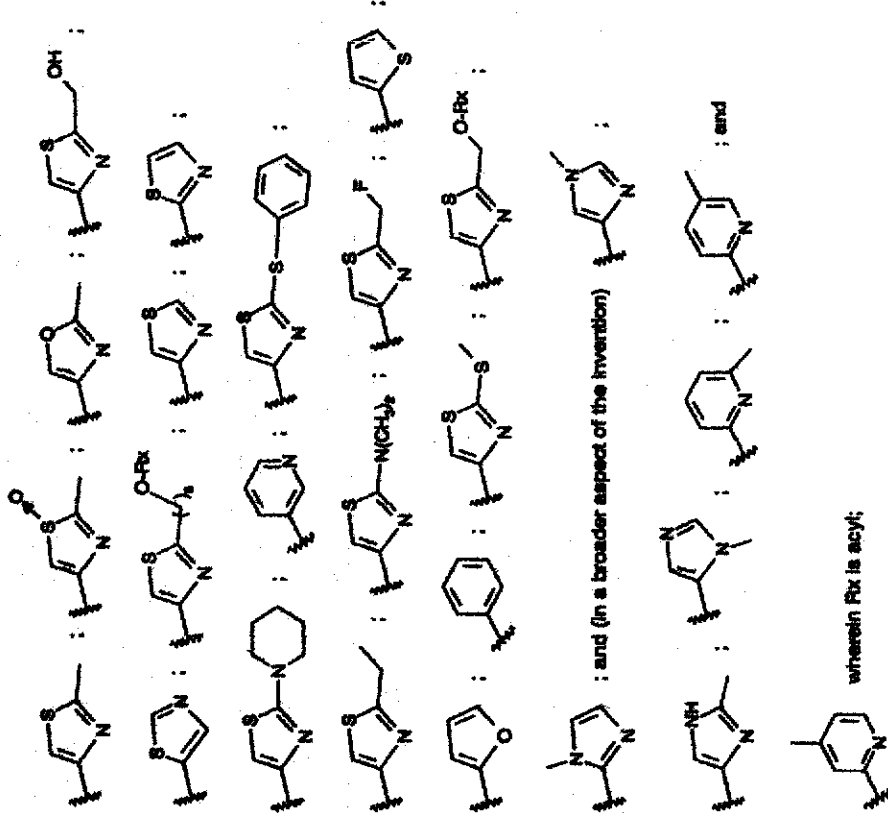
1. A compound represented by the following structure (formula (I)):



wherein n is 1 to 6; either R¹ is -OR, and R² is hydrogen, or R¹ and R² together form a further bond so that a double bond is present between the two carbon atoms carrying R¹ and R²; R₁ is a radical selected from the group consisting of hydrogen or methyl, or a protecting group; R₂ is a radical selected from the group consisting of hydrogen, methylene and methyl; R₃ is a radical selected from the group consisting of hydrogen, methylene and methyl; R₄ is a radical selected from the group consisting of hydrogen or methyl, or is a protecting group; R₅ is a radical selected from the group consisting of hydrogen, methyl, CHO, -COOH, -CO₂Me, -CO₂(isobutyl), -CO₂(phenyl), -CO₂(benzyl), -CONH(turkey), -CO₂(N-benzyl-2R,3S)-3-phenylisoserine), -CON(methyl)₂, -CON(ethyl)₂, -CONH(benzyl), -CH=CH₂, HC≡C-, and -CH₂R₁₁; R₁₁ is a radical selected from the group consisting of -OH, -O-Triyl, -O-(C₁-C₈ alkyl), -O-benzyl, -O-allyl, -O-COOCH₃, -O-COCH₂Cl, -O-COCH₂CH₃, -O-COCH₂(CH₂)₂, -O-CO-C(CH₃)₃, -O-CO(cyclopropane), -O-CO(cyclohexane), -O-COCH=CH₂, -O-CO-Phenyl, -O-(2-furyl), -O-(N-benzyl-2R,3S)-3-phenylisoserine), -O-dimethyl, -O-(acetyl-phenyl), -O-(2-thiophene-5-yl), -O-(2-furyl), -SH, -S-Phenyl, -S-Benzyl, -S-turkey, -NH₂, -N₃, -NHCOOCH₃, -NHCOOCH₂CH₃, -NHCOOCH₂(CH₂)₂, -NHCOO-C(CH₃)₃, -NHCO(cyclopropane), -NHCO(cyclohexane), -NHCOCH=CH₂, -NHCO-Phenyl, -NH(2-furyl), -NH-(N-benzyl-2R,3S)-3-phenylisoserine), -NH-(dimethyl), -NH-(acetyl-phenyl), -NH-(2-thiophene-5-yl), -NH-(2-furyl), -CO₂H and methyl; R₆ is absent, methylene, or hydrogen; R₇ is hydrogen; R₈ is a radical selected from the group represented by the following formulae:

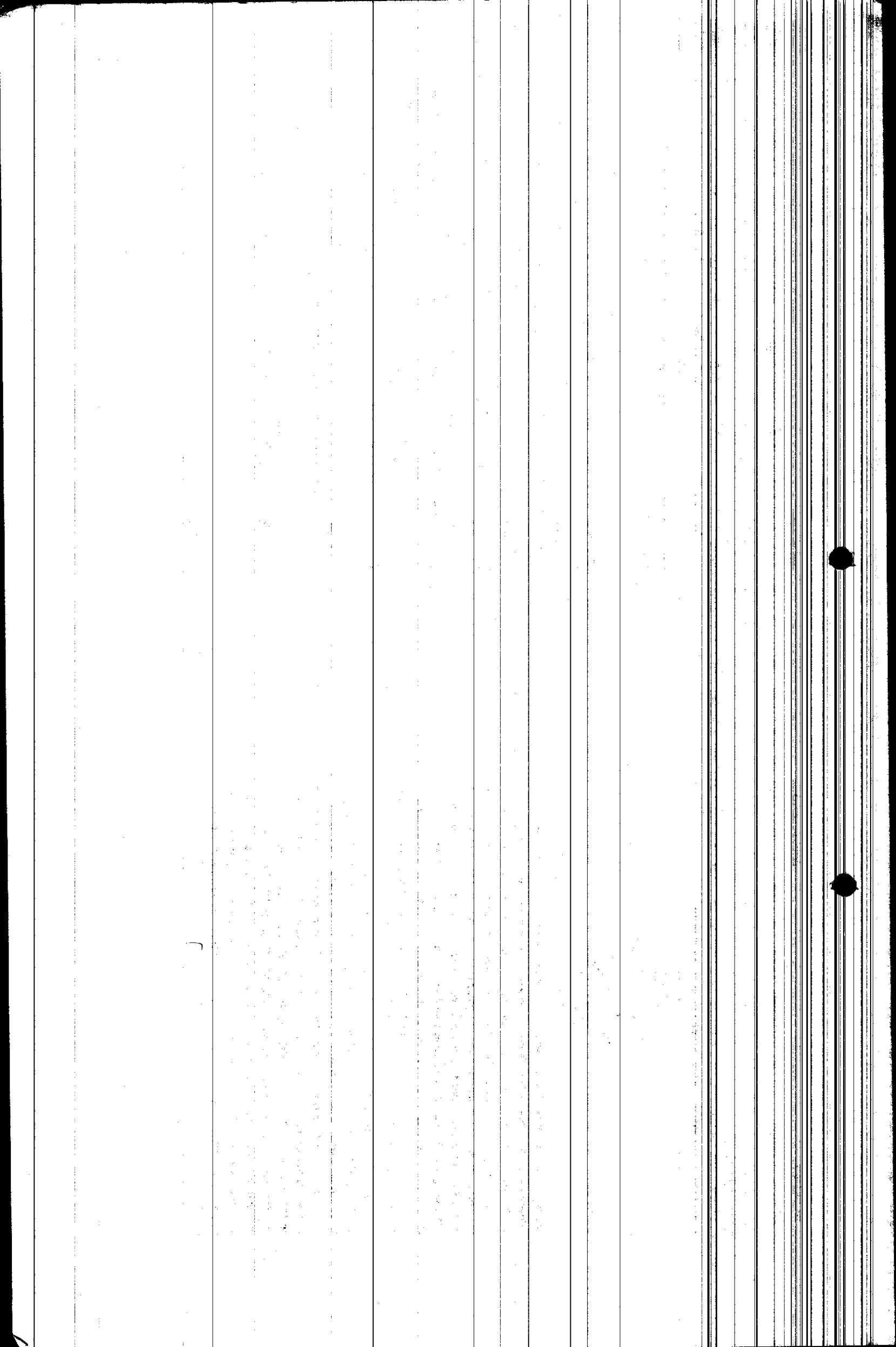


wherein R₉ is a radical selected from the group consisting of hydrogen and methyl; R₁₀ is a radical selected from the group represented by the formulae:

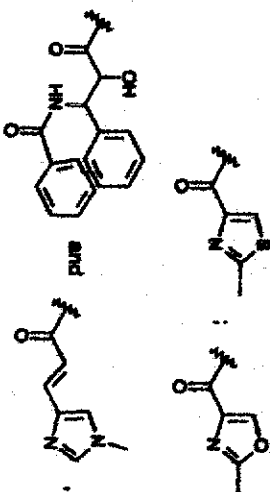


wherein R₉ is acyl;

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R_{11} is a radical selected from the group consisting of hydrogen, methyl or a protecting group, preferably *tert*-butyldimethylsilyl, *tert*-butyldimethylsilyl, trimethylsilyl, acetyl, benzoyl, *tert*-butoxycarbonyl and a group represented by any one of the following formulas:



or a salt thereof where a salt-forming group is present;

where, in the above structures, "a" can be either absent or a single bond; "b" can be either a single or double bond; "c" can be either absent or a single bond; "d" can be either absent or a single bond, and the following provisoce pertains:

- If R_2 is methylene, then R_3 is methylene;
- If R_2 and R_3 are both methylene, then "a" is a single bond;
- If R_2 and R_3 are selected from the group consisting of hydrogen and methyl, then the single bond "a" is absent;
- If n is 5, R_2 is methyl, R_3 is methyl, R_4 is selected from the group consisting of methyl and hydrogen, R_5 is oxygen, R_7 is hydrogen, R_8 is represented by the formula:



wherein R_6 is hydrogen, and R_{10} is represented by the formula



- then R_1 and R_4 cannot both be simultaneously hydrogen or methyl or acetyl;
- If R_6 is oxygen, then "c" and "d" are both a single bond and "b" is a single bond;
- If R_6 is absent, then "c" and "d" are absent and "b" is a double bond; and
- If "b" is a double bond then R_6 , "c", and "d" are absent.

- A compound of the formula I according to claim I, wherein n, a, b, c, d, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 have the meanings given in claim I, or a salt thereof where a salt-forming group is present, with the exception of a compound of the formula I wherein n is 3;

- R_1 is hydrogen, methyl, acetyl, benzoyl, trialkyl silyl or benzoyl;
- R_2 is methyl;
- R_3 is methyl;
- R_4 is hydrogen, methyl, acetyl, benzoyl, trialkyl silyl or benzoyl;
- R_5 is hydrogen or methyl;
- R_6 is O or
- R_6 is absent and a is a double bond;
- R_7 is hydrogen;

R_8 is a radical of the formula

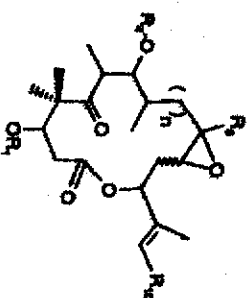


wherein

- R_9 is a radical selected from the group consisting of hydrogen and methyl;
- and R_{10} is a radical represented by the formula:



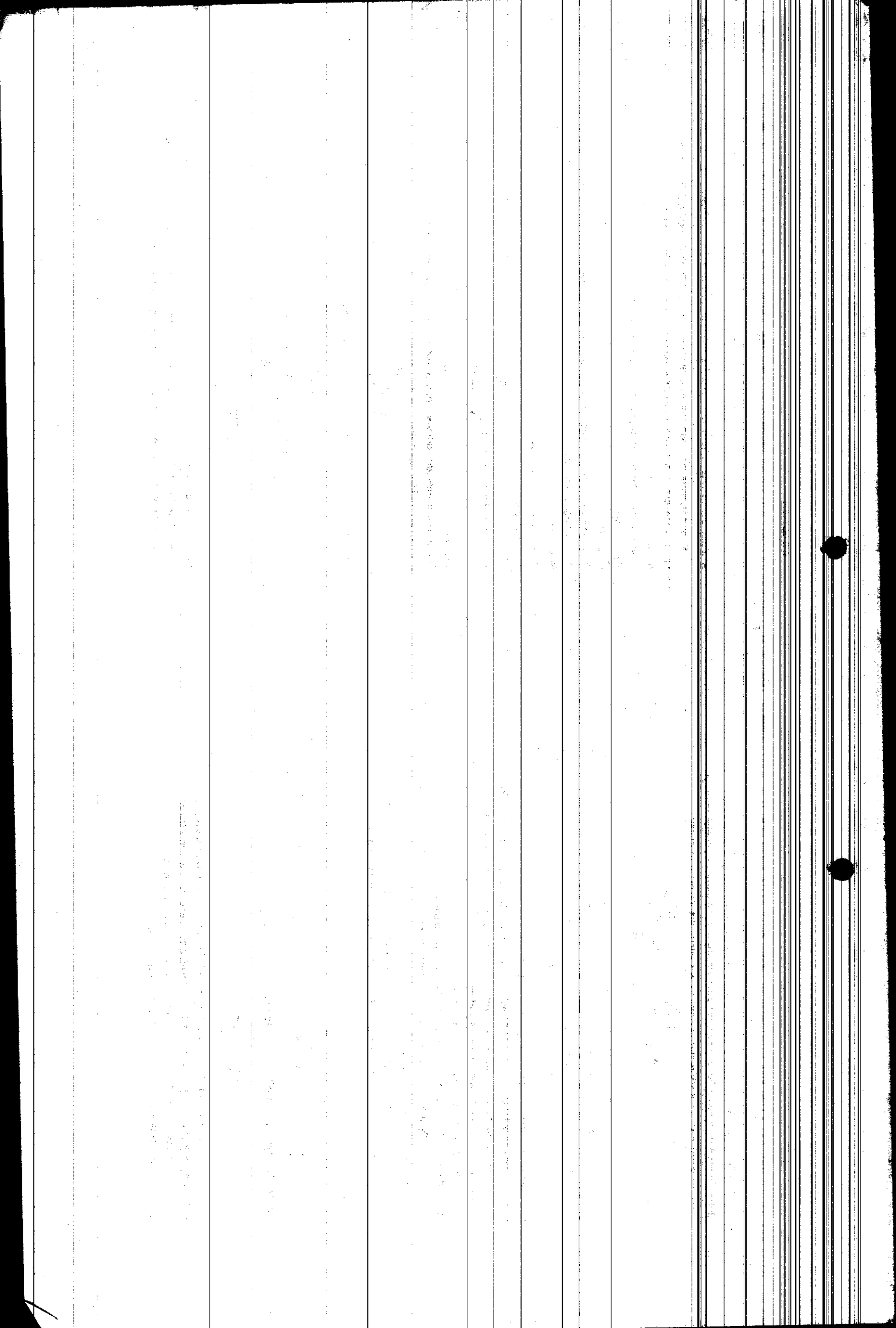
- A compound according to claim I, represented by formula II,



(II).

wherein n is one to five,

- R_1 is a radical selected from the group consisting of hydrogen, methyl or a protecting group,
- R_4 is a radical selected from the group consisting of hydrogen, methyl or a protecting group,



**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

202075
Bogotá, D.C.,

Abogado
JIMENA ESCOBAR URIBE.

ASUNTO	Radicación	05025149
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	- 10774
	Folios	027

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒

No. Sol. Internacional	PCT/EP2003/010171
Fecha de Presentación Internal.	12 de Septiembre de 2003.

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

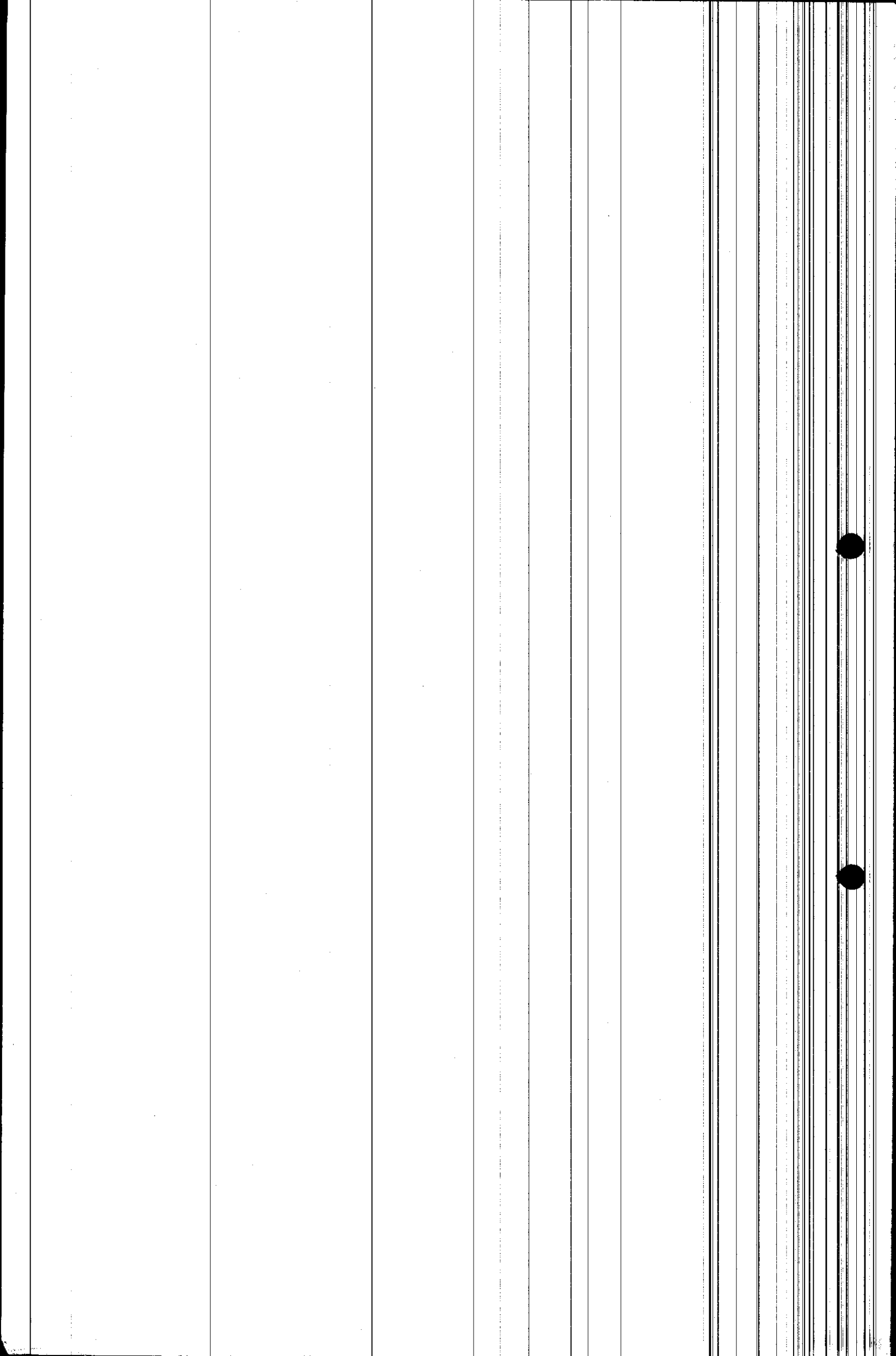
- 1.1. Descripción: Folios: 9 a 68 (como se radicó inicialmente)
- 1.2. Reivindicaciones: Folios: 69 a 93 (como se radicó inicialmente)
- 1.3. Prioridad: Folio 1 (13 de Septiembre de 2002, GB0221312.2).

2. Objeto de la invención

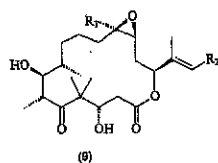
- Título de la solicitud: UN NUEVO PROCESO PARA LA PREPARACION DE DERIVADOS DE EPOTILONA , NUEVOS DERIVADOS DE EPOTILONA , ASI COMO NUEVOS PRODUCTOS INTERMEDIARIOS PARA EL PROCESO , Y LOS METODOS PARA SU PREPARACION.

El objeto de la presente solicitud de patente de invención consiste en un proceso para la preparación de derivados de epotilona.

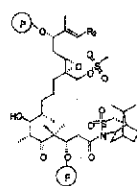
Reivindicaciones 1-8 : Un proceso para la preparación de derivados de epotilona de fórmula 9 .



Reivindicaciones 9-10 : Compuestos de formula 9.

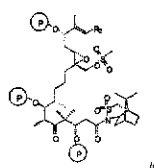


Reivindicación 11 : Compuestos de formula 3



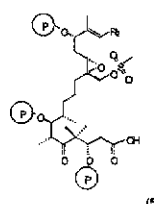
Reivindicación 12 : Un proceso para obtener los compuestos de formula 3.

Reivindicación 13: Compuestos de formula 4.



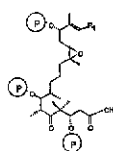
Reivindicación 14: Un proceso para la producción de los compuestos de formula 4

Reivindicación 15 : Compuestos de formula 5



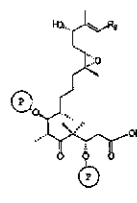
Reivindicación 16 : Un proceso para la producción de los compuestos de formula 5

Reivindicación 17 : Compuestos de formula 6.



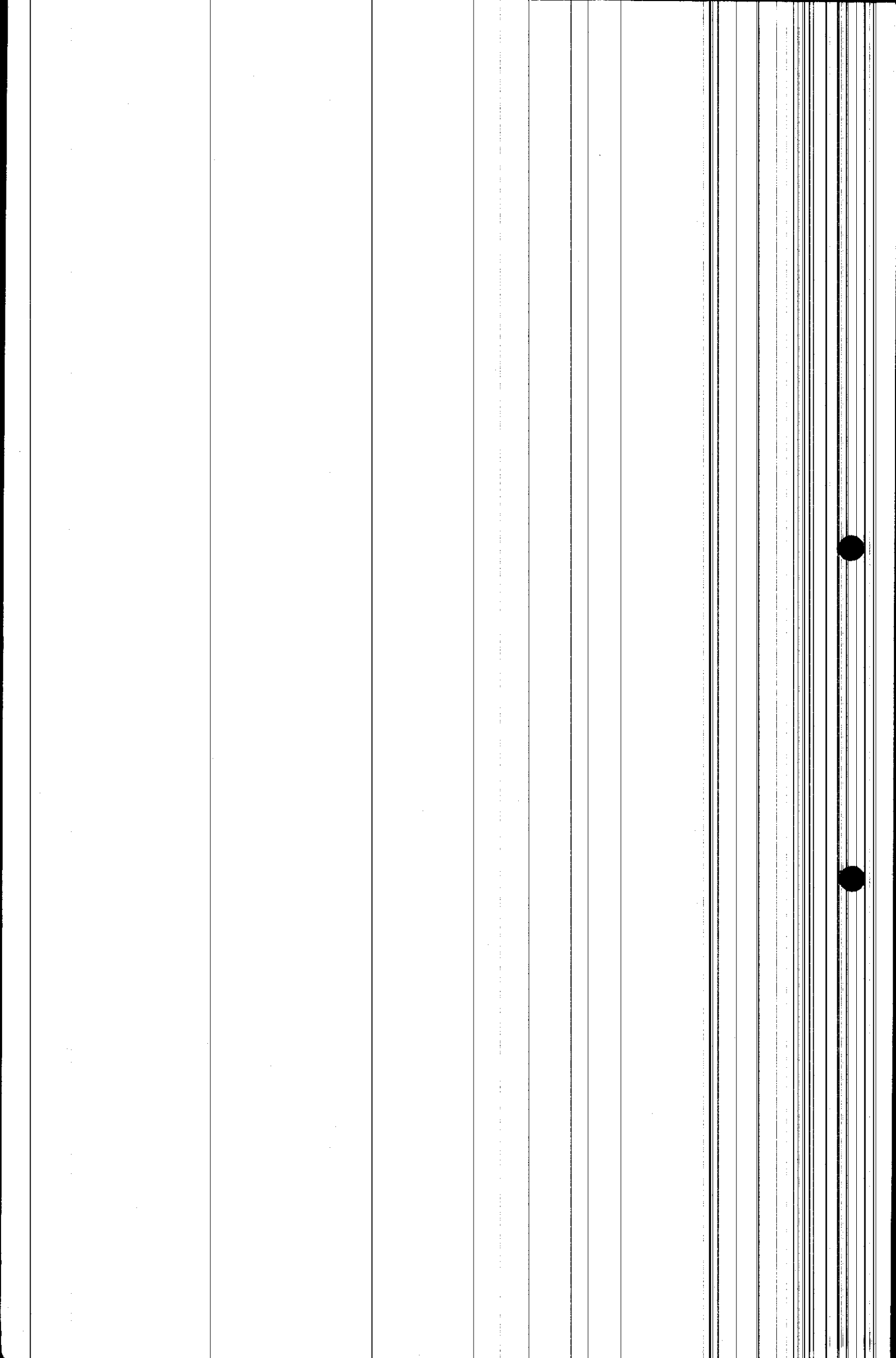
Reivindicación 18 : Un proceso para la producción de los compuestos de formula 6

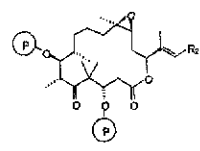
Reivindicación 19 : Compuestos de formula 7 :



Reivindicación 20 : Un proceso para la producción de los compuestos de formula 7

Reivindicación 21 : Compuestos de formula 8.

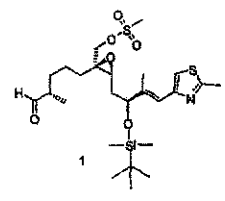




(8)

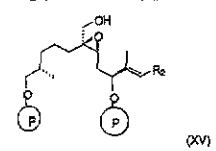
Reivindicación 22 :Un proceso para la producción de los compuestos de formula 8.

Reivindicación 23: Compuestos de formula 1.



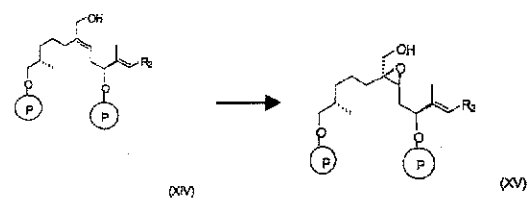
Reivindicación 24 : Un proceso para la producción de los compuestos de formula 1

Reivindicación 25: Compuestos de formula XV.

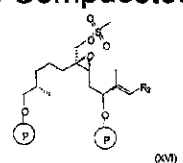


(XV)

Reivindicación 26: Un proceso para la producción de compuestos de formula XV.



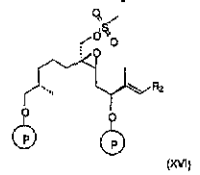
Reivindicación 27 : Compuestos de fórmula XVI.



(XVI)

Reivindicación 28: Un proceso para la producción de compuestos de formula XVI.

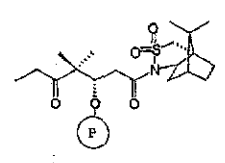
Reivindicación 29 : Compuestos de formula XVII.



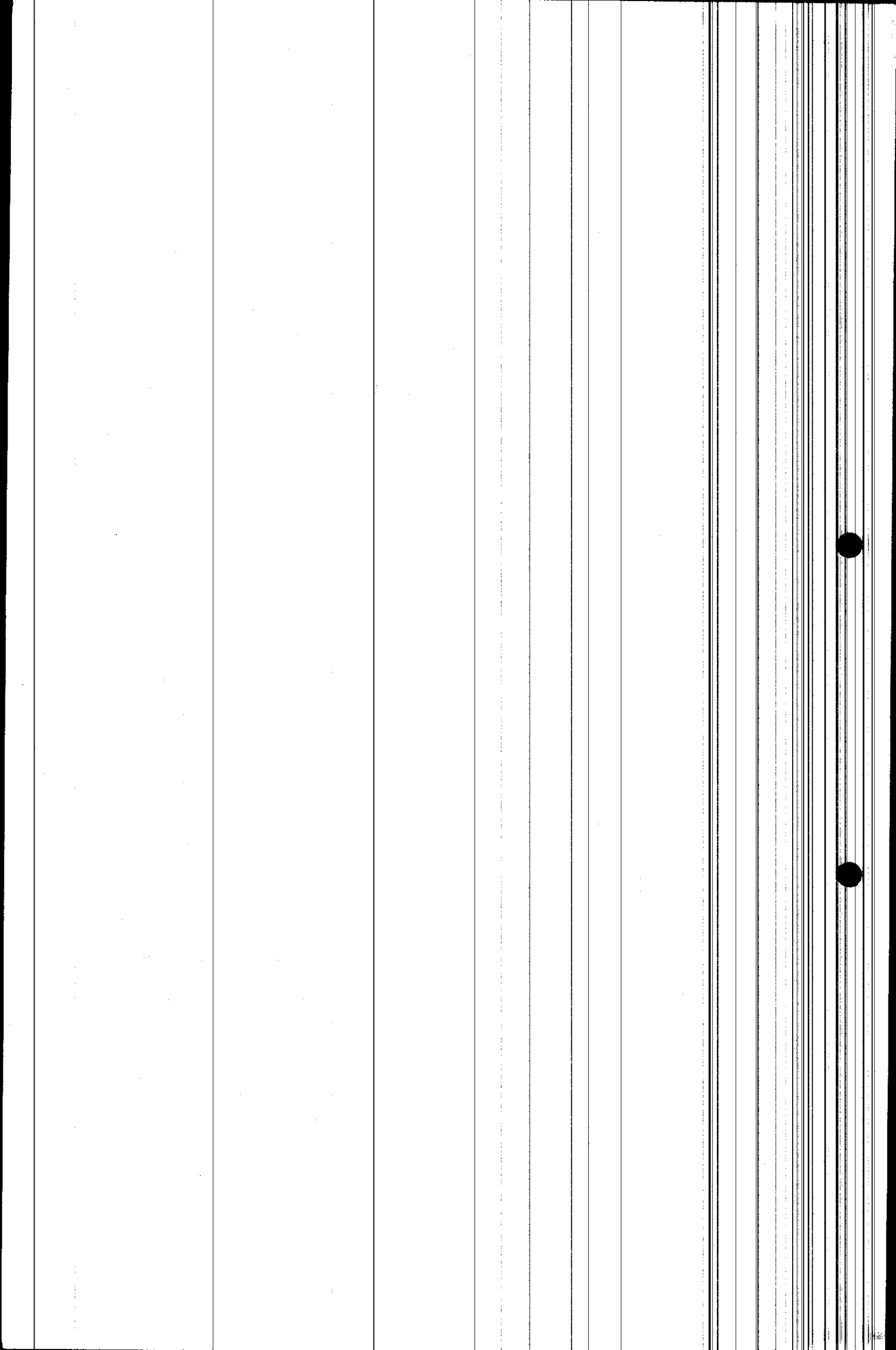
(XVII)

Reivindicación 30: Un proceso para la producción de compuestos de formula XVII.

Reivindicación 31 : Un compuesto de formula 2.



(2)



Reivindicación 32 : Método de tratamiento.

Reivindicación 33: Una composición farmacéutica del compuesto de fórmula 9.

Reivindicación 34: De uso.

El problema planteado en esta solicitud es la necesidad de proporcionar un procedimiento más simple mejorado para la preparación de epotilonas , derivados y sales de las mismas , factibles a escala industrial reduciendo la etapa sintética , con un rendimiento global alto en promedio.

Para solucionar este problema técnico la solicitud en estudio proporciona un proceso para la preparación de derivados de epotilona, nuevos derivados de epotilona y nuevos precursores de síntesis.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC) : **C07D493/04; A61P35/00; C07D275/06; C07D303/14; C07D303/16.**

3. De la solicitud de Patente

3.1. Descripción (artículo 28 D. 486)

- En el folio 55, en donde se habla de la formación del compuesto de fórmula 4 (éter de TBDMS), en la línea 18 se encuentra el siguiente párrafo “ proporcionar el compuesto 16”, no es acaso el compuesto de fórmula 4 el que se forma?. Además en el aparte de descriptivo dicho compuesto 16 no se encuentra sustentado.

3.2. Reivindicaciones (artículo 30 D 486).

- Para la reivindicación 1, se realiza la misma observación realizada en el aparte descriptivo para definir cual es la fórmula correcta para el compuesto de fórmula 1.
- Las reivindicaciones 1 ,9,23 no son **concisas** en R2 cuando se habla de **arilo o heteroarilo o heterocíclico insustituido o sustituido** (ya que no se define el numero de átomos de carbono o miembros que lo conforman , el tamaño de los anillos , el número y clase de heteroátomos , ni tampoco se define los grupos sustituyentes que pudieran llegar a tener) . Se le requiere al interesado en lo posible definir los grupos arilo , heteroarilo o heterociclo de interes con sus posibles sustituyentes y que se encuentren debidamente sustentados.
- En las reivindicaciones 1, 12,18 ,28 se encuentra el término “....y un grupo tosilato y **similar**” el cual no es conciso, ya que no aporta ninguna característica definida.
- Para la reivindicación 1 se recomienda definir los grupos protectores de alcohol P.

[illegible]

- La reivindicación 10 , no es clara ya que figura como independiente, pero por sus características técnicas debe ser dependiente de la 9.
- Para la reivindicación 33, se recomienda eliminar las siguientes frases en negrilla " de un ingrediente activo de la fórmula 9 , **en donde R2 es un radical arilo insustituido o sustituido** de acuerdo con la reivindicación 9 , **el cual es efectivo para el tratamiento de esa enfermedad de cáncer,** junto con cuando menos un vehículo farmacéuticamente aceptable.

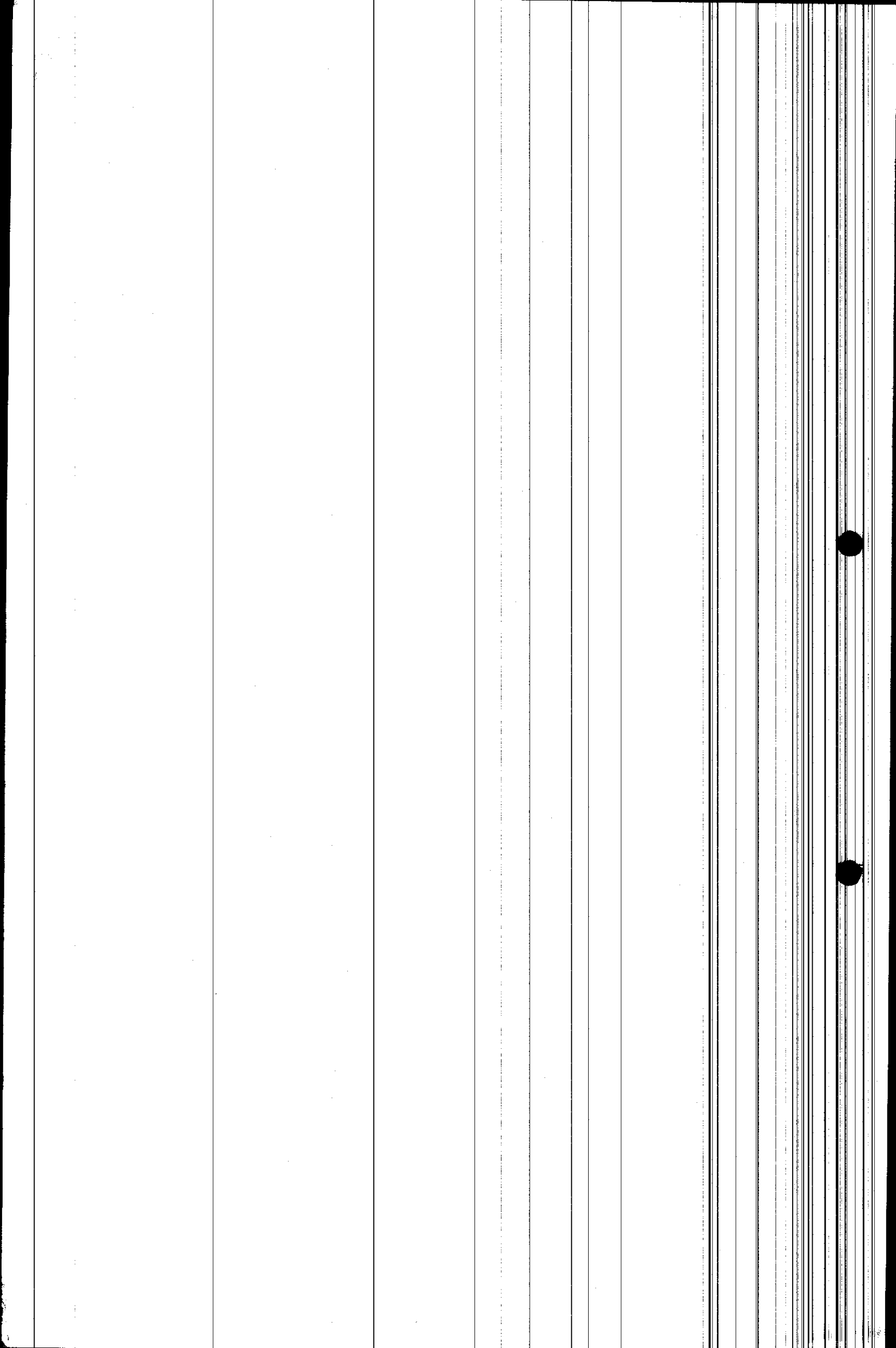
4. Unidad de invención (artículo 25 D 486)

Se aclara que, de acuerdo al Art 25 , las reivindicaciones 1-31 (Folios 69-93), carecen de unidad de invención por lo siguiente:

Se distinguen los siguientes de grupos de invención

1. Reivindicaciones 1-10, 21-22, 33: Compuestos de fórmula 8 Y 9, proceso para prepararlos y composiciones farmacéuticas del compuesto de fórmula 9. .
2. Reivindicaciones 11-12 : Compuestos de fórmula 3 y proceso para prepararlos.
3. Reivindicaciones 13-14 : Compuestos de fórmula 4 y proceso para prepararlos.
4. Reivindicaciones 15-16: Compuestos de fórmula 5 y proceso para prepararlos.
5. Reivindicaciones 17-18: Compuestos de fórmula 6 y proceso para prepararlos.
6. Reivindicaciones 19-20: Compuestos de fórmula 7 y proceso para prepararlos.
7. Reivindicaciones 23-24: Compuestos de fórmula 1 y proceso para prepararlos.
8. Reivindicaciones 25-26: Compuestos de fórmula XV y proceso para prepararlos.
9. Reivindicaciones 27-28: Compuestos de fórmula XVI y proceso para prepararlos.
10. Reivindicaciones 29-30: Compuestos de fórmula XVII y proceso para prepararlos.
11. Reivindicación 31 : Compuestos de fórmula 2.

Cada una de estas invenciones , es una invención distinta caracterizada por su propia característica técnica y no se encuentran tan unidas como para formar un concepto general inventivo único.



En consecuencia, dado que las realizaciones preferidas de la invención reivindicada, manifiestan una falta evidente de un concepto inventivo común a todas ellas, toda vez que en el desarrollo y caracterización del compuesto de fórmula I se identifican varios núcleos estructuralmente diferentes, esta Dependencia recomienda realizar las modificaciones correspondientes y seleccionar el o los grupos que son relevantes para la invención y que se encuentren debidamente sustentados en la descripción.

5. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)) (según causal)

- Se aclara que, de acuerdo al Art 20 literal d) el método de tratamiento de la reivindicación 32 no es patentable.

6. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Se aclara que, de acuerdo con el Art 14, el uso de la reivindicación 34, no es patentable.

7. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 13 de Septiembre del 2002, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

N°	Documento	Título	Fecha de Publicación*
D1	WO02/30356	SYNTHESIS OF EPOTHILONES AND RELATES ANALOGS	18 de Abril 2002.
D2	WO01/07439	PROCESS FOR THE PRODUCTION OF EPOTHIOLONE B AND A DERIVATES AS WELL AS INTERMEDIATE PRODUCTS FOR THIS PROCESS.	1 de Febrero de 2001.
D3	WO98/25929	EPOTHILONE ANALOGS	18 de Junio de 1998.

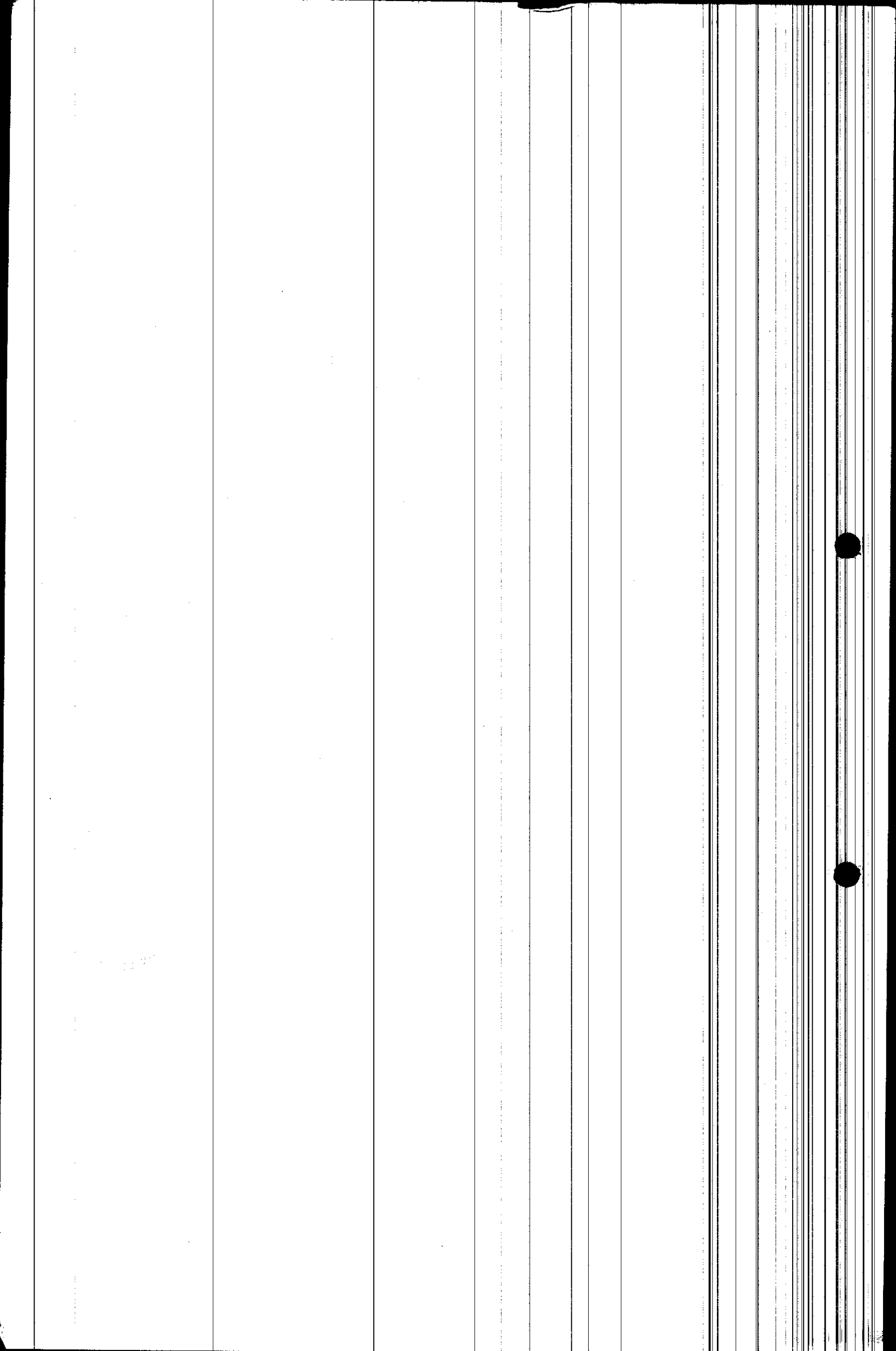
8. Análisis de patentabilidad (artículo 14 D486)

8.1. Novedad (artículo 16 D486)

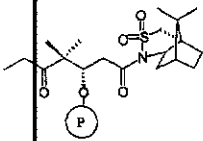
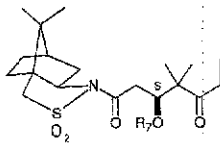
Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 05025149, se refiere a:

Para la reivindicación 31 .



D1 (folios 134-135) enseña síntesis de epotilonas , sus análogos , derivados e intermediarios involucrados.

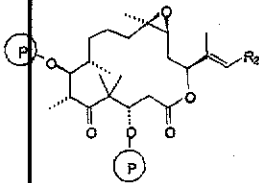
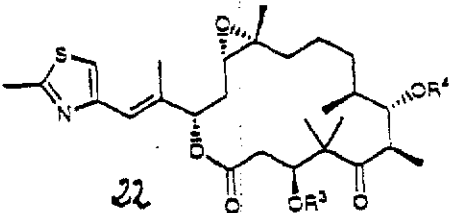
SOLICITUD	D1
 (2) En donde P es un grupo protector de alcohol.	 En donde R7 es un grupo protector de alcohol.

Este compuesto específico de la anterioridad D1 (Folio 135, página 98, reivindicación 65 , compuesto numeral a) es igual al compuesto de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado en 31 era conocido en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de novedad.

Para la reivindicación 21.

D2 (folios 136-143) enseña un proceso para la producción de epotilona B y sus productos intermediarios.

SOLICITUD	D2
 (8) Endonde: P es un grupo protector. R2 es un heterociclo sustituido.	 22 En donde : R3 y R4 son grupos protectores

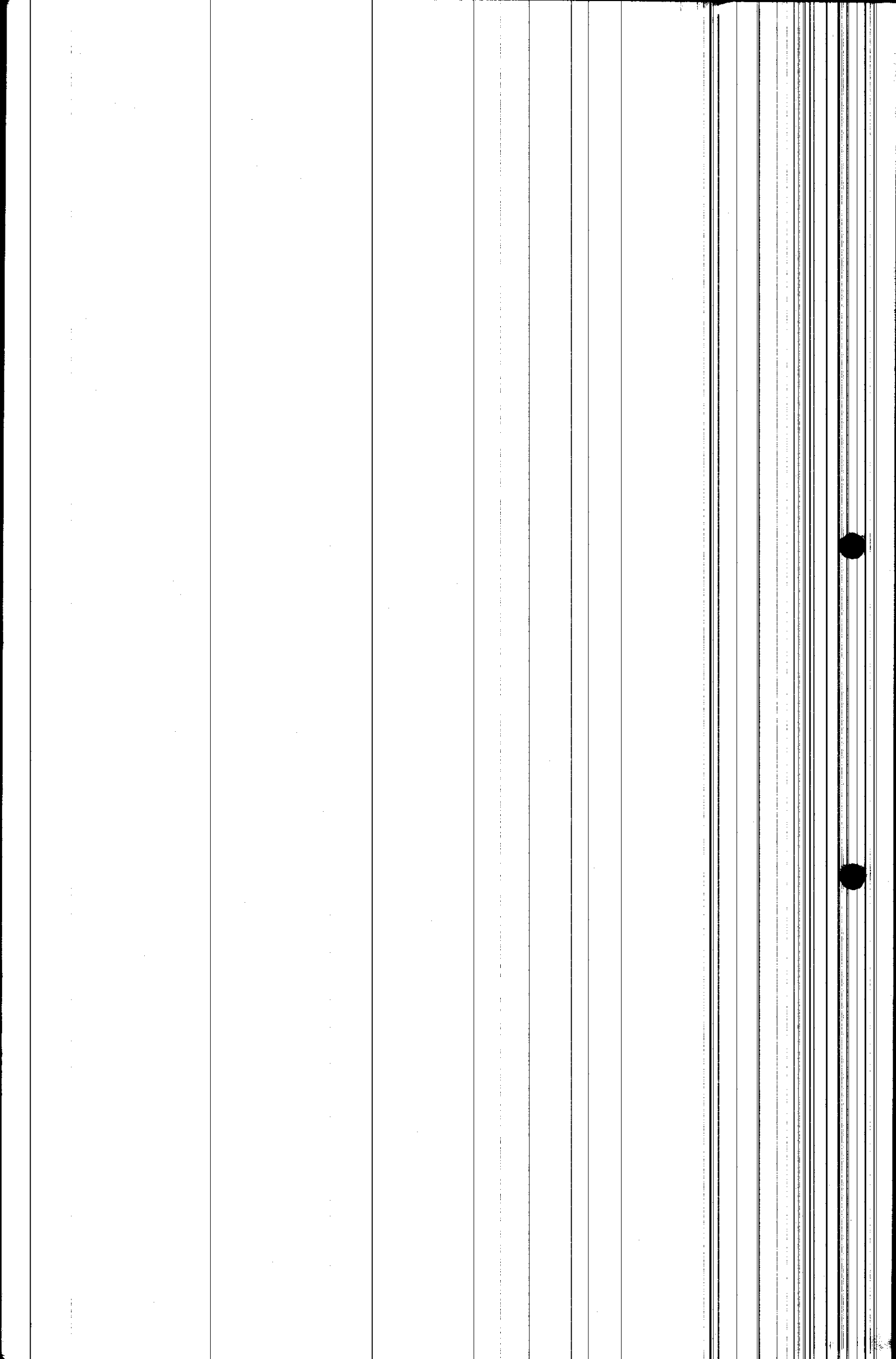
Este compuesto específico de la anterioridad D2 (Folio 141, página 33 , compuesto 22) es igual al compuesto de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado en 21 era conocido en D2 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de novedad.

8.2. Nivel inventivo.

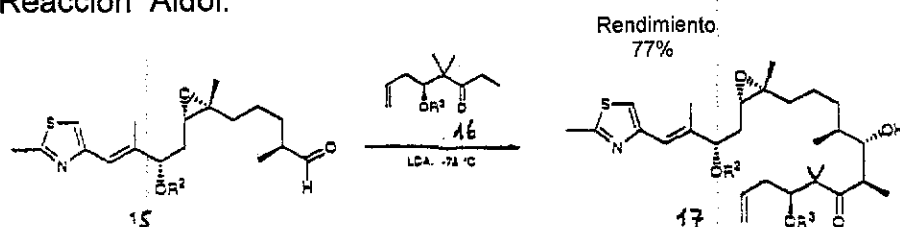
Para las reivindicaciones 1-8.

Para entender más el concepto se realizará el siguiente cuadro comparativo.

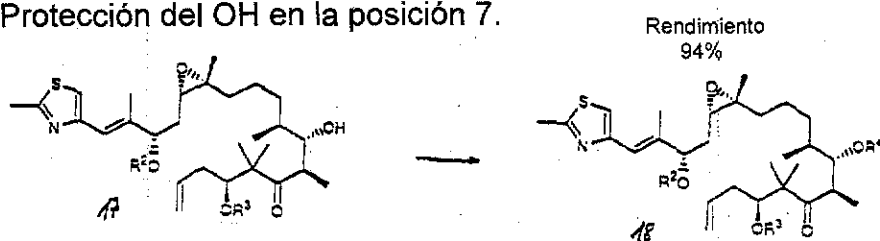


D2

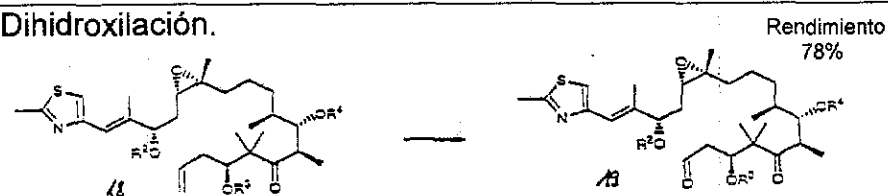
Reacción Aldol.



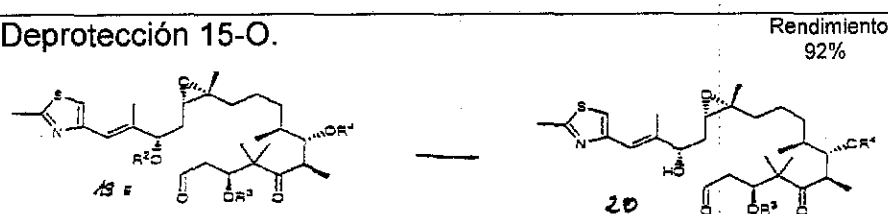
Protección del OH en la posición 7.



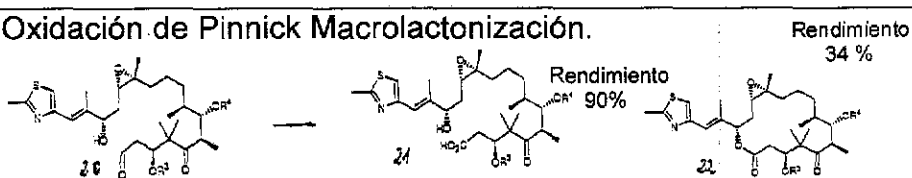
Dihidroxilación.



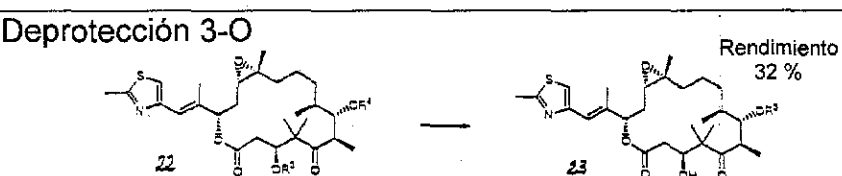
Deprotección 15-O.



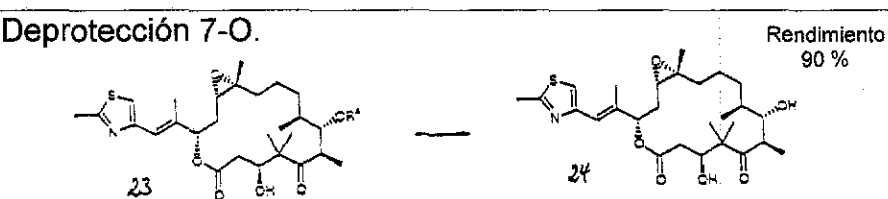
Oxidación de Pinnick Macrolactonización.

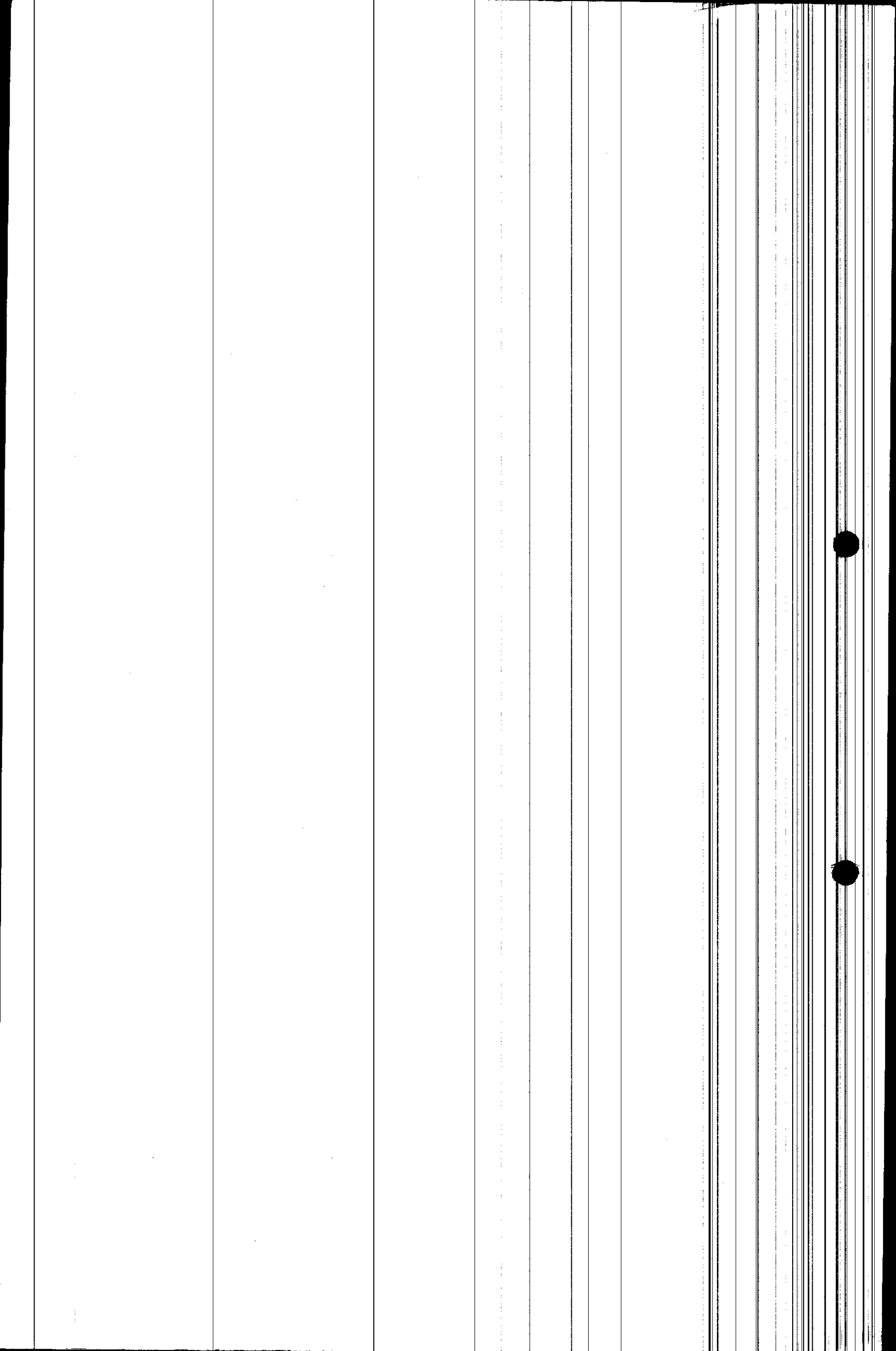


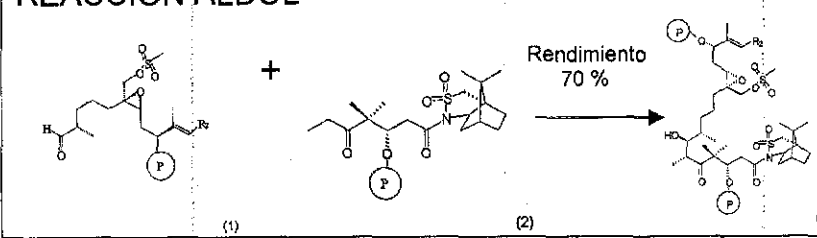
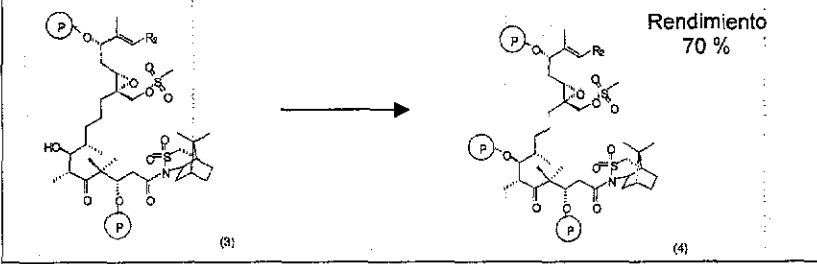
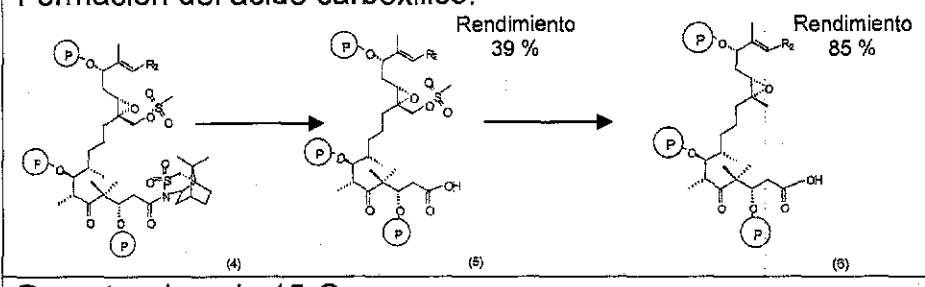
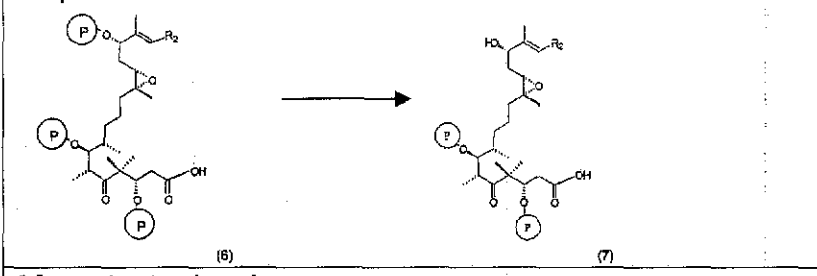
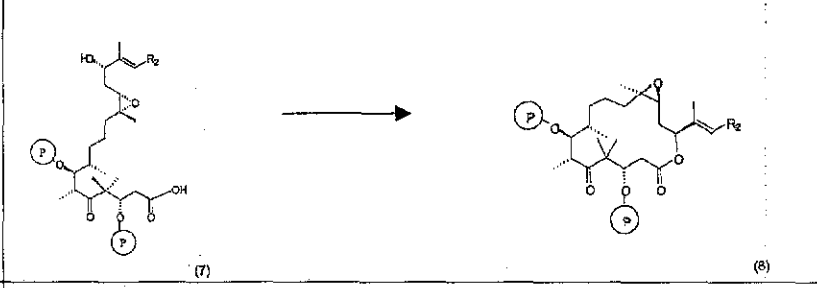
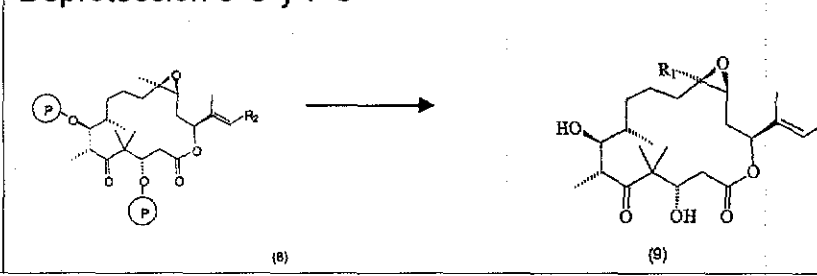
Deprotección 3-O



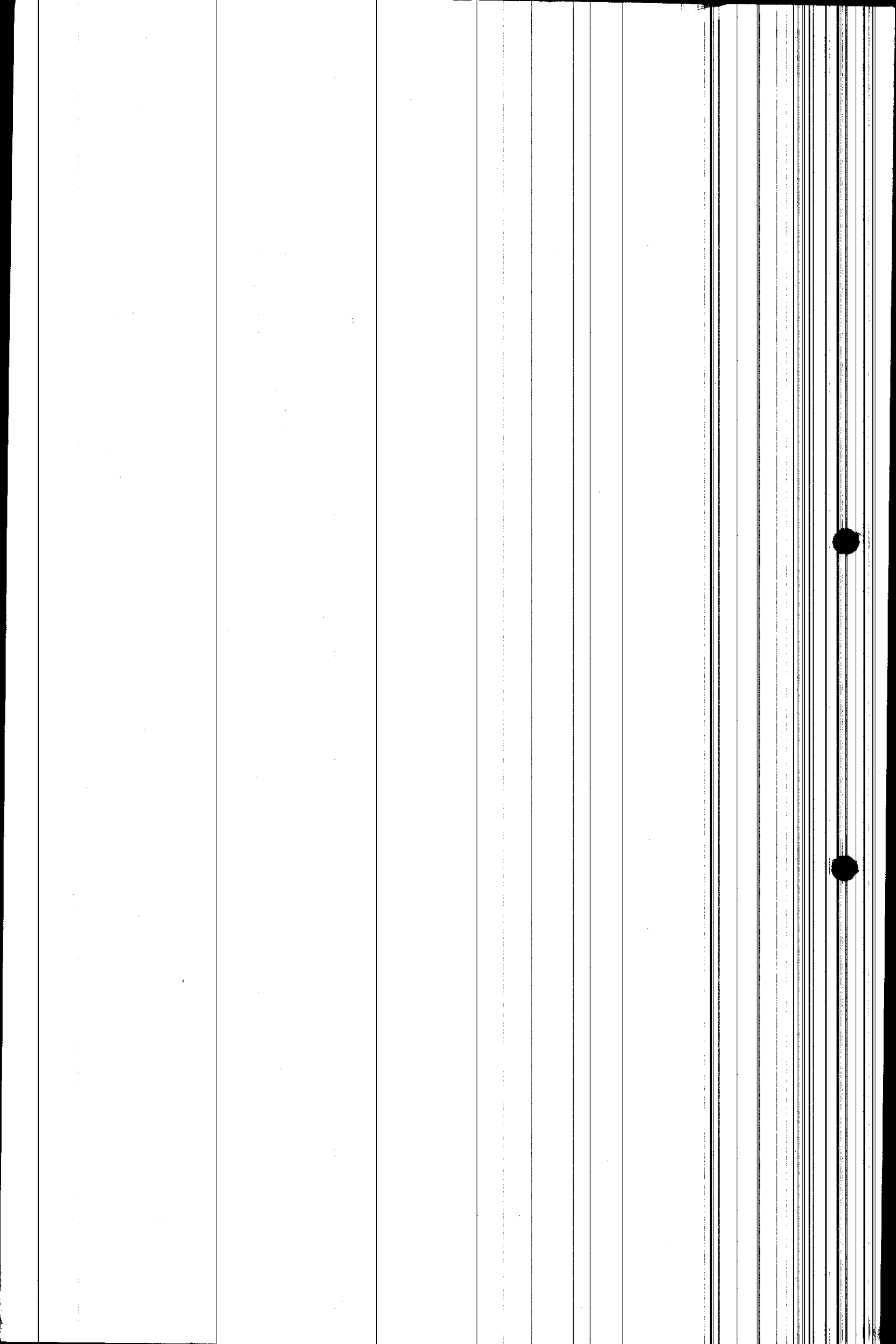
Deprotección 7-O.





SOLICITUD	REACCION ALDOL  (1) + (2) → (3) Rendimiento 70 %
	PROTECCION DEL OH en la posición 7.  (3) → (4) Rendimiento 70 %
	Formación del ácido carboxílico.  (4) → (5) Rendimiento 39 % → (6) Rendimiento 85 %
	Deproteccion de 15-O.  (6) → (7)
	Macrolactonizacion  (7) → (8)
	Deprotección 3-O y 7 O  (8) → (9)

La diferencia con D2 (Folio 137, diagrama 2) es que en esta solicitud se utiliza en la reacción de aldol una sultama quiral (compuesto 2).como grupo protector de carboxilato.



Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja al proceso reivindicado en comparación con el proceso del Estado de la Técnica más cercano (Ver folio 137); porque este proceso **no presenta un rendimiento global más alto (Ver folios 53-57)**

Así que el Problema Técnico planteado en esta solicitud : la necesidad de proporcionar un proceso más simple , mejorado para la preparación de epotilonas , derivados y sales de las mismas , factible a escala industrial con una etapa sintética reducida y con un rendimiento global alto en promedio. , se había solucionado previamente mediante el proceso descrito en D2. De manera que el nuevo procedimiento **es una alternativa a los procesos ya conocidos porque no presenta un rendimiento global más alto.**

Como se puede observar en la tabla comparativa, en general se presentan pasos de reacción comunes como por ejemplo la reacción aldol, protección del OH en la posición 7 , formación del ácido carboxílico, macrolactonización y deprotección de los 15-O, 3-O y 7-O.

A pesar de que el procedimiento reivindicado muestra menos pasos y menos intermediarios (debido a el uso de la sultama quirál) en la preparación de derivados de epotilona , en el aparte descriptivo no se muestra de manera completa el alcance total de la invención reivindicada.

En los folios 53-57 , no se muestra con ejemplos los pasos e)-g). reclamados en las reivindicaciones 1-8 .

Por consiguiente el experto en la materia no podría ejecutar de manera clara la invención tal como se reclama . Además la falta de dichos ejemplos, cuyo objetivo final es obtener los compuestos de fórmula 9 , en donde una de las ventajas radica en obtener un rendimiento global alto , dicha ventaja no puede ser comprobada frente al estado del arte más cercano a la falta de sustento en el aparte descriptivo.

Por lo tanto no se puede reconocer un nivel inventivo ya que el proceso reivindicado **no parece presentar un rendimiento global más alto.**

Para las reivindicaciones 9-10, 33

El documento del estado de la técnica más cercano es D3 (144-148) que enseña análogos de epotilona que se caracterizan por tener un efecto inhibitorio en la proliferación celular, útiles en el tratamiento de cáncer de pulmón , próstata, intestino, colorectales, mama entre otros.

La diferencia con D3 es que en esta solicitud los derivados de epopilona estan sustituidos en el radical R2 por un grupo arilo (fenilo sustituido o insustituido).

Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja a los compuestos reivindicados en comparación con los compuestos del Estado de la Técnica más cercano; porque estos compuestos **no presentan un efecto superior inhibitorio en la proliferación celular.**

El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D3 , hubiera sugerido sin mucho esfuerzo de su parte, reemplazar el grupo heteroarilo sustituido de D3 , por el grupo arilo sustituido o no sustituido en el radical equivalente a R2 y así lograr los derivados de epotilona reivindicados



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que no parecen presentar un efecto inhibitorio superior en la proliferación celular.

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

La composición farmacéutica que contiene el compuesto reivindicado (reivindicación 33), carece de nivel inventivo porque el componente que la caracteriza no es inventivo .

9. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO02/30356	31	Novedad
D2	WO01/07439	21 1-8	Novedad Nivel inventivo.
D3	WO98/25929	9-10,33	Nivel inventivo.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
22 AGO. 2008

CONCEPTO TÉCNICO No. 1866	EXAMINADOR TÉCNICO Código No. 202075
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