

**FORMULARIO UNICO DE OPOSICION
2000-12**

1

OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

2

**SOLICITUD
PUBLICADA**

Número del expediente: 05-111.045
Solicitante: PFIZER INC.
Apoderado: CARLOS R. OLARTE
Título de la nueva creación o denominación del signo:
**"INTERMEDIOS ÚTILES EN LA SÍNTESIS DE LOS INHIBIDORES DE
LAS PROTEASAS DE VIH Y PROCEDIMIENTOS PARA PREPARAR
LOS MISMOS".**
Gaceta: 570 de 30-11-2006 Página 712- Número de Publicación 812

3

OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: TECNOQUIMICAS S.A., Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: (1) 621.28.31 E-mail: info@reyes-abogados.com Fax: (1) 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

4

FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 16 (una invención se considera nueva cuando no es obvia, ni se deriva de manera evidente del estado de la técnica) y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia). Artículo 30 (Reivindicaciones) y artículo 42 (oposiciones) de la Decisión 486 de la Comisión de la Comunidad Andina.

Justificación: Ver Anexo

5

Comprobante de pago No. 07-17,755
07-17,758

(Oposición) Fecha Febrero 28 de 2007
(Prórroga) Fecha Febrero 28 de 2007

6

Anexos:

- ☒ Comprobante de pago de la tasa
- ☒ Poderes, si fuere el caso
- ☐ Pruebas de los fundamentos de la oposición
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☒ Copia de la oposición para el traslado al solicitante.

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA:



Señor**SUPERINTENDENTE DE INDUSTRIA Y COMERCIO****E.****S.****D.**

REF: EXPEDIENTE 05-111-045**TÍTULO SOLICITADO: "INTERMEDIOS UTILES EN LA SINTESIS DE LOS INHIBIDORES DE LAS PROTEASAS DE VIH Y PROCEDIMIENTOS PARA PREPARAR LOS MISMOS"****PUBLICACIÓN: GACETA 570 de 30/11/2006, NÚMERO DE PUBLICACION 812.****SOLICITANTE: PFIZER INC.****PRIORIDAD: US 60/469.235 DEL 8 DE MAYO DE 2003****APODERADO: CARLOS R. OLARTE****TRÁMITE: PRESENTACIÓN DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente:

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente 05-111-045, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos

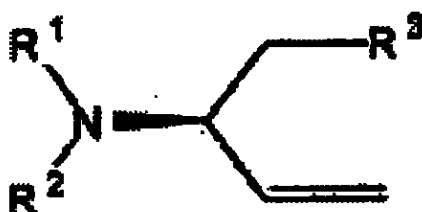
14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

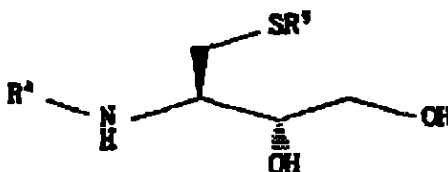
III. FUNDAMENTOS DE LA OPOSICIÓN

La patente **05-111-045** colombiana en trámite se refiere a un proceso de obtención de 1,2-dihidroxi-3-amino-butanos y a sus precursores 3-amino-butenos ópticamente activos que pueden ser usados en la síntesis de inhibidores de proteasa de VIH de formula general:

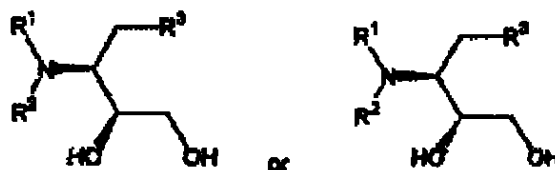


En la que R1 es un grupo protector de nitrógeno adecuado, R2 es H o R1 junto con R2 forman un grupo protector de nitrógeno adecuado, y R3 es tioalquilo o tioarilo, y carece de novedad y nivel inventivo por obra de las revelaciones previas comprendidas en las siguientes anterioridades:

- 3.1 La patente europea **EP 0 984 000 A1** publicada el **03 de Agosto de 2000**, y prioridad JP 24818495 del 26 de Septiembre de 1995, titulada **"PROCESS FOR PRODUCING AMIDE DERIVATIVES AND INTERMEDIATE COMPOUNDS."** Revela compuestos de la formula:

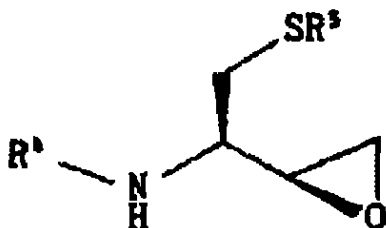


Donde R4 se define como un grupo amino protector y R5 es un átomo de hidrógeno, opcionalmente alquilo, alquenil, aril o aralquil, un enantiómero del mismo o una sal del mismo, que resultan idénticos a los compuestos de la patente colombiana en trámite mencionados en la reivindicación 4:

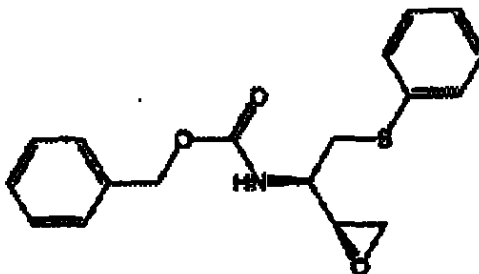


En las que R1 es un grupo protector de nitrógeno adecuado y R2 es H o R1 junto con R2 forman un grupo protector de nitrógeno adecuado, y R3 es tioalquilo o tioarilo.

Así mismo, se pueden encontrar intermediarios de la patente europea tales como:

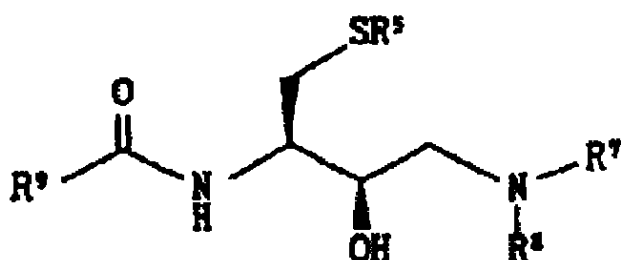


que resultan idénticos a los mencionados en la reivindicación 13 de la patente colombiana en trámite:

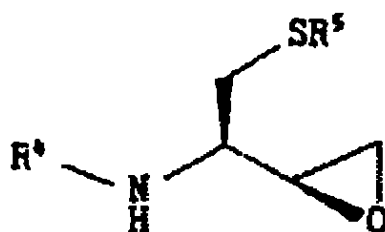


Si se tiene en cuenta que R4 se define como un grupo amino protector y R5 como un átomo de hidrógeno, opcionalmente alquilo, alquenil, aril o aralquil, un enantiómero del mismo o una sal del mismo, en esta patente europea.

En este mismo documento se menciona de la siguiente manera un procedimiento que involucra la obtención del compuesto:

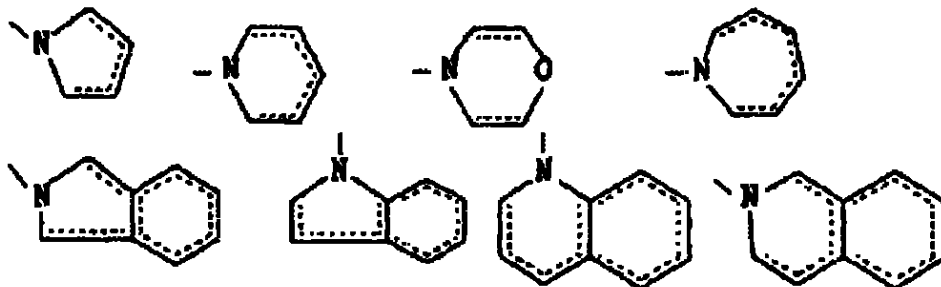


[0020] wherein: R^5 is as defined above, R^7 and R^8 are the same or different and each is a hydrogen atom, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted aralkyl, or R^7 and R^8 combinedly form a hetero ring together with the adjacent nitrogen atom, said hetero ring being optionally substituted by halogen atom, alkyl, alkenyl, alkoxy, amino, alkoxycarbonyl, carboxamide or alkyl-substituted carbamoyl, and R^9 is an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl or an optionally substituted heteroarylalkyl, and an enantiomer thereof, comprising reacting a substituted 1-butene oxide derivative of the formula (XII)

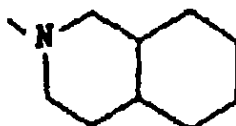


Donde adicionalmente se tiene que:

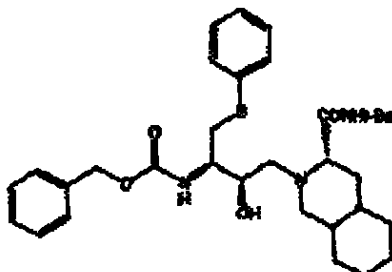
[0040] The hetero ring to be formed by R^7 and R^8 together with the adjacent nitrogen atom is, for example, saturated or unsaturated heteroaryl having one or more nitrogen atom(s). Specific examples include imidazolyl, triazolyl, tetrazolyl, pyrrolyl, pyrrolidinyl, imidazolidinyl, hydroxyridyl, piperidino, piperazinyl, oxazinyl, morpholino, azapinyl, hydroazepinyl, indolyl, hydroindolyl, isoindolyl, hydroisoindolyl, hydroquinolyl, hydroisoquinolyl, and the like. Preferred are the groups represented by the following formulas



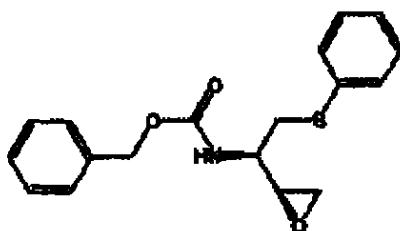
wherein the broken line may be either double bond or single bond, and more preferred is the group represented by the following formula:



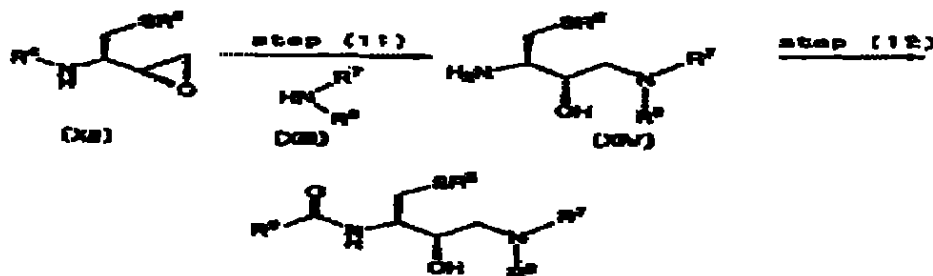
Al compararse estos apartes de la anterioridad europea con el procedimiento que se menciona en la reivindicación 13 de la solicitud colombiana en trámite para la obtención del compuesto de fórmula:

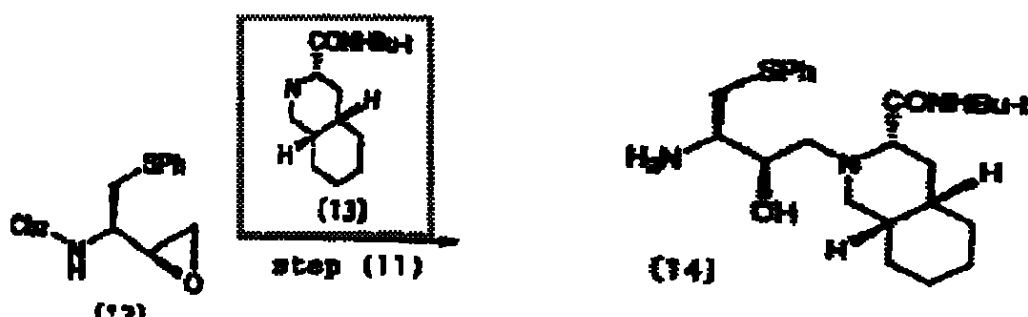


que involucra la reacción de un compuesto de formula:



con t-butilamida del ácido (3s, 4aS, 8aS)-decahidroisoquinolina-3-carboxílico en alcohol isopropílico, se hace evidente que la patente colombiana en trámite puede derivar su procedimiento aplicando la información que se brinda en esta anterioridad, mas aún cuando dicha información se describe de una manera exhaustiva en la patente europea, con las características de la amina, los solventes, y demás condiciones que conllevan al éxito en la obtención del compuesto planteado, tal y como se muestra a continuación:





Step (11): Epoxy ring opening with amine and removal of amino-protecting group

[0116] This step comprises treating compound [XII] or an enantiomer thereof with amine [XIII] in a suitable solvent to open epoxy ring and, with or without isolation, removing amino-protecting group (R^4) to give compound [XIV] or an enantiomer thereof.

[0117] The amine may be any as long as it has at least one hydrogen atom on nitrogen, and is exemplified by ammonia, methylamine, ethylamine, propylamine, isopropylamine, aniline, enalane, dimethylamine, diethylamine, dipropylamine, diisopropylamine, methyl ethylamine, methyl isopropylamine, methylaniline, pyrrolidine, piperidine, decahydroisoquinoline, (3S, 4aS, 8aS)-decahydroisoquinoline-3-carboxylic acid t-butylamide, and the like.

[0118] Suitable solvent includes, for example, alcohol solvents such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and t-butyl alcohol; hydrocarbon solvents such as benzene, toluene, hexane and xylene; ether solvents such as diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and diglyme; halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and water; and mixed solvents thereof. Preferred is alcohol solvent, and more preferred is isopropyl alcohol.

[0119] The reaction temperature of ring opening with amine is suitably 0-100°C and preferably 50-80°C. The reaction time is preferably 1 to 10 hours.

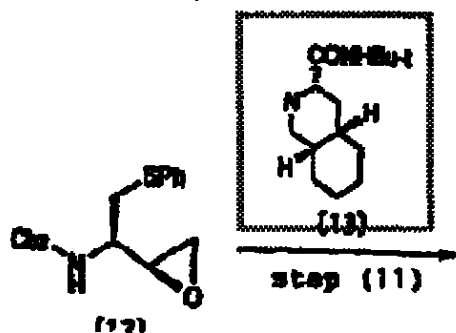
[0120] The method for eliminating amino-protecting group (R^4) can be suitably selected according to the kind of the protecting group. When the protecting group is a carbamate such as t-butoxycarbonyl and benzyloxycarbonyl, for example, the compound is treated with a suitable base in a suitable solvent for deprotection.

[0121] Suitable base includes, for example, inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and calcium carbonate; and organic bases such as alkoxides (e.g., sodium methoxide, sodium ethoxide and potassium t-butoxide), ammonia, methylamine, ethylamine, dimethylamine and diethylamine, with preference given to inorganic base, particularly potassium hydroxide.

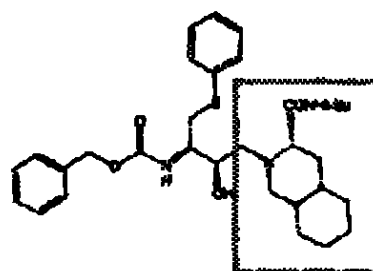
[0122] Suitable solvent includes, for example, alcohol solvents such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and t-butyl alcohol; hydrocarbon solvents such as benzene, toluene, hexane and xylene; ether solvents such as diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and diglyme; polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and water; and mixed solvents thereof. Preferred is a mixed solvent of alcohol solvent and water, and more preferred is a mixed solvent of isopropyl alcohol and water.

[0123] The reaction temperature is suitably 0-100°C and preferably 50-80°C. The reaction time is preferably 5 to 20 hours.

Resaltando que el reactivo utilizado en esta parte del proceso descrito en la patente europea tantas veces mencionada, es el mismo que se usa en la solicitud colombiana en trámite (t-butilamida del ácido (3s, 4aS, 8aS)-decahidroisoquinolina-3-carboxílico) para la obtención del compuesto discutido:



Patente EP 0984000



Patente Colombiana 05 111 045

3.2 Las publicaciones científicas "A Total Synthesis of Biotin Based on the Stereoselective Alkylation of Sulfoxides"¹, "Total Synthesis of (+)-Kalkitoxin"² y "New Diastereoselective Synthesis of Oxazolidin-2-ones through Carbon-Carbon Bond Formation on Cyclic Carbamoyloxy Radicals"³ contienen información técnica y experimental que puede guiar a cualquier persona versada en la materia para la obtención estereoselectiva de compuestos relacionados a los que se reivindican en la solicitud colombiana en trámite (dichos documentos se encuentran en el Informe de Búsqueda internacional practicado a la solicitud equivalente WO 2004/099129 A3 y catalogados con la categoría X).

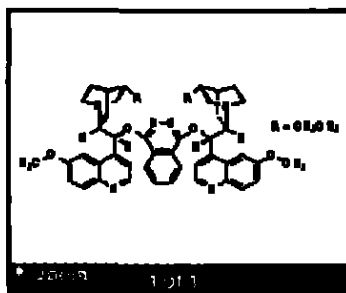
3.3 DHQD 2PHAL es un reactivo caracterizado y ampliamente utilizado en procesos de síntesis química semejantes al de la solicitud colombiana en trámite, en donde se requiere estereoselectividad, tal y como se demuestra a continuación:

¹ Solange Lavieille, Sonia Bory, Bernard Moreau, M. Jacqueline Luche, A Total Synthesis of Biotin Based on the Stereoselective Alkylation of Sulfoxides. *Journal of the American Chemical Society* / 100:5 / March 1 . 1978.

² James D. White* Chang-Sun Lee, and Qing Xu. Total Synthesis of (+)-Kalkitoxin. Supplementary Material (ESI) for Chemical Communications This journal is © The Royal Society of Chemistry 2003.

³ New Diastereoselective Synthesis of Oxazolidin-2-ones through Carbon-Carbon Bond Formation on Cyclic Carbamoyloxy Radicals. *Communications of The Organic Chemistry Journal*. VOLUME4 , NUMBER3. FEBRUARY 1989. Copyright 1989 by the American Chemical Society.

Aldrich 295%



Synonym	Hydroquinidine 1,4-phthalazinediyl diether
Molecular Formula	C ₄₈ H ₅₂ N ₆ O ₈
Molecular Weight	778.88
CAS Number	140663-10-7
Beilstein Registry Number	5475678
MDL number	MFCD00198107

Expand/Collapse All

Price and Availability

[Click For Pricing and Availability](#)

Description

Application Ligand for Sharpless Asymmetric Dihydroxylation.

Packaging 1 g in glass bottle

Legal Information Sold under license from Rhodia Pharma Solutions.

Properties

assay 295%

optical activity [α]_D²⁵ -232°, c = 1.2 in methanol

mp 190 °C (dec) (lit.)

References

Fieser Fieser 17,236

4

Las siguientes publicaciones científicas también evidencian el uso de esta molécula DHQD 2PHAL junto a catalizadores que contienen osmio y otros co-oxidantes para obtener una dihidroxidación estereoselectiva tal y como se busca con los agentes mencionados en la reivindicación 9 de la solicitud Colombiana en trámite (K2OsO2(OH)/K3Fe(CN)6, K2CO3, NaOHCO3 y CH3SO2NH2 en presencia de DHQD2PHAL) :

1. **Asymmetric aminohydroxylation of substituted styrenes: applications in the synthesis of enantiomerically enriched arylglycinols and a diamine.**⁵

The catalytic asymmetric aminohydroxylation of a variety of styrene derivatives and vinyl aromatics using osmium tetroxide in conjunction with alkaloid-derived ligands [e.g. (DHQ)2PHAL or (DHQD)2PHAL] and haloamine salts of alkyl carbamates (e.g. ethyl carbamate or tert-butyl carbamate) has been investigated. By observing the effect of different aromatic substituents and alkyl carbamates on the regioselectivity, yield and enantioselectivity of the aminohydroxylation reactions, a number of conclusions have been reached: (i) the 1-aryl-2-hydroxyethylamine regioisomers were obtained as

⁴ www.sigmaaldrich.com/catalog/search/ProductDetail/ALDRICH/392731

⁵ Journal of the Chemical Society, Perkin Transactions 1, August 21, 1998, Vol. 1998 Issue: Number 16 p2519-2526, 8p. (AN 7998808)

the major products in reasonable yield and high (>87%) enantiomeric excess; (ii) tert-butyl carbamate was superior to ethyl carbamate in terms of yield, enantioselectivity and ease of removal of the N-protecting group; (iii) high ($\geq 96\%$) enantioselectivity was observed with a 4-methoxy-substituted styrene whereas ortho-substituted styrenes gave lower enantioselectivities; (iv) chiral ligands (DHQ)2PHAL and (DHQD)2PHAL gave essentially equal and opposite senses and degrees of asymmetric induction; (v) regioselectivity was ligand dependent with better regioselectivity (and therefore higher isolated yields) obtained with (DHQ)2PHAL than with (DHQD)2PHAL. The products of the aminohydroxylation reactions were used to prepare enantiomerically enriched arylglycinols and a chiral diamine.

2. **Synthesis of enantiomerically enriched Baylis-Hillman alcohols from their acetates: combination of kinetic resolution during the salt formation with (DHQD) 2 PHAL and following asymmetric induction during hydrolysis with NaHCO 3 as a water surrogate.⁶**

Enantiomerically enriched Baylis-Hillman alcohols 2a - d (S) were prepared in 25-42% yields with optical purities of 54-92% ee by using the combined concept of kinetic resolution during the salt formation of racemic Baylis-Hillman acetates 1a - d with (DHQD) 2 PHAL and the asymmetric induction during the S N 2' type reaction with sodium bicarbonate as a water surrogate.

3. **Asymmetric synthesis of biologically useful 3,4-disubstituted gamma- lactone (3,4-db).⁷**

3,4-Disubstituted gamma-lactones 9 and 10 were stereoselectively synthesized from 3,4-unsaturated aliphatic alcohol. The synthetic methods of homoallylic alcohol were discussed. Asymmetric dihydroxylation of the double bond was performed by Sharpless' method with (DHQD)2 PHAL or (DHQ)2 PHAL. The stereochemistry of the product was assigned. The (3R,4R)- and (3S,4S)-compounds were obtained with high enantiomeric excess.

4. **A trifunctional catalyst for one-pot synthesis of chiral diols via Heck coupling-N-oxidation-asymmetric dihydroxylation: application for the synthesis of diltiazem and taxol side chain.⁸**

⁶ Kim, Jae Nyoung; Lee, Hong Jung; Gong, Ji Hyeon. *Tetrahedron Letters*, 2002, Vol. 43 Issue: Number 50 p9141-9146, 6p. (AN 3943665)

⁷ Cheong CS, *Enantiomer [Enantiomer]*, 2000 Dec; Vol. 5 (6), pp. 585-90; PMID: 11342294

⁸ Choudary BM. *The Journal Of Organic Chemistry [J Org Chem]*, 2003 Mar 7; Vol. 68 (5), pp. 1736-46; PMID: 12608786

A heterogeneous bifunctional catalyst composed of $\text{OsO}_4(2-)\text{-WO}_4(2-)$ and a trifunctional catalyst comprising $\text{PdCl}_4(2-)\text{-OsO}_4(2-)\text{-WO}_4(2-)$, designed and prepared by an ion-exchange technique using layered double hydroxides (LDH) as an ion-exchanger and their homogeneous bifunctional analogue, $\text{K}_2\text{OsO}_4\text{-Na}_2\text{WO}_4$ and trifunctional analogue, $\text{Na}_2\text{PdCl}_4\text{-K}_2\text{OsO}_4\text{-Na}_2\text{WO}_4$, devised for the first time are evaluated for the synthesis of chiral vicinal diols. These bifunctional and trifunctional catalysts perform asymmetric dihydroxylation-N-oxidation and Heck-asymmetric dihydroxylation-N-oxidation, respectively, in the presence of Sharpless chiral ligand, (DHQD)2PHAL in a single pot using H_2O_2 as a terminal oxidant to provide N-methylmorpholine oxide (NMO) in situ by the oxidation of N-methylmorpholine (NMM) (...)

5. Catalytic asymmetric dihydroxylation of olefins with reusable $\text{OsO}_4(2-)$ on ion-exchangers: the scope and reactivity using various cooxidants.⁹

Exchanger- $\text{OsO}_4(2-)$ catalysts are prepared by an ion-exchange technique using layered double hydroxides and quaternary ammonium salts covalently bound to resin and silica as ion-exchangers. The ion-exchangers with different characteristics and opposite ion selectivities are specially chosen to produce the best heterogeneous catalyst that can operate using the various cooxidants in the asymmetric dihydroxylation reaction. LDH- $\text{OsO}_4(2-)$ catalysts composed of different compositions are evaluated for the asymmetric dihydroxylation of trans-stilbene. Resin- $\text{OsO}_4(2-)$ and $\text{SiO}_2\text{-OsO}_4(2-)$ designed to overcome the problems associated with LDH- $\text{OsO}_4(2-)$ indeed show consistent activity and enantioselectivity in asymmetric dihydroxylation of olefins using $\text{K}_3\text{Fe}(\text{CN})_6$ and molecular oxygen as cooxidants. Compared to the Kobayashi heterogeneous systems, resin- $\text{OsO}_4(2-)$ is a very efficient catalyst for the dihydroxylation of a wide variety of aromatic, aliphatic, acyclic, cyclic, mono-, di-, and trisubstituted olefins to afford chiral vicinal diols with high yields and enantioselectivities irrespective of the cooxidant used. Resin- $\text{OsO}_4(2-)$ is recovered quantitatively by a simple filtration and reused for a number of cycles with consistent activity. The high binding ability of the heterogeneous osmium catalyst enables the use of an equimolar ratio of ligand to osmium to give excellent enantioselectives in asymmetric dihydroxylation in contrast to the homogeneous osmium system in which excess molar quantities of the expensive chiral ligand to osmium are invariably used. The complexation of the chiral ligand (DHQD)2PHAL, having very large dimension,

⁹ Choudary BM, Journal Of The American Chemical Society [J Am Chem Soc], 2002 May 15; Vol. 124 (19). pp. 5341-9; PMID: 11996575

a prerequisite to obtain higher ee, is possible only with the $\text{OsO}_4(2-)$ located on the surface of the supports.

6. **Catalytic asymmetric dihydroxylation using phenoxyethoxymethyl-polystyrene (PEM)-based novel microencapsulated osmium tetroxide (PEM-MC OsO_4).**¹⁰

A phenoxyethoxymethyl-polystyrene (PEM)-based novel polymer-supported osmium catalyst has been developed. The catalyst was readily prepared from PEM polymer based on a microencapsulation technique, and asymmetric dihydroxylation of olefins has been successfully performed using (DHQD)2PHAL as a chiral ligand and $\text{K}_3\text{Fe}(\text{CN})_6$ as a cooxidant in H_2O /acetone. The catalyst was recovered quantitatively by simple filtration and reused without loss of activity several times.

7. De la misma forma la patente americana US 6,372,911 publicada el 16 de abril de 2002 titulada "PROCESS FOR PREPARING BETA-HYDROXICARBAMATES AND THEIR CONVERSION TO OXAZOLIDINONES" hace mención a sistemas oxidativos similares a los de la solicitud colombiana en trámite y DHQD 2PHAL tanto en la parte descriptiva como en las reivindicaciones 8 y 9:

Abstract: A process for preparing a beta-hydroxy carbamate product is disclosed. The process comprises reacting an olefin compound containing at least one carbon-carbon double bond with a carbamate in an aqueous solvent and in the presence of a base, an osmium catalyst, a co-oxidant selected from a halohydantoin, a haloisocyanuric acid, and an alkali metal salt of a haloisocyanuric acid, and optionally an asymmetric ligand, to form a reaction mixture containing the a beta-hydroxy carbamate product. The process optionally further comprises treating the a beta-hydroxy carbamate product with additional base to form an oxazolidinone. The oxazolidinones are useful as chiral auxiliary agents and as intermediates for the formation of pharmaceutically active substances such as alpha 1 a adrenergic receptor antagonists. A process for preparing nitrogen-functionalized derivatives of the oxazolidinones is also disclosed.

Claims

8. The process according to claim 1, wherein the base is selected from alkali metal hydroxides and alkali metal carbonates

¹⁰ Kobayashi S, Organic Letters [Org Lett], 2001 Aug 23; Vol. 3 (17). pp. 2649-52; PMID: 11506600

9. The process according to claim 1, wherein the asymmetric ligand is selected from (DHQ).sub.2 PHAL, (DHQD).sub.2 PHAL, (DHQ).sub.2 AQN, and (DHQD).sub.2 AQN.

Teniendo en cuenta los argumentos anteriores reitero que la solicitud de la referencia incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 (Requisitos de Patentabilidad), el artículo 30 (Reivindicaciones) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

1. La patente europea EP 0 984 000 A1 publicada el 03 de Agosto de 200, y prioridad JP 24818495 del 26 de Septiembre de 1995, titulada **"PROCESS FOR PRODUCING AMIDE DERIVATIVES AND INTERMEDIATE COMPOUNDS."** Pg. 6 – 9, 11, 13, 18, 20, 27 – 30.
2. Las publicaciones científicas **"A Total Synthesis of Biotin Based on the Stereoselective Alkylation of Sulfoxides"**(Pg. 1558), **"Total Synthesis of (+)-Kalkitoxin"**(Pg. 1-13) y **"New Diastereoselective Synthesis of Oxazolidin-2-ones through Carbon-Carbon Bond Formation on Cyclic Carbamoyloxy Radicals"**(Pg. 1).
3. La publicación científica **"Asymmetric aminohydroxylation of substituted styrenes: applications in the synthesis of enantiomerically enriched arylglycinols and a diamine"**. (Ver abstract).

4. La publicación científica **"Synthesis of enantiomerically enriched Baylis-Hillman alcohols from their acetates: combination of kinetic resolution during the salt formation with (DHQD) 2 PHAL and following asymmetric induction during hydrolysis with NaHCO₃ as a water surrogate"**. (Ver abstract)
5. La publicación científica **"Asymmetric synthesis of biologically useful 3,4-disubstituted gamma-lactone (3,4-db)." (Ver abstract)**
6. La publicación científica **"A trifunctional catalyst for one-pot synthesis of chiral diols via Heck coupling-N-oxidation-asymmetric dihydroxylation: application for the synthesis of diltiazem and taxol side chain."** (Ver abstract)
7. La publicación científica **"Catalytic asymmetric dihydroxylation of olefins with reusable OsO₄(2-) on ion-exchangers: the scope and reactivity using various cooxidants"**. (Ver abstract)
8. La publicación científica **"Catalytic asymmetric dihydroxylation using phenoxyethoxymethyl-polystyrene (PEM)-based novel microencapsulated osmium tetroxide (PEM-MC OsO₄)." (Ver abstract)**
9. La patente americana US 6,372,911 publicada el 16 de abril de 2002 titulada **"PROCESS FOR PREPARING BETA- HYDROXICARBAMATES AND THEIR CONVERSION TO OXAZOLIDINONES"**. Pg. 1 y 19.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 No. 7-39 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44.655 de C.S.J.

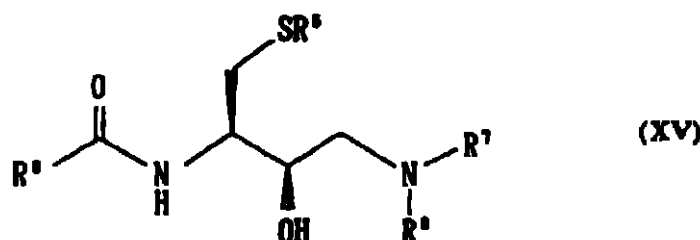
(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication: 08.03.2000 Bulletin 2000/10
(21) Application number: 96931297.4
(22) Date of filing: 24.09.1996
(51) Int. Cl.⁷: C07C 323/25, C07C 319/20,
C07D 321/06, C07D 493/04,
C07D 303/36, C07D 317/28,
C07B 53/00
// C07M7:00
(86) International application number:
PCT/JP96/02757
(87) International publication number:
WO 97/11838 (03.04.1997 Gazette 1997/15)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE
(30) Priority: 26.09.1995 JP 24818495
(71) Applicants:
• Japan Tobacco Inc.
Minato-Ku Tokyo 105 (JP)
• AGOURON PHARMACEUTICALS, INC.
La Jolla, CA 92037 (US)
(72) Inventors:
• INABA, Takashi,
Central Pharmaceutical Research
Takatsuki-shi, Osaka 569-11 (JP)

• YAMADA, Yasuki,
Central Pharmaceutical Research
Takatsuki-shi, Osaka 569-11 (JP)
• SHANLEY, James
San Diego, CA 92117 (US)
• DEASON, Michael
Poway, CA 92084 (US)
(74) Representative:
von Kreisler, Alek, Dipl.-Chem. et al
Patentanwälte,
von Kreisler-Setling-Werner,
Bahnhofsvorplatz 1 (Deichmannhaus)
50667 Köln (DE)

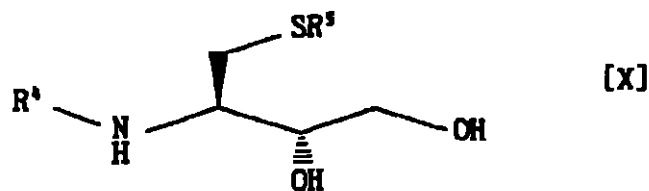
(54) **PROCESS FOR PRODUCING AMIDE DERIVATIVES AND INTERMEDIATE COMPOUNDS**
(57)



EP 0 984 000 A1

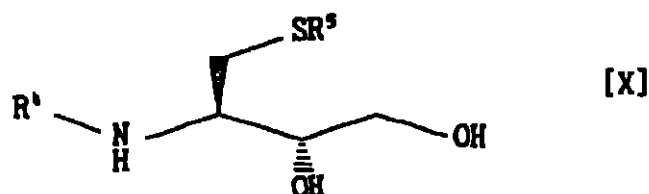
A process for producing amide derivatives represented by general formula (XV) or enantiomers thereof, novel intermediate compounds useful for producing these compounds, etc., and a process for producing the same, wherein each symbol is as defined in the specification. Compared with the conventional processes, the above process can be very easily effected and enables an efficient production of the compounds (XV), i.e., those involving the compounds (XVI) having an HIV protease inhibitory effect in high yields. The novel intermediates are highly advantageous as intermediates for producing not only the above compounds (XVI) but also those which are useful as an X-ray contrast medium, etc.

(7) A 3-substituted aminobutane-1,2-diol derivative of the formula [X]

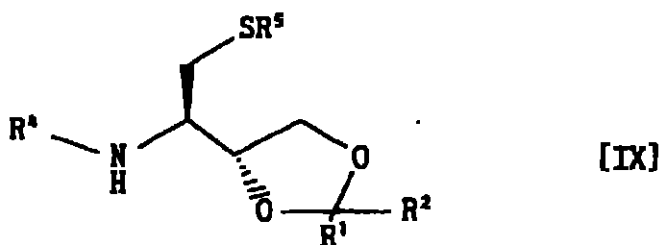


[0013] wherein R^4 and R^5 are as defined above, an enantiomer thereof and a salt thereof.

(8) A method for producing a 3-substituted aminobutane-1,2-diol derivative of the formula [X]

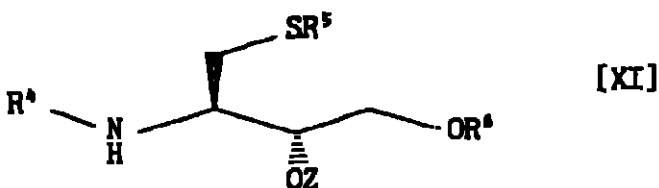


[0014] wherein R^4 and R^5 are as defined above, and an enantiomer thereof, comprising hydrolyzing a 1,3-dioxolane-1-yl-ethylidene derivative of the formula [IX]



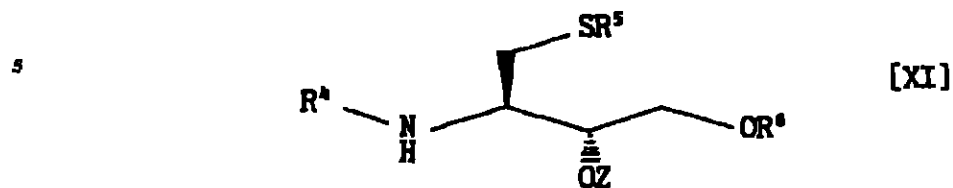
wherein R^1 , R^2 , R^4 and R^5 are as defined above, or an enantiomer thereof in the presence of an acid.

(9) A 3-substituted aminobutane derivative of the formula [XI]



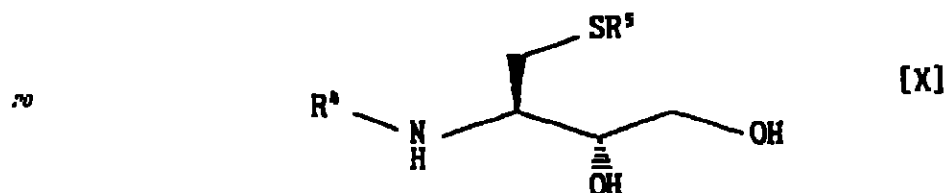
[0015] wherein R^4 and R^5 are as defined above, R^6 is a hydroxy-protecting group and Z is a substituent which functions as a leaving group with an oxygen atom, an enantiomer thereof and a salt thereof.

(10) A method for producing a 3-substituted aminobutane derivative of the formula [XI]



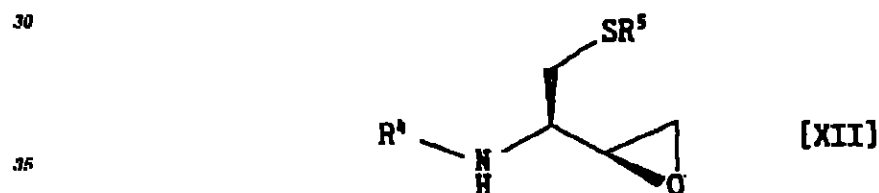
[0016] wherein R⁴, R⁵, R⁶ and Z are as defined above, and an enantiomer thereof, comprising protecting a primary hydroxy of a 3-substituted aminobutane-1,2-diol derivative of the formula [X]

15



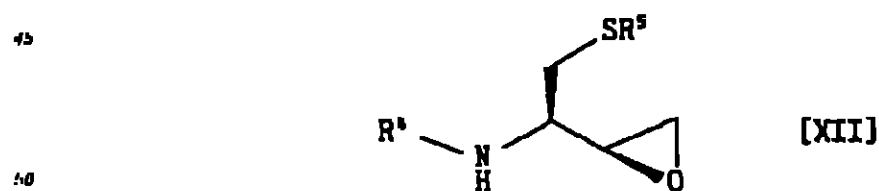
wherein R⁴ and R⁵ are as defined above, or an enantiomer thereof, and, with or without isolating the obtained compound, converting a secondary hydroxy to a leaving group.

(11) A substituted 1-butene oxide derivative of the formula [XII]



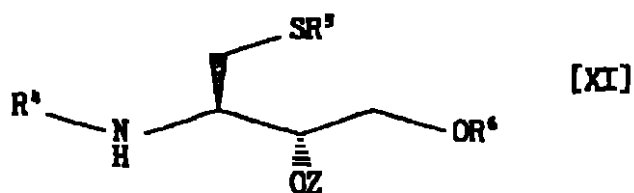
[0017] wherein R⁴ and R⁵ are as defined above, an enantiomer thereof and a salt thereof.

(12) A method for producing a substituted 1-butene oxide derivative of the formula [XII]



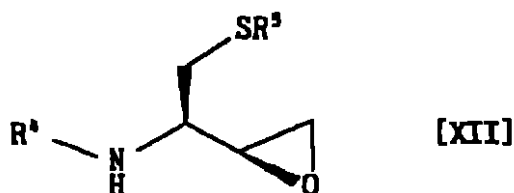
[0018] wherein R⁴ and R⁵ are as defined above, and an enantiomer thereof, comprising treating a 3-substituted aminobutane derivative of the formula [XI]

50

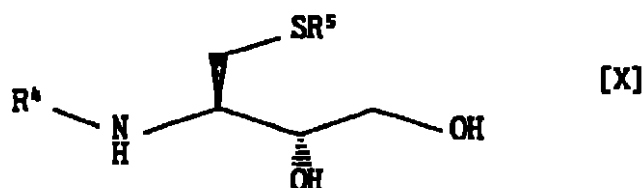


10 wherein R^4 , R^5 , R^6 and Z are as defined above, or an enantiomer thereof, in the presence of a base, and simultaneously conducting epoxidation and deprotection of primary hydroxy.

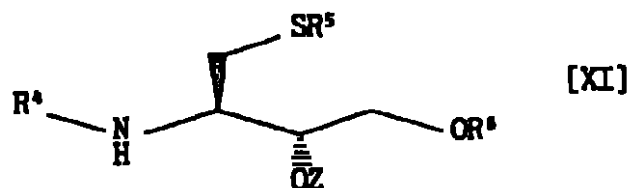
15 (13) A method for producing a substituted 1-butane oxide derivative of the formula [XII]



25 [0019] wherein R^4 and R^5 are as defined above, and an enantiomer thereof, comprising protecting a primary hydroxy of a 3-substituted aminobutane-1,2 diol derivative of the formula [X]

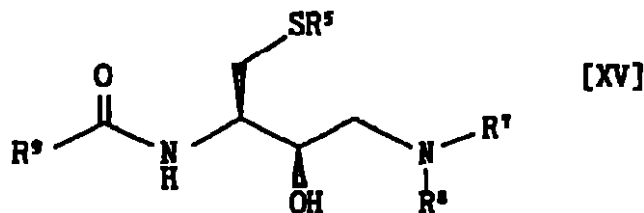


35 wherein R^4 and R^5 are as defined above, or an enantiomer thereof, converting, with or without isolating the obtained compound, a secondary hydroxy to a leaving group to give a 3-substituted aminobutane derivative of the formula [XI]



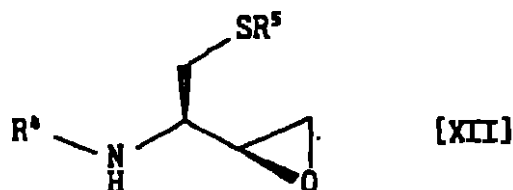
45 wherein R^4 , R^5 , R^6 and Z are as defined above, or an enantiomer thereof, and treating the obtained compound in the presence of a base to simultaneously conduct epoxidation and deprotection of the primary hydroxy.

(14) A method for producing an amide derivative of the formula [XV]



15 [0020] wherein R⁵ is as defined above, R⁷ and R⁸ are the same or different and each is a hydrogen atom, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted aralkyl, or R⁷ and R⁸ combinedly form a hetero ring together with the adjacent nitrogen atom, said hetero ring being optionally substituted by halogen atom, alkyl, alkenyl, alkoxy, amino, alkoxycarbonyl, carboxamide or alkyl-substituted carbamoyl, and R⁸ is an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl or an optionally substituted heteroarylalkyl, and an enantiomer thereof, comprising

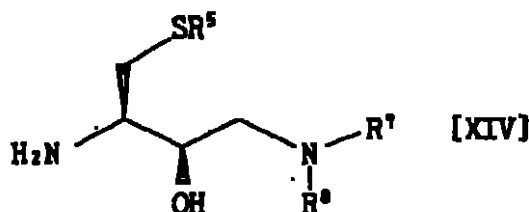
20 reacting a substituted 1-butene oxide derivative of the formula [XII]



wherein R⁴ and R⁵ are as defined above, or an enantiomer thereof, with an amine of the formula [XIII]



45 wherein R⁷ and R⁸ are as defined above, removing the amino-protecting group to give a 1,3-diamino-2-hydroxybutane derivative of the formula [XIV]



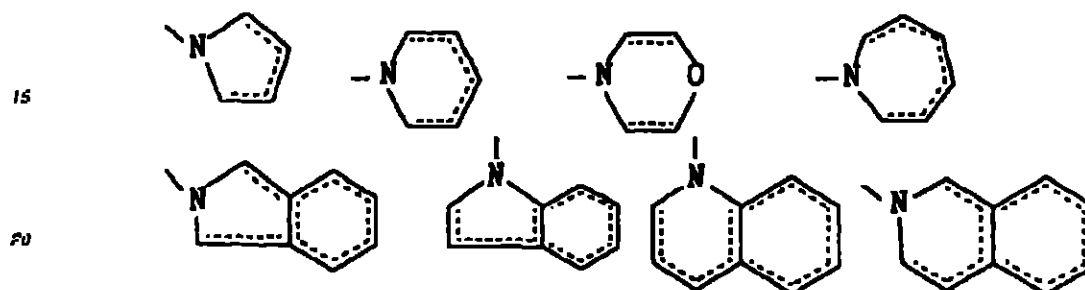
55 wherein R⁵, R⁷ and R⁸ are as defined above, or an enantiomer thereof, and reacting the obtained compound with an acylating agent, followed by deprotection of the protecting group on R⁸ where necessary.

[0021] As used herein, alkyl may be linear or branched and preferably has 1 to 6 carbon atoms. Specific examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, hexyl, isohexyl, neohexyl and the like, with preference given to lower alkyl having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl and t-butyl.

[0038] The optionally substituted heteroarylalkyl is that which may be substituted by one or more substituent(s) exerting no influence on the reaction. Examples of the substituent include those exemplified with respect to the aforementioned optionally substituted heteroaryl, and the like.

[0039] While the position and number of the substituents on heteroaryl of the above-mentioned heteroarylalkyl are not particularly limited, preferred are compounds having 1 to 3 substituent(s).

[0040] The hetero ring to be formed by R⁷ and R⁸ together with the adjacent nitrogen atom is, for example, saturated or unsaturated heteroaryl having one or more nitrogen atom(s). Specific examples include imidazolyl, triazolyl, tetrazolyl, pyrrolyl, pyrrolidinyl, imidazolidinyl, hydroxypyridyl, piperidino, piperazinyl, oxazinyl, morpholino, azepinyl, hydroazepinyl, indolyl, hydroindolyl, isoindolyl, hydroisoindolyl, hydroquinolyl, hydroisoquinolyl, and the like. Preferred are the groups represented by the following formulas



wherein the broken line may be either double bond or single bond, and more preferred is the group represented by the following formula:



[0041] Said hetero ring may be substituted by halogen atom; alkyl having 1 to 6 carbon atom(s); alkenyl having 2 to 6 carbon atoms; alkoxy having 1 to 6 carbon atom(s); amino; alkoxycarbonyl having 2 to 6 carbon atoms; carboxamide; or alkyl-substituted carbamoyl wherein the alkyl moiety has 1 to 6 carbon atom(s).

[0042] While the position and number of substituents on the hetero ring are not particularly limited, preferred are compounds having 1 to 3 substituent(s) and more preferred are compounds having 1 or 2 substituent(s).

[0043] The halogen atom as the substituent for hetero ring includes, for example, fluorine, chlorine, bromine and iodine.

[0044] The alkyl as the substituent for hetero ring includes, for example, the aforementioned ones having 1 to 6 carbon atom(s).

[0045] The alkenyl as the substituent for hetero ring includes, for example, those mentioned above preferably having 2 to 6 carbon atoms.

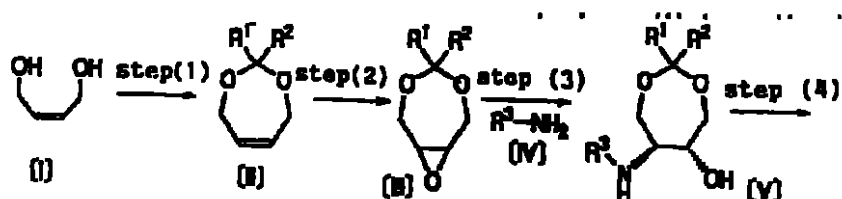
[0046] The alkoxy as the substituent for hetero ring includes, for example, linear or branched alkoxy preferably having 1 to 6 carbon atom(s), which is exemplified by methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy, t-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, and the like. More preferred are those having 1 to 4 carbon atom(s) such as methoxy, ethoxy, propoxy, isopropoxy and butoxy, with further preference given to those having 1 or 2 carbon atom(s) such as methoxy and ethoxy.

[0047] The alkoxycarbonyl as the substituent for hetero ring includes, for example, alkoxycarbonyl preferably having 2 to 6 carbon atoms, which is exemplified by the above-mentioned alkoxy having 1 to 5 carbon atom(s) with carbonyl group, and the like.

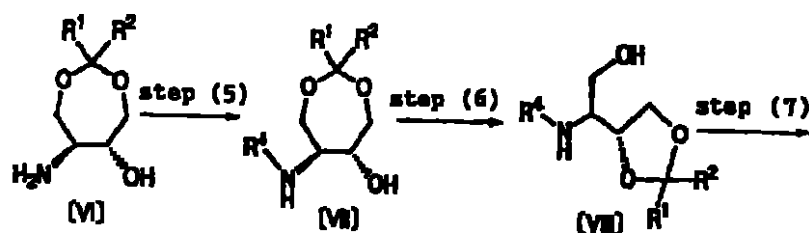
[0048] The alkyl-substituted carbamoyl as the substituent for hetero ring includes, for example, those wherein the alkyl moiety preferably has 1 to 6 carbon atom(s), which is exemplified by N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-t-butylcarbamoyl, N-pentylcarbamoyl, N-hexylcarbamoyl, and the like. Preferred is N-t-butylcarbamoyl.

[0049] The amino-protecting group includes, for example, optionally substituted aralkylidene such as benzylidene, 4-

5

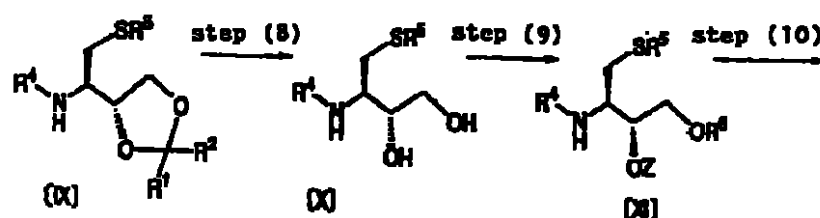


10



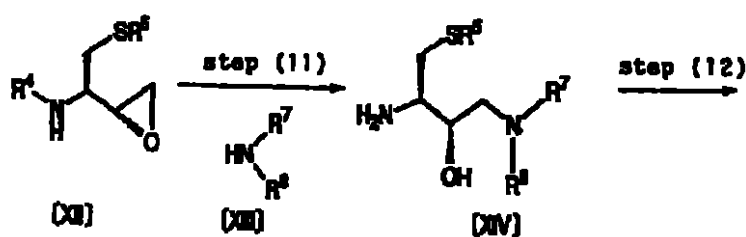
20

25



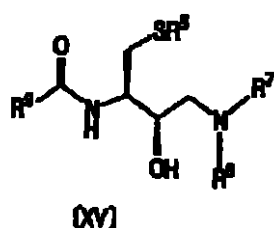
30

35



40

45



50

55 wherein $R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9$ and Z are as defined above and R^3 is alkylamine residue or amino acid derivative residue.

N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and water; mixed solvents thereof; and the like. Preferred is a mixed solvent of ether solvent and water, and more preferred is a mixed solvent of 1,4-dioxane and water.

[0115] The reaction temperature is suitably 0-30°C and preferably 0-20°C. The reaction time is preferably 30 minutes to 5 hours.

Step (11) : Epoxy ring opening with amine and removal of amino-protecting group

[0116] This step comprises treating compound [XII] or an enantiomer thereof with amine [XIII] in a suitable solvent to open epoxy ring and, with or without isolation, removing amino-protecting group (R^4) to give compound [XIV] or an enantiomer thereof.

[0117] The amine may be any as long as it has at least one hydrogen atom on nitrogen, and is exemplified by amines, methylamine, ethylamine, propylamine, isopropylamine, aniline, anilidine, dimethylamine, diethylamine, dipropylamine, diisopropylamine, methylethylamine, methylisopropylamine, methylaniline, pyrrolidine, piperidine, decahydroisoquinoline, (3S, 4aS, 8aS)-decahydroisoquinoline-3-carboxylic acid t-butylamide, and the like.

[0118] Suitable solvent includes, for example, alcohol solvents such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and t-butyl alcohol; hydrocarbon solvents such as benzene, toluene, hexane and xylene; ether solvents such as diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and diglyme; halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and water; and mixed solvents thereof. Preferred is alcohol solvent, and more preferred is isopropyl alcohol.

[0119] The reaction temperature of ring opening with amine is suitably 0-100°C and preferably 50-80°C. The reaction time is preferably 1 to 10 hours.

[0120] The method for eliminating amino-protecting group (R^4) can be suitably selected according to the kind of the protecting group. When the protecting group is a carbamate such as t-butoxycarbonyl and benzyloxycarbonyl, for example, the compound is treated with a suitable base in a suitable solvent for deprotection.

[0121] Suitable base includes, for example, inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and calcium carbonate; and organic bases such as alkoxides (e.g., sodium methoxide, sodium ethoxide and potassium t-butoxide), ammonia, methylamine, ethylamine, dimethylamine and diethylamine, with preference given to inorganic base, particularly potassium hydroxide.

[0122] Suitable solvent includes, for example, alcohol solvents such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and t-butyl alcohol; hydrocarbon solvents such as benzene, toluene, hexane and xylene; ether solvents such as diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and diglyme; polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and water; and mixed solvents thereof. Preferred is a mixed solvent of alcohol solvent and water, and more preferred is a mixed solvent of isopropyl alcohol and water.

[0123] The reaction temperature is suitably 0-100°C and preferably 50-80°C. The reaction time is preferably 5 to 20 hours.

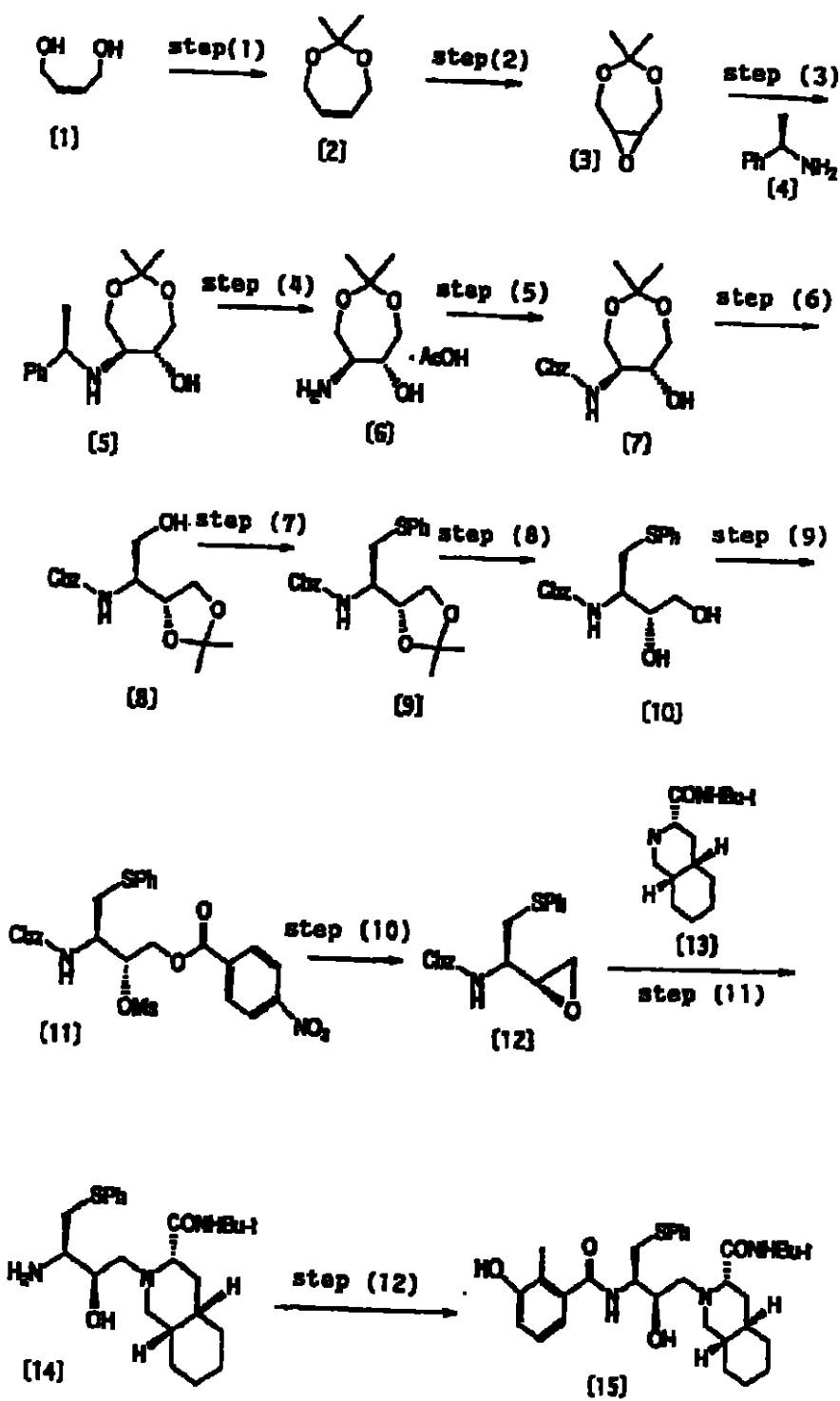
Step (12) : Modification of amino

[0124] This step comprises acylating the amino group of compound [XIV] or an enantiomer thereof with a desirable acylating agent in a suitable solvent in the presence of a base and, where necessary, removing the protecting group on R^5 to give compound [XV] or an enantiomer thereof.

[0125] Suitable base includes, for example, organic bases such as pyridine, lutidine, picoline, triethylamine, diisopropylethylamine, dimethylaminopyridine, DBU and DBN; and inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, sodium carbonate and potassium carbonate, with preference given to inorganic base, particularly sodium hydrogencarbonate.

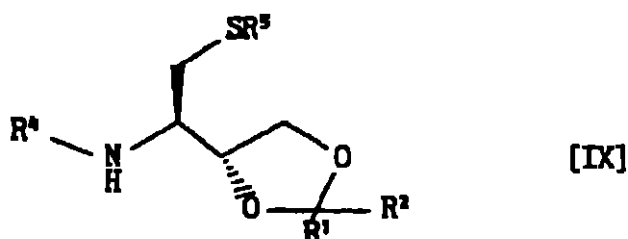
[0126] The acylating agent may be any as long as it reacts with primary amino, and is exemplified by optionally substituted alkylcarboxylic anhydrides such as acetic anhydride and pivalic anhydride; optionally substituted arylcarboxylic anhydrides such as benzoic anhydride and toluic anhydride; optionally substituted alkylcarbonyl chlorides such as acetyl chloride and pivaloyl chloride; optionally substituted arylcarbonyl chlorides such as benzoyl chloride and toluoyl chloride; optionally substituted heteroarylcarboxylic anhydrides and optionally substituted heteroarylcarbonyl chlorides; optionally substituted aralkylcarboxylic anhydrides and optionally substituted aralkylcarbonyl chlorides; optionally substituted heteroarylalkylcarboxylic anhydrides and optionally substituted heteroarylalkylcarbonyl chlorides; and the like. In addition, an acid chloride having a protecting group, such as 3-acetoxy-2-methylbenzoyl chloride can be used.

[0127] Suitable solvent is appropriately selected according to the kind of the base to be used. Examples thereof include alcohol solvents such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and t-butyl alcohol; hydrocarbon solvents such as benzene, toluene, hexane and xylene; ether solvents such as diethyl ether, 1,2-



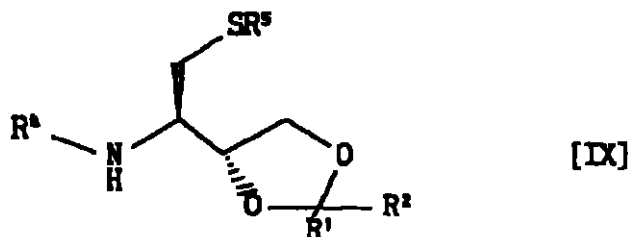
wherein Ph is phenyl, Ac is acetyl, Cbz is benzyloxycarbonyl, Ms is methanesulfonyl and Bu-t is t-butyl.

28
195

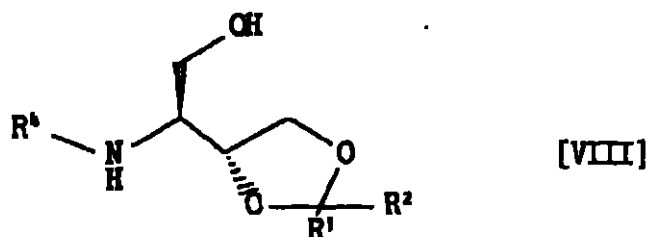


15 wherein R^1 and R^2 are the same or different and each is a hydrogen atom, an alkyl or an aryl, or R^1 and R^2 combinedly form a cycloalkyl ring together with the adjacent carbon atom, R^4 is an amino-protecting group and R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, an enantiomer thereof or a salt thereof.

6. A method for producing a 1,3-dioxolan-4-yl-ethylthio derivative of the formula [IX]



30 wherein R^1 and R^2 are the same or different and each is a hydrogen atom, an alkyl or an aryl, or R^1 and R^2 combinedly form a cycloalkyl ring together with the adjacent carbon atom, R^4 is an amino-protecting group and R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, or an enantiomer thereof, comprising reacting a 1,3-dioxolan-4-yl-ethanol derivative of the formula [VIII]



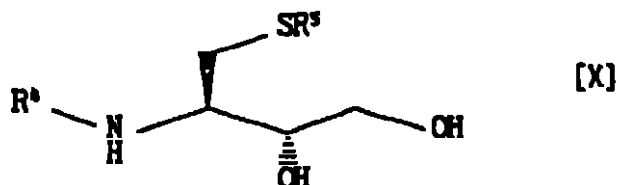
45 wherein R^1 , R^2 and R^4 are as defined above, or an enantiomer thereof, with a halogenating agent or a sulfonylating agent, and reacting the obtained compound with a mercaptan of the formula



55 wherein R^5 is as defined above, for thioetherification.

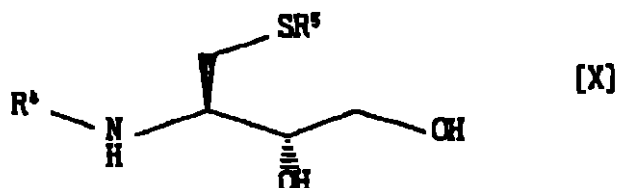
7. A 3-substituted aminobutane-1,2-diol derivative of the formula [X]

27
196

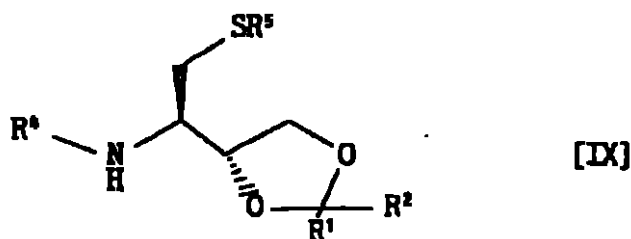


wherein R^4 is an amino-protecting group and R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, an enantiomer thereof or a salt thereof.

8. A method for producing a 3-substituted aminobutane-1,2-diol derivative of the formula [X]

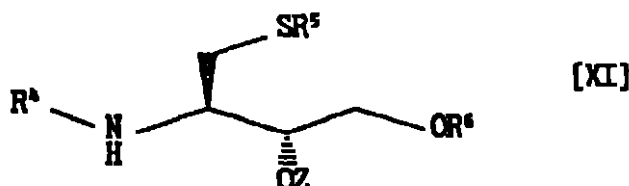


wherein R^4 is an amino-protecting group and R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, or an enantiomer thereof, comprising hydrolyzing a 1,3-dioxolan-4-yl-ethylthio derivative of the formula [IX]



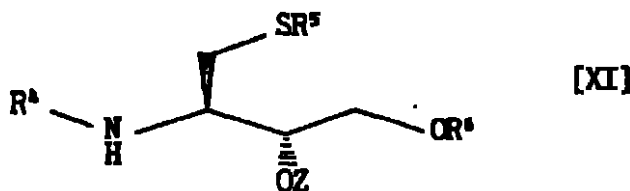
wherein R^1 and R^2 are the same or different and each is a hydrogen atom, an alkyl or an aryl, or R^1 and R^2 combinedly form a cycloalkyl ring together with the adjacent carbon atom, and R^4 and R^5 are as defined above, or an enantiomer thereof in the presence of an acid.

9. A 3-substituted aminobutane derivative of the formula [XI]



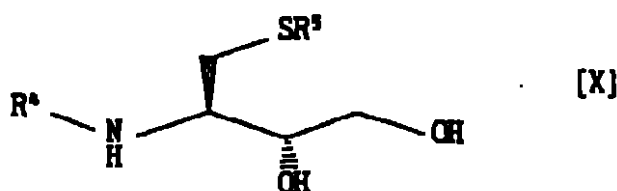
wherein R^4 is an amino-protecting group, R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, R^6 is a hydroxy-protecting group and Z is a substituent which functions as a leaving group with an oxygen atom, an enantiomer thereof or a salt thereof.

10. A method for producing a 3-substituted aminobutane derivative of the formula [XI]



wherein R^4 is an amino-protecting group, R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, R^6 is a hydroxy-protecting group and Z is a substituent which functions as a leaving group with an oxygen atom, or an enantiomer thereof, comprising protecting a primary hydroxy of a 3-substituted aminobutane-1,2-diol derivative of the formula [X]

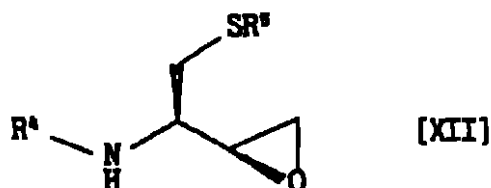
15



wherein R^4 and R^5 are as defined above, or an enantiomer thereof, and, with or without isolating the obtained compound, converting a secondary hydroxy to a leaving group.

11. A substituted 1-butene oxide derivative of the formula [XII]

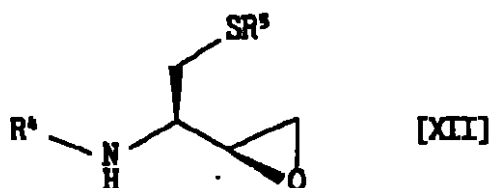
30



wherein R^4 is an amino-protecting group and R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, an enantiomer thereof or a salt thereof.

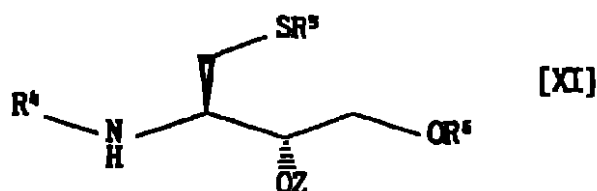
12. A method for producing a substituted 1-butene oxide derivative of the formula [XII]

45



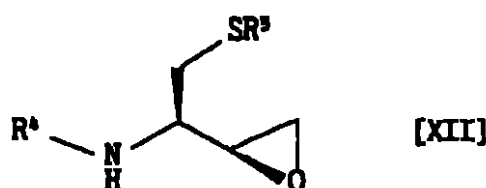
wherein R^4 is an amino-protecting group, and R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, or an enantiomer thereof, comprising treating a 3-substituted aminobutane derivative of the formula [XI]

27
199

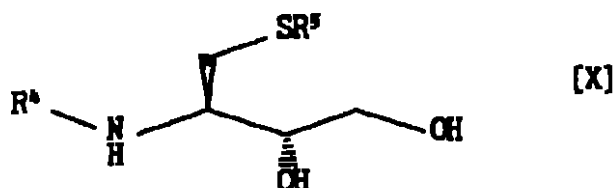


wherein R^4 and R^5 are as defined above, R^6 is a hydroxy-protecting group and Z is a substituent which functions as a leaving group with an oxygen atom, or an enantiomer thereof, in the presence of a base, and simultaneously conducting epoxidation and deprotection of primary hydroxy.

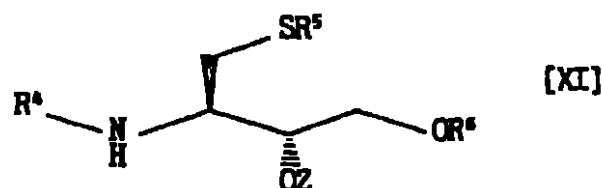
13. A method for producing a substituted 1-butene oxide derivative of the formula [XII]



wherein R^4 is an amino-protecting group and R^5 is a hydrogen atom, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted aryl or an optionally substituted aralkyl, or an enantiomer thereof, comprising protecting a primary hydroxy of a 3-substituted aminobutane-1,2-diol derivative of the formula [X]



wherein R^4 and R^5 are as defined above, or an enantiomer thereof, converting, with or without isolating the obtained compound, a secondary hydroxy to a leaving group to give a 3-substituted aminobutane



derivative of the formula [XI] wherein R^4 and R^5 are as defined above, R^6 is a hydroxy-protecting group and Z is a substituent which functions as a leaving group with an oxygen atom, or an enantiomer thereof, and treating the obtained compound in the presence of a base to simultaneously conduct epoxidation and deprotection of the primary hydroxy.

14. A method for producing an amide derivative of the formula [XV]



US006372911B1

30
199(12) **United States Patent**
Barta et al.(10) Patent No.: **US 6,372,911 B1**
(45) Date of Patent: **Apr. 16, 2002**(54) **PROCESS FOR PREPARING β -HYDROXYCARBAMATES AND THEIR CONVERSION TO OXAZOLIDINONES**

(75) Inventors: Nancy Barta, Brighton, MI (US); Robert D. Larsen, Bridgewater, NJ (US); Daniel R. Sidler, Whitehouse Station, NJ (US); Steven A. Wellesman, Short Hills, NJ (US)

(73) Assignee: Merck & Co., Inc., Rahway, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(h) by 0 days.

(21) Appl. No.: 09/482,799

(22) Filed: Jan. 13, 2000

Related U.S. Application Data

(60) Provisional application No. 60/119,234, filed on Feb. 9, 1999.

(51) Int. Cl.⁷ C07D 413/12; A61K 31/445

(52) U.S. Cl. 546/208; 514/326

(58) Field of Search 514/326; 506/208

(56) **References Cited****U.S. PATENT DOCUMENTS**5,028,340 A * 7/1991 Gallup 210/753
5,911,840 A * 6/1999 Coyle-Rees**FOREIGN PATENT DOCUMENTS**WO 97/44316 11/1997
WO 97/46516 12/1997
WO 98/57940 * 12/1998**OTHER PUBLICATIONS**

Jonini et al., "2-oxazolidinones as regioselective protection of . . . " Ca 107:6859 (1986).*

Cristiani et al., "Microbial corrosion prevention . . . " CA 129:279455 (1997).*

Smoot et al., "Chemistry a modern course" p.413, (1975).*

G. Li et al., "N-Halocarbamate Salts Lead to More Efficient Catalytic Asymmetric Aminohydroxylation", Angew. Chem. Int. Ed. Engl., 1996, vol. 35, No. 23/24, pp. 2813-2817.

E. Herranz et al., "Osmium-Catalyzed Vicinal Oxyamination of Olefins by N-Chloro-N-metalloxy-carbamates", J. Org. Chem., 1980, vol. 45, pp. 2710-2713.

J. Rudolph et al., "Smaller Substitutes on Nitrogen Facilitate the Osmium-Catalyzed Asymmetric Aminohydroxylation", Angew. Chem. Int. Engl., 1996, vol. 35, No. 23/24, pp. 2810-2812.

G. Li et al., "Catalytic Asymmetric Aminohydroxylation (AA) of Olefins", Angew. Chem. Int. Engl., 1996, vol. 35, No. 4, pp. 451-454.

G. Li et al., "Catalytic Asymmetric Aminohydroxylation Provides a Short Taxol Side-chain Synthesis", ACTA Chemica Scandinavica 1996, vol. 50, pp. 649-651.

M. Bruncko et al., "N-Bromoacetylamine—A New Nitrogen Source for the Catalytic Asymmetric Aminohydroxylation of Olefins", Angew. Chem. Int. Ed. Engl., 1997, vol. 36, No. 13/14, pp. 1483-1486.

O. Reiser, "The Sharpless Asymmetric Aminohydroxylation of Olefins", Angew. Chem. Int. Ed. Engl., 1996, vol. 35, No. 12, pp. 1308-1309.

R. Angelaud et al., "Asymmetric Amino-Hydroxylation of Dienylsilanes. An Efficient Route to Amino-Cyclitols", Tetrahedron Letters, 1997, vol. 38, No. 8, pp. 1407-1410.

H. C. Kolb et al., "Asymmetric Dihydroxylation", Transition Metals for Organic Synthesis, 1998, vol. 2, pp. 219-242.

B. Tao et al., "Reversal of Regioselection in the Asymmetric Aminohydroxylation of Cinnamates", Tetrahedron Letters, 1998, vol. 39, pp. 2507-2510.

K. L. Reddy et al., "N-Chloro-N-Sodio-2-(Trimethylsilyl) Ethyl Carbamate: A New Nitrogen Source for the Catalytic Asymmetric Aminohydroxylation", Tetrahedron Letters, 1998, vol. 39, pp. 3667-3670.

K. L. Reddy et al., "From Styrenes to Enantiopure Alpha Arylglycines in Two Steps", J. Amer. Chem. Soc., 1998, vol. 120, pp. 1217-1217.

D. J. Ager et al., "1,2-Amino Alcohols and Their Heterocyclic Derivatives as Chiral Auxiliaries in Asymmetric Synthesis", Chem. Rev., 1996, vol. 96, pp. 835-875.

G. Li et al., "New Synthesis of Evans chiral oxazolidinones by using Sharpless AA reaction", J. Chem. Soc., 1998, Perkin Trans. vol. 1, pp. 1753-1754.

M. E. Dyen et al., "2-Oxazolidinones", Chem. Rev., 1967, vol. 67, pp. 197-246.

H. C. Kolb et al., "Asymmetric Aminohydroxylation", Transition Metals for Organic Synthesis, 1998 vol. 2, pp. 243-260.

* cited by examiner

Primary Examiner—Coila Chang

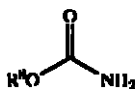
(74) Attorney, Agent, or Firm—Barbel R. Brown; Catherine D. Fitch; Kenneth R. Walton

(57) **ABSTRACT**

A process for preparing a β -hydroxy carbamate product is disclosed. The process comprises reacting an olefin compound containing at least one carbon-carbon double bond with a carbamate in an aqueous solvent and in the presence of a base, an osmium catalyst, a co-oxidant selected from a halohydrantoin, a haloisocyanuric acid, and an alkali metal salt of a haloisocyanuric acid, and optionally an asymmetric ligand, to form a reaction mixture containing the β -hydroxy carbamate product. The process optionally further comprises treating the β -hydroxy carbamate product with additional base to form an oxazolidinone. The oxazolidinones are useful as chiral auxiliary agents and as intermediates for the formation of pharmaceutically active substances such as alpha 1 a adrenergic receptor antagonists. A process for preparing nitrogen-functionalized derivatives of the oxazolidinones is also disclosed.

38 Claims, No Drawings

35



(IV)

wherein R^4 is selected from C_1-C_{20} hydrocarbyl and substituted C_1-C_{20} hydrocarbyl.

8. The process according to claim 1, wherein the base is selected from alkali metal hydroxides and alkali metal carbonates.

9. The process according to claim 1, wherein the asymmetric ligand is selected from $(DHQD)_2PHAL$, $(DHQD)_2PIAL$, $(DHQD)_2AQN$, and $(DHQD)_2AQN$.

10. The process according to claim 1, wherein the osmium catalyst is $K_2[OsO_2(OH)_4]$.

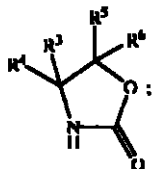
11. The process according to claim 1, wherein the co-oxidant is selected from 1,3-dichloro-5,5-dimethylhydantoin, 1,3-dibromo-5,5-dimethylhydantoin, 1-bromo-3-chloro-5,5-dimethylhydantoin, 3-bromo-1-chloro-5,5-dimethylhydantoin, 1,3-dichloro-5-methyl-5-isopropylhydantoin, trichloroisocyanuric acid, dichloroisocyanuric acid, and sodium dichloroisocyanurate.

12. The process according to claim 1, further comprising treating the reaction mixture with additional base to form at least one oxazolidinone.

13. The process according to claim 12, further comprising recovering the oxazolidinone from the reaction mixture.

14. The process according to claim 13, further comprising treating the recovered oxazolidinone with a deprotonation agent; contacting the treated oxazolidinone with a formylating agent to provide a formulated intermediate; and then contacting the formulated intermediate with a primary or secondary amine to obtain a coupled amine product.

15. The process according to claim 4, further comprising treating the reaction mixture with additional base to form an oxazolidinone of Formula (V):



(V)

wherein R^3 , R^4 , R^5 and R^6 are as heretofore defined, except that when R^3 and R^5 together with the carbon atoms to which they are attached form a 5- to 10-membered monocyclic or bicyclic carbocyclic ring system, the ring system is saturated or unsaturated.

16. The process according to claim 15, further comprising recovering the oxazolidinone from the reaction mixture.

17. The process according to claim 16, wherein the additional base used to form the oxazolidinone is an alkali metal carbonate and recovering comprises acidifying the reaction mixture, neutralizing the acidified mixture with base, and extracting the oxazolidinone with organic solvent.

18. The process according to claim 1, wherein the olefin compound is characterized by the absence of a C_2 axis of symmetry parallel to the double bond, the reaction mixture includes the asymmetric ligand, and the product is an asymmetric β -hydroxy carbamate.

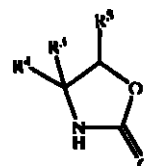
19. The process according to claim 18, further comprising treating the reaction mixture with additional base to form an asymmetric oxazolidinone, and recovering the asymmetric oxazolidinone.

36

20. The process according to claim 19, wherein the additional base used to form the asymmetric oxazolidinone is an alkali metal carbonate and recovering comprises acidifying the reaction mixture, neutralizing the acidified mixture with base, and extracting the oxazolidinone with organic solvent.

21. The process according to claim 19, further comprising treating the recovered oxazolidinone with a deprotonation agent; then contacting the treated oxazolidinone with a formylating agent to provide a formulated intermediate; and then contacting the formulated intermediate with a primary or secondary amine to obtain a coupled amine product.

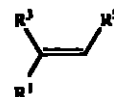
22. A process for preparing an asymmetric oxazolidinone of Formula (V-1):



(V-1)

which comprises:

(A) reacting an olefin compound of formula (VI):



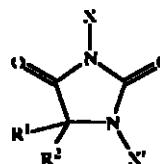
(VI)

in aqueous solvent in the presence of a base, an osmium catalyst, an asymmetric ligand, and a co-oxidant to form a reaction mixture containing an asymmetric β -hydroxy carbamate product; and

(B) contacting the reaction mixture with additional base to form the oxazolidinone;

wherein the co-oxidant employed in (A) is

(1) a hydantoin is of Formula (Ia):



(Ia)

wherein X and X' are each independently H, Cl, or Br, and at least one of X and X' is Cl or Br; R^1 and R^2 are each independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{20} alkylcycloalkyl, and C_1-C_{20} cycloalkyl-alkyl; or

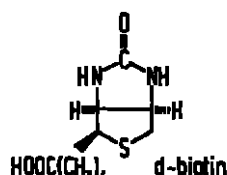
A Total Synthesis of Biotin Based on the Stereoselective Alkylation of Sulfoxides¹

Solange Lavielle, Sonia Bory, Bernard Moreau, M. Jacqueline Luche, and Andrée Marquet*

Contribution from C.N.R.S.-C.E.R.C.O.A., 94320 Thiais, France. Received July 29, 1977

Abstract: A total synthesis of biotin, based on the stereoselective alkylation of sulfoxides, has been achieved. An intermediate sulfide, with the biotin bicyclic moiety, is first prepared. Oxidation of this sulfide with NaIO_4 yields 90% of the isomer with the sulfoxide *cis* to the junction hydrogens. The α carbanion, generated by CH_3Li in a HMPA-THF or HMPA-diglyme mixture, is then alkylated by *tert*-butyl ω -iodovalerate. The reaction is highly stereoselective and a single isomer, with the side chain *trans* to the $\text{S}=\text{O}$ bond, is obtained with a 80% yield. The choice of the base and solvent is crucial for the alkylation yield. With BuLi a reaction at sulfur is taking place. Without HMPA, the reprotonation of the intermediate carbanion competes strongly with alkylation. After reduction of the sulfoxide and removal of the nitrogen protecting groups, *d*-biotin is obtained. This synthesis is very versatile for the preparation of biotin analogues since different substituents can be introduced by alkylating the same key intermediate sulfoxide. This is illustrated by the preparation of the two isomeric 5-methylbiotins.

Biotin total synthesis has recently been the subject of a renewed interest and several new syntheses, involving very different strategies, have been reported.²



The synthesis that we have achieved takes advantage of the high stereoselectivity of the alkylation of sulfoxides.^{3,4} We have already shown in previous studies that the methylation of six-membered cyclic sulfoxides occurs exclusively axially in axial sulfoxides and more than 90% equatorially in their equatorial isomers, thus always *trans* to the $\text{S}=\text{O}$ bond.⁴

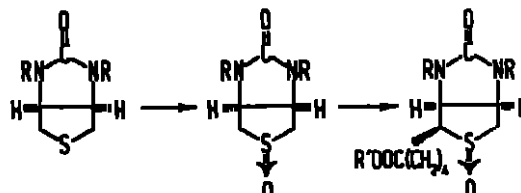
Assuming that this empirical rule was valid for five-membered rings, which proved to be true, we designed a simple route, summarized in Scheme I, for the preparation of *d*-biotin.

One of the advantages of this route is its versatility for the preparation of biotin analogues differing in the side chain and/or possessing an α' substituent. It should provide an easy access to many biotin derivatives, including functionalized ones, very useful for the affinity labeling of biotin enzymes.

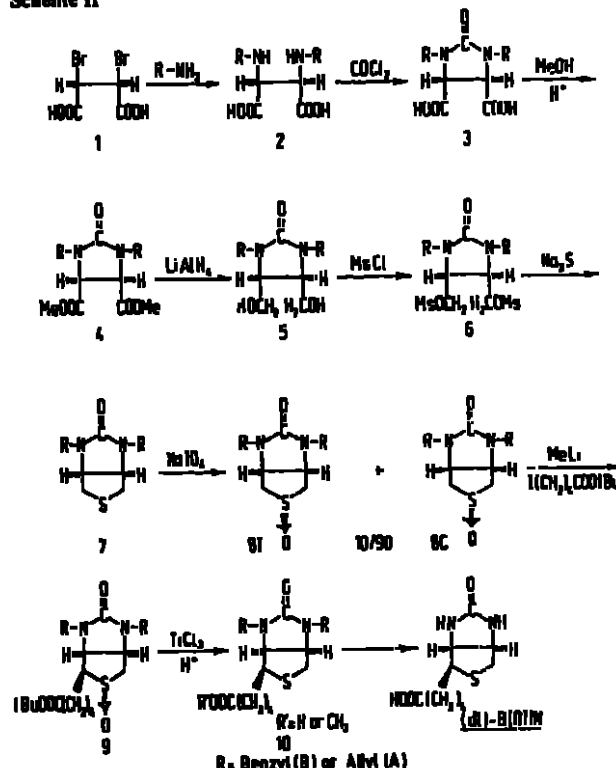
Synthesis of the Key Intermediate Sulfoxide 8C. The reaction sequence is depicted in Scheme II. The imidazolidone nitrogens had to be protected at least for the sulfoxide alkylation. We chose to introduce the protecting group at the beginning since the free NH derivatives are highly insoluble in most organic solvents. This group had to be stable to lithium aluminum hydride reduction and butyllithium treatment. The benzyl group, which fulfills these conditions, was first selected but the final debenzilation requires a very drastic acidic treatment. Therefore it must be avoided for compounds bearing acid-sensitive functions. The use of the allyl group, which can be cleaved under mild conditions, was then explored and the reactions are described in both series: R = B (benzyl) or A (allyl).

meso-Dibromosuccinic acid (1) was treated with allyl- or benzylamine to produce 2, which was next cyclized to the diacid 3 by reaction with phosgene.⁵ The corresponding diester 4 was then reduced by lithium aluminum hydride giving the alcohol 5 which was mesylated. The dimesylate 6 was cyclized with sodium sulfide into the key intermediate sulfide 7. All these reactions are practically quantitative except one, the reduction of the diester 4A.⁶

Scheme I



Scheme II



Oxidation of this sulfide 7 yielded a mixture of the two sulfoxides 8C and 8T. It is well known, since the classical work of Johnson,⁷ that the oxidation stereochemistry of sulfides generally depends on the nature of the oxidizing agents. So in the hope of increasing the selectivity, we attempted different oxidation methods using sulfide 7B (Table I).

The Journal of Organic Chemistry

VOLUME 54, NUMBER 3

FEBRUARY 3, 1989

© Copyright 1989 by the American Chemical Society

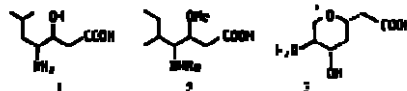
Communications

New Diastereoselective Synthesis of Oxazolidin-2-ones through Carbon-Carbon Bond Formation on Cyclic Carbamoyloxy Radicals

Summary: Photoinitiated radical alkylation by using 5-(phenylthio)oxazolidin-2-ones, derived from (*S*)- α -amino acids, afforded the corresponding *trans* 4,5-disubstituted oxazolidin-2-ones with high diastereoselectivity. As an application of this C-C bond formation on the cyclic carbamoyloxy radical species, (3*S*,4*S*)-statine was effectively synthesized.

Sir: Development of methods for stereocontrolled synthesis of biologically important compounds containing the 2-amino alcohol moiety such as amino sugars¹ and unusual amino acids² continues to receive significant attention. Among various procedures, selective heterofunctionalization of acyclic olefinic systems to yield 4,5-disubstituted oxazolidin-2-ones, a protected form of 2-amino alcohols, has been widely investigated in recent years.³ Direct stereoselective alkylation of an oxazolidinone at the 5-position provides a new, convergent methodology for the synthesis of 2-amino alcohols.⁴ In this paper, we disclose a new and highly diastereoselective synthesis of 4,5-*trans*-4-substituted-5-allyloxazolidin-2-ones and thus valuable for the preparation of biologically important unusual amino acids having the 2-amino alcohol moiety such as statine (1),^{5a,b} dolaisoleucine (2) in dolastatin 10,⁶

and galantinic acid (3) in galantin 1.⁷ Our synthesis involves a highly diastereoselective carbon-carbon bond formation using a novel cyclic carbamoyloxy radical⁸ generated from 5-(phenylthio)oxazolidin-2-one possesses major advantages for the synthesis of 2-amino alcohols from α -amino acids, since it does not involve α -amino aldehydes, which are prone to racemization.



Our initial effort was focused on examining the feasibility and efficiency of the sulfonium ion induced cyclo-carbamation. (*S*)-*N*-Cbz- or (*S*)-*N*-Boc-amino alcohols 4a-j⁹ were easily converted to the sulfides 5a-j^{10,11} in 80-95% yield by the conventional method (diphenyl disulfide, *n*-Bu₃P, THF, or DMF, room temperature).¹²

(1) (a) Arcamone, F.; Cassinelli, G.; Orzari, P.; Franceschi, G.; Mendell, R. *J. Am. Chem. Soc.* 1984, 106, 5335. (b) Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett.* 1988, 1007.

(2) (a) Umemura, H.; Aoyagi, T.; Morishima, H.; Matsunaka, M.; Hamada, M.; Takouchi, T. *J. Antibiot.* 1970, 23, 258. (b) Nakamura, H.; Suda, H.; Takita, T.; Aoyagi, T.; Umemura, H. *J. Antibiot.* 1978, 29, 102. (c) Rich, D. H. *J. Med. Chem.* 1985, 28, 263.

(3) (a) Kobayashi, S.; Isebe, T.; Ohno, M. *Tetrahedron Lett.* 1984, 25, 1079. (b) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* 1988, 110, 1797. (c) Roush, W.; Adams, M. A. *J. Org. Chem.* 1985, 50, 3782. (d) Hirama, M.; Shigemoto, T.; Ito, S. *J. Org. Chem.* 1987, 52, 3342. (e) Trout, B. M.; Sudhaker, A. R. *J. Am. Chem. Soc.* 1987, 109, 5782.

(4) (a) Fujita, M.; Miyama, T. *J. Am. Chem. Soc.* 1984, 106, 4428. (b) Hasegawa, S.; Klose, J. *Tetrahedron Lett.* 1985, 26, 1281. (c) Mukahama, T.; Goto, Y.; Shoda, S. *Chem. Lett.* 1988, 871. (d) Claremont, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* 1988, 110, 8285. (e) Kano, R.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Lett.* 1987, 1831.

(5) Recent publication on a synthesis of statine: (a) Wou, P. W. K. *Tetrahedron Lett.* 1983, 24, 2973. (b) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* 1987, 311. (c) Juola, P.; Poncet, J.; Pontaroni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1*, 1988, 1805. (d) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* 1987, 28, 3887. (e) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* 1988, 53, 3885 and references cited therein.

(6) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuiman, A. A.; Postner, F. E.; Klu, H.; Tomer, K. B.; Bontemps, H. *J. Am. Chem. Soc.* 1987, 109, 6882. Relative and absolute configuration of 2 was not verified.

(7) (a) Shoji, R.; Sakurai, R.; Wakimaka, Y.; Kozumi, K.; Mayama, M.; Matsura, J. *Antibiot.* 1975, 28, 123. (b) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* 1984, 25, 1587.

(8) Reviews on radicals: Glaze, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Organic Chemistry Series*, Bakwin, J. E., Ed.; Pergamon Press: Oxford, 1988; Vol. 5, p 281.

(9) Compounds 4a-j were easily available from L-amino acids. For 4h: Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* 1984, 24, 1071.

(10) All new compounds were fully characterized by spectroscopic analyses (IR, NMR, MS) and gave satisfactory high-resolution MS and/or satisfactory microanalyses.

(11) Selected physical data for 5 are as follows. 5a: mp 47-49 °C; [α]_D +13.8° (c 0.99, CHCl₃). 5b: mp 82-84 °C; [α]_D +28.3° (c 1.01, CHCl₃). 5c: oil; [α]_D -9.5° (c 1.4, CHCl₃). 5d: mp 80-83 °C; [α]_D +28.3° (c 0.99, CHCl₃). 5e: mp 80-81 °C; [α]_D +23.1° (c 0.97, CHCl₃). 5f: mp 59-62 °C; [α]_D +29.8° (c 0.81, CHCl₃). 5g: mp 49-51 °C; [α]_D +35.5° (c 0.9, CHCl₃). 5h: oil; [α]_D -4.1° (c 0.68, CHCl₃). 5i: mp 54-56 °C; [α]_D -5.6° (c 2.14, CHCl₃). 5j: oil; [α]_D +18.5° (c 0.9, CHCl₃).

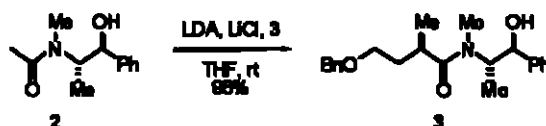
(12) Nakagawa, T.; Hata, T. *Tetrahedron Lett.* 1978, 1409.

Total Synthesis of (+)-Kalkitoxin

James D. White* Chang-Sun Lee, and Qing Xu

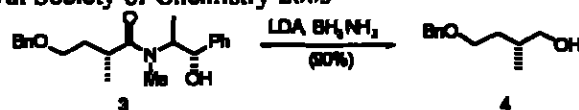
Department of Chemistry, Oregon State University, Corvallis, OR 97331-4003

- *Experimental procedure*
- *Characterization data*
- *X-ray crystallographic data for 8*

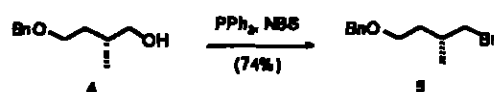


LiCl (2.16 g, 54.8 mmol) was placed in a 100 mL round-bottomed flask which was flame-dried under argon. To the flask were added dry THF (8 mL) at -78°C , diisopropylamine (2.24 mL, 16 mmol), and *n*-BuLi (7.6 mL, 15.2 mmol, 2.0 M hexane solution). The suspension was stirred for 10 min at -78°C and for 15 min at 0°C , and then was cooled to -78°C . To the suspension was slowly added a THF (8 mL) solution of **2** (1.91 g, 8.64 mmol) by cannula, and the mixture was stirred for 1 h at -78°C , for 15 min at 0°C , and for 5 min at ambient temperature. The mixture was cooled to 0°C , a THF (4 mL) solution of benzyl 2-iodoethyl ether (1.15 g, 4.4 mmol) was added, and the mixture was stirred for 15 h at ambient temperature. The reaction was quenched with sat'd aqueous NH_4Cl , and the solution was extracted with EtOAc (200 mL $\times$ 2). The combined extract was washed with aqueous NH_4Cl and brine, dried over MgSO_4 , and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (40 to 60% EtOAc/hexanes) to give 1.39 g (98%) of **3** as a colorless oil: $[\alpha]_D^{24} +52.8$ (*c* 0.8, CHCl_3); ^1H NMR (7:3 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, CDCl_3) δ 7.29 (m, 10H), 4.78–4.40 (m, 4H), 4.12* (m, 1H), 3.68* (m, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 3.29 (m, 1H), 3.21* (m, 1H), 2.88 (m, 1H), 2.83 (s, 3H), 2.81* (s, 3H), 2.25* (m, 1H), 1.93 (m, 1H), 1.68* (m, 1H), 1.65 (m, 1H), 1.1 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.1, 176.9*, 142.4, 141.4*, 138.1, 128.3*, 128.1, 128.0*, 127.8, 127.5, 127.4*, 127.3, 127.2*, 126.7, 126.1*, 75.8, 75.0*, 72.6, 68.2*, 67.7, 57.9, 33.8, 32.8, 32.3*, 26.6*, 18.1*, 17.1, 15.5*, 14.1; IR (neat) 3386, 2968, 2932, 2869, 1618, 1454, 1089 cm^{-1} ; MS (CI) m/z 356 ($\text{M}+\text{H}^+$), 338, 279, 248, 191, 148, 121, 91; HRMS (CI) m/z 356.2224 ($\text{M}+\text{H}^+$) (calcd for $\text{C}_{22}\text{H}_{30}\text{O}_3\text{N}$: 356.2226)

35
201

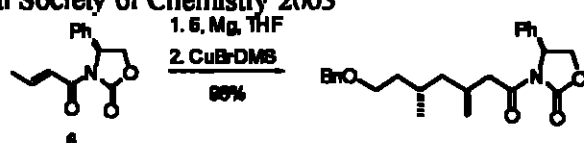


(2R)-4-Benzyloxy-2-methylbutanol. To a solution of diisopropylamine (8.45 mL, 60.3 mmol) in THF (80 mL) was added *n*-BuLi (2.1M, 28.7 mL, 60.3mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 20 min. Borane-ammonia complex (90%, 1.90 g, 61.5 mmol) was added in one portion, the suspension was stirred at 0 °C for 20 min, and was warmed to room temperature. After 15 min, the suspension was cooled to 0 °C and a solution of 3 (4.28 g, 12.06 mmol) in THF (12 mL) was added via cannula. The mixture was warmed to room temperature during 10 min, held at that temperature for 2.5 h, and then cooled to 0 °C. A 3N HCl solution was added slowly to quench the excess hydride, and the biphasic solution was stirred for 30 min at 0 °C and for 15 min at room temperature, and then separated. The aqueous layer was extracted with Et₂O and the extract was washed with brine, dried, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 2:1) gave 4 as a colorless oil (2.11g, 90%): $[\alpha]_D^{20} +10.4$ (c 7.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.38 (m, 5H), 4.51 (s, 2H), 3.38-3.62 (m, 4H), 2.94 (br, 1H), 1.66-1.83 (m, 2H), 1.49-1.59 (m, 1H), 0.92 (d, 3H, *J* = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 137.9, 128.3, 127.6, 127.5, 72.9, 68.5, 67.8, 33.8, 17.0; IR (neat) 3404, 2926, 2869, 1454, 1097 cm⁻¹; HRMS (CI, M⁺) calcd for C₁₂H₁₈O₂ *m/z* 194.1307, found *m/z* 194.1303.

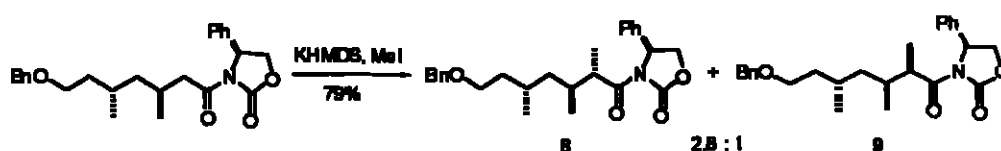


(2R)-4-Benzyloxy-1-bromo-2-methylbutane. To a solution of 4 (0.25 g, 1.31 mmol) in CH₂Cl₂ (2 mL) was added PPh₃ (0.24g, 1.37 mmol) and NBS (0.36 g, 1.37 mmol) at room temperature. The solution was stirred for 10 min and concentrated under vacuum. The crude product was treated with hexane and filtered, the filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 20:1) to yield 5 as a colorless oil (0.25 g, 74%): $[\alpha]_D^{20} -4.7$ (c 0.32, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.29- 7.42 (m, 5H), 4.54 (s, 2H), 3.57 (dt, *J* = 3.3, 0.1 Hz, 2H), 3.47 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.40 (dd, *J* = 9.9, 5.7 Hz, 1H), 2.03-2.11 (m, 1H), 1.83 (ddd, *J* = 12.9, 12.9, 6.3 Hz, 1H), 1.59 (ddd, *J* = 13.8, 13.8, 6.3 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.9, 128.8, 128.0, 73.4, 68.3, 42.0, 35.1, 32.6, 19.2; IR (film) 2961, 2858, 1454 cm⁻¹; HRMS (FAB, M⁺+H) calcd for C₁₂H₁₈OBr *m/z* 259.0521, found *m/z* 259.0532.

Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2003



(4*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-3',5'-dimethylheptanoyl)-4-phenyloxazolidin-2-one. To a suspension of magnesium (0.52 g, 21.4 mmol) in THF (10 mL) was added dibromoethane (0.0384 mL, 0.44 mmol), and the mixture was heated to reflux for 10 min and then cooled to room temperature. A solution of **5** (2.29 g, 8.91 mmol) in THF (2 mL) was added via syringe, and the mixture was heated at reflux for 20 min then cooled and added to a solution of CuBr.DMS (1.83 g, 8.91 mmol) in THF (8 mL) at -78°C . The resulting suspension was warmed to -20°C , stirred for 25 min. and cooled to -78°C . 3-(2'-butenoyl)-4-phenyloxazolidin-2-one (0.68 g, 2.94 mmol) in THF (6 mL) was added dropwise, and the dark brown suspension was stirred for 2.5 h at -78°C , then slowly warmed to -30°C during 45 min. The reaction was quenched with saturated NH_4Cl , and extracted with Et_2O , and the organic extract was washed with brine, dried over MgSO_4 , and concentrated. Purification of the residue by flash column chromatography (hexanes/ethyl acetate, 3:1) gave (4*S*,3'*S*,5'*S*)-3-(7'-benzyloxy-3',5'-dimethylheptanoyl)-4-phenyloxazolidin-2-one as a colorless oil (1.16 g, 96%): $[\alpha]_{\text{D}}^{20} +20.0$ (*c* 2.30, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.29-7.45 (m, 10H), 5.47 (dd, $J = 8.7, 3.6$ Hz, 1H), 4.71 (t, $J = 8.7$ Hz, 1H), 4.52 (s, 2H), 4.30 (dd, $J = 9.0, 3.9$ Hz, 1H), 3.50 (dt, $J = 7.5, 0.9$ Hz, 2H), 2.96 (dd, $J = 15.9, 5.4$ Hz, 1H), 2.76 (dd, $J = 15.9, 8.1$ Hz, 1H), 2.09-2.22 (m, 1H), 1.66-1.75 (m, 1H), 1.58 (ddd, $J = 12.6, 12.6, 6.6$ Hz, 1H), 1.44 (ddd, $J = 13.2, 13.2, 6.9$ Hz, 1H), 1.22 (ddd, $J = 13.5, 9.6, 4.5$ Hz, 1H), 1.09 (ddd, $J = 13.8, 9.3, 4.8$ Hz, 1H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.1, 153.6, 139.2, 138.6, 129.1, 128.6, 128.3, 127.6, 127.4, 125.9, 72.8, 69.8, 68.4, 57.5, 44.2, 43.2, 37.4, 27.1, 19.1; IR (film) 2925, 1782, 1705 cm^{-1} ; HRMS (FAB, $\text{M}+\text{H}^+$) calcd for $\text{C}_{25}\text{H}_{32}\text{O}_4\text{N}$ m/z 410.2331, found m/z 410.2339.

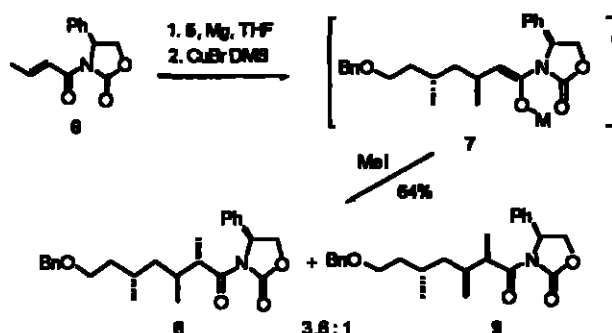


(4*S*,2'*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (8) and (4*S*,2'*R*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (9). To a solution of (4*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-3',5'-dimethylheptanoyl)-4-phenyloxazolidin-2-one (0.93 g, 2.27 mmol) in THF (8.5 mL) was added HMPA (1.58 mL, 9.08 mmol) at -78°C , followed by slow addition of KHMDS (0.5M in toluene, 6.81 mL, 3.40 mmol). The resulting yellow solution was stirred

Supplementary Material (ESI) for Chemical Communications

This journal is © The Royal Society of Chemistry 2003

for 20 min at -78°C , and MeI (0.56 mL, 9.08 mmol) was added dropwise. After stirring for 2 h at -78°C , the solution was quenched with MeOH and diluted with Et_2O , and the solution was washed with saturated NH_4Cl and brine, dried over MgSO_4 , and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 5:1) gave **8** (0.55 g, 58%) and **9** (0.20 g, 21%). **8**: mp $75-76^{\circ}\text{C}$ (from hexanes); $[\alpha]_{\text{D}}^{20} +49.7$ (c 1.65, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.27-7.41 (m, 10H), 5.40 (dd, $J = 8.4, 3.3$ Hz, 1H), 4.62 (t, $J = 8.7$ Hz, 1H), 4.50 (s, 2H), 4.22 (dd, $J = 9.0, 3.3$ Hz, 1H), 3.70 (quin, $J = 7.2$ Hz, 1H), 3.51 (t, $J = 6.6$ Hz, 2H), 1.84-1.92 (m, 1H), 1.46-1.71 (m, 3H), 1.15 (ddd, $J = 10.5, 10.5, 3.6$ Hz, 2H), 1.04 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.2, 153.4, 139.3, 138.6, 129.1, 128.5, 128.3, 127.6, 127.4, 125.6, 72.9, 69.6, 68.4, 57.7, 43.1, 39.6, 37.9, 32.7, 27.0, 18.9, 17.8, 13.6; IR (film) 2925, 1780, 1704 cm^{-1} ; HRMS (FAB, $\text{M}+\text{H}^+$) calcd for $\text{C}_{26}\text{H}_{34}\text{O}_4\text{N}$ m/z 424.2488, found m/z 424.2509. **9**: $[\alpha]_{\text{D}}^{20} -20.6$ (c 1.88, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.26-7.41 (m, 10H), 5.46 (dd, $J = 9.0, 4.5$ Hz, 1H), 4.68 (t, $J = 9.0$ Hz, 1H), 4.51 (s, 2H), 4.28 (dd, $J = 9.0, 4.5$ Hz, 1H), 3.68 (quin, $J = 6.6$ Hz, 1H), 3.48 (t, $J = 6.6$ Hz, 2H), 1.89-1.97 (m, 1H), 1.46-1.62 (m, 2H), 1.36-1.42 (m, 1H), 1.16 (ddd, $J = 13.5, 10.5, 3.6$ Hz, 1H), 1.05 (d, $J = 6.9$ Hz, 3H), 0.83-0.96 (m, 1H), 0.74 (d, $J = 6.3$ Hz, 3H), 0.62 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.0, 153.8, 139.6, 139.1, 129.4, 129.1, 128.8, 128.0, 127.9, 126.8, 73.3, 69.9, 69.0, 58.1, 43.2, 42.9, 38.1, 33.4, 27.6, 19.3, 14.7, 12.3; IR (film) 2926, 1780, 1704 cm^{-1} ; HRMS (FAB, $\text{M}+\text{H}^+$) calcd for $\text{C}_{26}\text{H}_{34}\text{O}_4\text{N}$ m/z 424.2488, found m/z 424.2490.

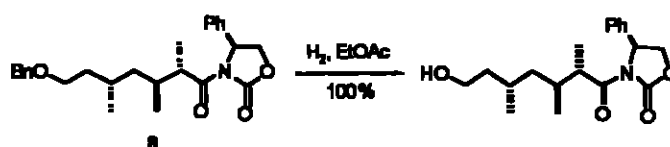


(4*S*,2'*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (**8**) and (4*S*,2'*R*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (**9**) from **5**. To a suspension of magnesium (0.10 g, 4.14 mmol) in THF (2 mL) was added dibromomethane (0.0074 mL, 0.086 mmol), and the mixture was heated at reflux for 10 min, then cooled to room temperature. A solution of **5** (0.443 g, 1.72 mmol) in THF (0.5 mL) was added via syringe, and the mixture was heated

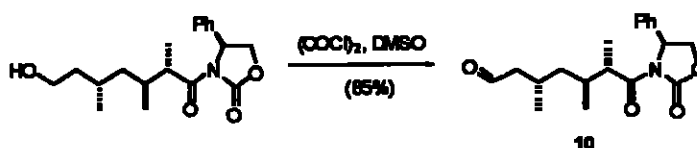
Supplementary Material (ESI) for Chemical Communications

This journal is © The Royal Society of Chemistry 2003

to reflux for 20 min then cooled and added to a solution of CuBr.DMS (0.34 g, 1.72 mmol) in THF (2 mL) at -78°C . The suspension was warmed to -20°C , stirred for 25 min, and cooled to -78°C . A solution of **6** (0.14 g, 0.57 mmol) in THF (1.5 mL) was added dropwise, and the suspension was stirred for 2.5 h at -78°C , then slowly warmed to -30°C during 45 min. The reaction was cooled again to -78°C and MeI (0.54 mL, 8.6 mmol) was added. The mixture was allowed to reach room temperature and was stirred overnight. Saturated NH_4Cl was added to quench the reaction, and the aqueous layer was extracted with Et_2O . The Et_2O extract was washed with brine, dried over MgSO_4 , and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 5:1) afforded **8** (0.117 g, 50%) and **9** (0.038 g, 14%).



(4S,2'S,3'S,5'S)-3-(7'-Hydroxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one. To a solution of **8** (0.753 g, 1.78 mmol) in EtOAc (12 mL) at room temperature was added $\text{Pd}(\text{OH})_2\cdot\text{O}(\text{C}_2\text{H}_5)_2$ (Pearlman's catalyst, 0.116 g), and a balloon containing H_2 was attached to the flask. The mixture was stirred for 2 h, the catalyst was filtered off, and the filtrate was concentrated. Flash column chromatography (hexanes/ethyl acetate, 1:1) of the residue gave a primary alcohol as a pale yellow oil (0.60 g, 100%): $[\alpha]_D^{20} +68.6$ (c 2.50, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.26–7.41 (m, 5H), 5.42 (dd, $J = 8.4, 3.3$ Hz, 1H), 4.66 (t, $J = 8.7$ Hz, 1H), 4.24 (dd, $J = 9.0, 3.3$ Hz, 1H), 3.61–3.73 (m, 3H), 1.83–1.92 (m, 1H), 1.62–1.64 (m, 1H), 1.34–1.55 (m, 3H), 1.09–1.20 (m, 2H), 1.03 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.3, 153.4, 139.2, 129.1, 128.5, 125.6, 69.6, 60.8, 57.7, 43.0, 41.0, 40.0, 32.6, 26.6, 18.8, 17.7, 13.7; IR (film) 3385, 2926, 1779, 1702 cm^{-1} ; HRMS (FAB, $\text{M}+\text{H}^+$) calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4\text{N}$ m/z 334.2018, found m/z 334.2018.

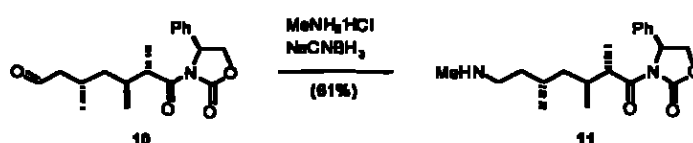


(4S,2'S,3'S,5'S)-3-(7'-Oxo-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (10). To a solution of $(\text{COCl})_2$ (0.261 mL, 3.0 mmol) in CH_2Cl_2 (3 mL) was added a solution of DMSO (0.284 mL, 4.0 mmol) in CH_2Cl_2 (3 mL) at -78°C . After stirring for 15 min, a solution of the alcohol prepared above (0.60 g, 1.78 mmol) in CH_2Cl_2 (8 mL) was added dropwise. The solution was stirred for 15 min

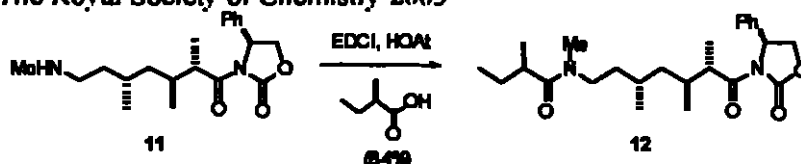
Supplementary Material (ESI) for Chemical Communications

This journal is © The Royal Society of Chemistry 2003

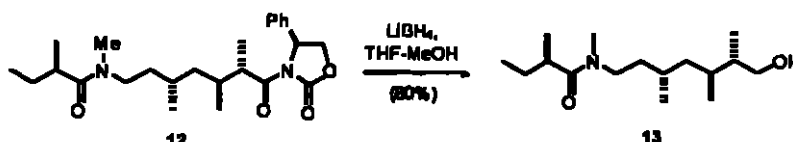
followed by addition of NEt_3 (1.09 mL, 8.0 mmol) in CH_2Cl_2 (4 mL) at -78°C . The mixture was slowly warmed to 0°C during 30 min, and was quenched with saturated NH_4Cl . The aqueous layer was extracted with Et_2O and the extract was washed with brine, dried over MgSO_4 , and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 3:1) gave **10** as a pale yellow oil (0.51 g, 85%): $[\alpha]_D^{20} +69.3$ (*c* 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.74 (t, $J = 2.1$ Hz, 1H), 7.26–7.41 (m, 5H), 5.42 (dd, $J = 8.7, 3.3$ Hz, 1H), 4.67 (t, $J = 9.0$ Hz, 1H), 4.25 (dd, $J = 9.0, 3.6$ Hz, 1H), 3.69 (quin, $J = 6.9$ Hz, 1H), 2.29–2.33 (m, 2H), 2.08–2.19 (m, 1H), 1.84–1.93 (m, 1H), 1.28 (ddd, $J = 13.5, 10.8, 3.0$, 1H), 1.10 (ddd, $J = 14.1, 10.8, 3.6$, 1H), 1.03 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 203.0, 176.6, 153.8, 140.0, 129.6, 129.1, 126.1, 70.1, 58.2, 52.6, 43.5, 40.0, 33.0, 25.8, 19.4, 18.1, 14.2; IR (film) 2964, 2930, 1777, 1721, 1702, 1383 cm^{-1} ; HRMS (FAB, $\text{M}+\text{H}^+$) calcd for $\text{C}_{19}\text{H}_{26}\text{O}_4\text{N}$ m/z 332.1862, found m/z 332.1872.



(4S,2'S,3'S,5'S)-3-(7'-Methylamino-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (11). To a solution of **10** (0.50 g, 1.51 mmol) in MeOH (10 mL) was added $\text{MeNH}_2\cdot\text{HCl}$ (0.204 g, 3.02 mmol), MeNH_2 (2M solution in THF, 2.76 mL, 4.53 mmol) and Na_2SO_4 (0.4 g) at room temperature. The mixture was stirred for 20 min and cooled to 0°C , and a solution of NaCNBH_3 (0.142 g, 2.26 mmol) in MeOH (1.5 mL) was added. The mixture was stirred for 1h, MeOH was removed under vacuum, and the residue was subjected to purification by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 20:1) to give **11** as a viscous oil (0.314 g, 61%): $[\alpha]_D^{20} +52.8$ (*c* 1.70, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.29–7.44 (m, 5H), 5.51 (dd, $J = 8.4, 3.6$ Hz, 1H), 4.76 (t, $J = 8.8$ Hz, 1H), 4.26 (dd, $J = 8.8, 3.6$ Hz, 1H), 3.74 (quin, $J = 6.8$ Hz, 1H), 2.98 (dd, $J = 8.4, 6.0$ Hz, 2H), 2.72 (s, 3H), 1.85–1.95 (m, 1H), 1.60–1.80 (m, 3H), 1.22–1.34 (m, 2H), 1.14–1.16 (m, 1H), 1.08 (d, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 6.4$ Hz, 3H), 0.91 (d, $J = 5.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.7, 154.2, 139.7, 129.6, 129.0, 126.0, 70.4, 58.3, 48.6, 43.4, 39.8, 34.2, 33.9, 33.0, 28.3, 18.8, 17.9, 14.3; IR (film) 2965, 2930, 2333, 2173, 1777, 1703, 1384 cm^{-1} ; HRMS (CI, M^+) calcd for $\text{C}_{20}\text{H}_{30}\text{O}_3\text{N}_2$ m/z 346.2256, found m/z 346.2249.



(2*R*,3'*S*,5'*S*,6'*S*,4''*S*)-2, *N*-Dimethyl-*N*-[3',5',6'-trimethyl-7'-oxo-7'-(2''-oxo-4''-phenyloxazolidin-3-yl)heptyl]butyramide (12). To a solution of 11 (0.314 g, 0.90 mmol) in DMF (4 mL) at 0 °C were added a solution of (*R*)-2-methylbutyric acid (0.183 g, 1.80 mmol) in DMF (5 mL), followed by 1-hydroxy-7-azabenzotriazole (HOAt, 0.245 g, 1.80 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.345 g, 1.80 mmol), and diisopropylethylamine (DIPEA, 0.313 mL, 1.80 mmol). The mixture was kept at room temperature for 12 h, and then diluted with EtOAc. The organic phase was separated and washed with 1N HCl, brine, dried over MgSO₄, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 3:2) gave 12 as pale yellow oil (0.326 g, 84%); $[\alpha]_D^{20}$ +40.0 (*c* 0.50, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.40 (m, 5H), 5.43 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.67 (t, *J* = 8.7 Hz, 1H), 4.25 (dd, *J* = 8.4, 4.2 Hz, 1H, one rotamer), 4.24 (dd, *J* = 8.4, 3.3 Hz, 1H, one rotamer), 3.66-3.72 (m, 1H), 3.37 (ddd, *J* = 10.2, 6.0, 3.6 Hz, 1H), 3.28 (ddd, *J* = 10.4, 6.0, 4.0 Hz, 1H), 3.00 (s, 3H, one rotamer), 2.91 (s, 3H, one rotamer), 2.50-2.63 (m, 1H), 1.81-1.90 (m, 1H), 1.64-1.75 (m, 1H), 1.31-1.48 (m, 3H), 1.01-1.11 (m, 9H), 0.84-0.93 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 176.9, 176.6, 176.5, 153.9, 139.8, 139.6, 129.6, 129.1, 129.0, 126.1, 70.1, 58.2, 48.4, 46.5, 43.5, 40.2, 37.8, 37.7, 37.6, 35.9, 35.6, 34.1, 33.2, 33.0, 28.4, 27.8, 27.5, 19.2, 18.2, 18.0, 17.5, 14.4, 14.1, 12.6, 12.4; IR (film) 2926, 1779, 1704, 1639, 1456 cm⁻¹; HRMS (FAB, M+H⁺) calcd for C₂₅H₃₉O₄N₂ *m/z* 431.2910, found *m/z* 431.2912.

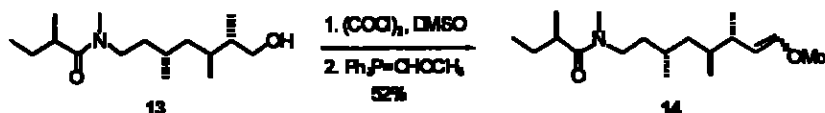


(2*R*,3'*S*,5'*S*,6'*S*)-2, *N*-Dimethyl-*N*-[7'-hydroxy-3',5',6'-trimethylheptyl]butyramide (13). To a solution of 12 (0.084 g, 0.20 mmol) in THF (1.7 mL) was added LiBH₄ (2M solution in THF, 0.30 mL, 0.6 mmol) at 0 °C, followed by MeOH (0.042 mL, 1.04 mmol). The solution was stirred for 40 min at 0 °C and for 10 min at room temperature, and quenched with water. The aqueous layer was extracted with EtOAc and the extract was washed with brine, dried over MgSO₄, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 3:2) gave 13 as a pale yellow oil (0.042 g, 80%); $[\alpha]_D^{20}$ -36.2 (*c* 0.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 3.58-3.62 (m, 1H), 3.25-3.48 (m, 3H), 3.02 (s, 3H, one rotamer), 2.93 (s, 3H, one rotamer), 2.58 (m, 1H), 1.92 (s, 1H), 1.33-1.73 (m, 6H), 1.11 (d, *J*

Supplementary Material (ESI) for Chemical Communications

This journal is © The Royal Society of Chemistry 2003

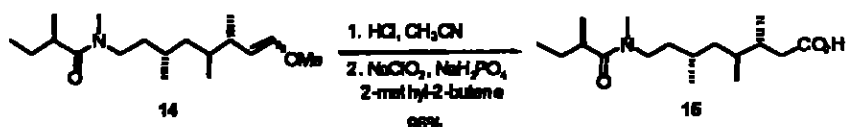
= 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 0.84–0.91 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.0, 176.7, 66.3, 66.2, 48.5, 46.7, 41.5, 41.3, 40.5, 40.2, 37.8, 37.6, 35.7, 35.6, 34.1, 31.8, 31.7, 28.8, 28.6, 27.8, 27.4, 19.6, 19.4, 18.1, 17.5, 17.4, 17.3, 13.8, 13.6, 12.6, 12.4; IR (film) 3419, 2961, 1624, 1458 cm^{-1} ; HRMS (FAB, $\text{M}+\text{H}^+$) calcd for $\text{C}_{16}\text{H}_{34}\text{O}_2\text{N}$ m/z 272.2589, found m/z 272.2605.



(2R,3'S,5'S,6'S)-2, N-Dimethyl-N-[8'-Methoxy-3',5',6'-trimethyloct-7-enyl]butyramide (14).

To a solution of $(\text{COCl})_2$ (0.073 mL, 0.84 mmol) in CH_2Cl_2 (0.8 mL) was added a solution of DMSO (0.079 mL, 1.12 mmol) in CH_2Cl_2 (0.8 mL) at -78°C . The mixture was stirred for 15 min, and a solution of 13 (0.151 g, 0.56 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred for 15 min at -78°C , and a solution of NEt_3 (0.314 mL, 2.24 mmol) in CH_2Cl_2 (0.8 mL) was added. The mixture was warmed to -10°C during 30 min, and the reaction was quenched with saturated NH_4Cl . The aqueous layer was extracted with Et_2O , and the extract was washed with brine, dried over MgSO_4 , and concentrated to give the crude, unstable aldehyde which was used without purification.

To a suspension of (methoxymethyl)triphenylphosphonium chloride (dried under vacuum at 50°C , 0.955 g, 2.80 mmol) in THF (4.5 mL) was added $n\text{-BuLi}$ (1.6 M in hexane, 1.57 mL, 2.52 mmol) at 0°C , and the resulting deep red solution was stirred for 30 min at room temperature. The solution was cooled to -20°C and added to a solution of the crude aldehyde prepared above in THF (2 mL). The mixture was kept at -20°C for 30 min, and then warmed to room temperature. The reaction was quenched with MeOH, diluted with Et_2O , and washed with saturated NH_4Cl and brine, dried over MgSO_4 , and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 5:1) gave 4 as a 1:1 *E/Z* mixture (0.086 g, 52% from 13).

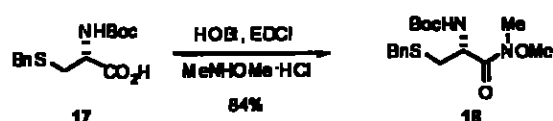


(2'R,3R,4S,6S)-3,4,6-Trimethyl-8-[methyl-2'-(methylbutyryl)amino]octanoic acid (15). To a solution of 14 (0.086 g, 0.29 mmol) in CH_3CN (2.1 mL) was added 1N HCl (0.7 mL) at room temperature. After stirring for 1 h, the solution was diluted with Et_2O , washed with brine, dried over MgSO_4 , and concentrated to give the crude aldehyde. To a solution of this aldehyde in MeOH (10 mL) was added 2-methyl-2-butene (1.02 g, 14.5 mmol) followed by a freshly prepared NaClO_2 solution (1.25

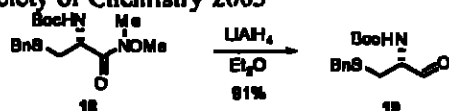
Supplementary Material (ESI) for Chemical Communications

This journal is © The Royal Society of Chemistry 2003

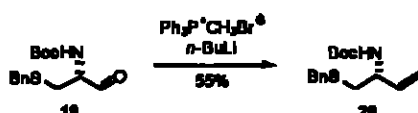
M in 20% NaH₂PO₄, 1.16 mL, 1.45 mmol). The solution was stirred for 2 h at room temperature, and diluted with Et₂O. The solution was washed with brine, dried over MgSO₄, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate/MeOH, 47.5:47.5:5) gave 15 as a colorless oil (0.083 g, 96%); [α]_D²⁰ -35.0 (*c* 0.40, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 3.24-3.41 (m, 2H), 3.02 (s, 3H, 1 rotamer), 2.93 (s, 3H, one rotamer), 2.53-2.62 (m, 1H), 2.35 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.10 (dd, *J* = 9.6, 7.2 Hz, 1H, one rotamer), 2.06 (dd, *J* = 9.2, 6.8 Hz, 1H, one rotamer), 1.91-2.01 (m, 1H), 1.65-1.74 (m, 1H), 1.30-1.58 (m, 5H), 1.04-1.16 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H, 1 rotamer), 1.08 (d, *J* = 6.8 Hz, 3H, 1 rotamer), 0.80-0.94 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 179.0, 178.8, 177.3, 177.0, 48.6, 46.7, 40.8, 40.6, 38.6, 38.5, 37.8, 37.6, 37.5, 35.8, 35.7, 35.6, 35.4, 34.7, 34.6, 34.3, 28.6, 27.7, 27.4, 19.5, 18.0, 17.4, 17.0, 16.9, 16.44, 16.39, 13.5, 12.4; IR (film) 2963, 1728, 1611 cm⁻¹; HRMS (CI, M⁺) calcd for C₁₇H₃₃O₃N *m/z* 299.2460, found *m/z* 299.2466.



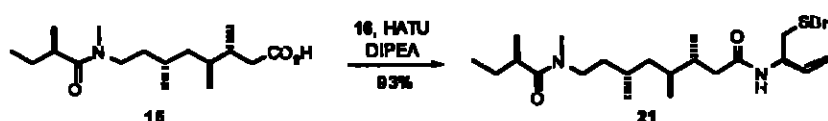
S-Benzyl-N α -(*tert*-butyloxycarbonyl)-cysteine-N-methoxy-N-methylamide (18). To a solution of S-Benzyl-N α -(*tert*-butyloxycarbonyl)-cysteine (17, 0.59 g, 1.90 mmol) in THF (38 mL) was added 1-hydroxybenzotriazole (HOBt, 0.282 g, 2.08 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.40 g, 2.08 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min, after which MeNHOMe·HCl (0.208 g, 2.09 mmol) and diisopropylethylamine (0.362 mL, 2.08 mmol) were added. The solution was kept at room temperature for 12 h, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 2:1) gave S-benzyl-N α -(*tert*-butyloxycarbonyl)-cysteine-N-methoxy-N-methylamide (0.56 g, 84%); [α]_D²⁰ -30.2 (*c* 1.04, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.36 (m, 5H), 5.38 (d, *J* = 8.4 Hz, 1H), 4.92 (bs, 1H), 3.76 (s, 2H), 3.74 (s, 3H), 3.22 (s, 3H), 2.82 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.65 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 171.9, 155.7, 138.3, 129.4, 128.9, 127.5, 80.2, 62.0, 50.0, 36.7, 33.9, 32.6, 28.8; IR (film) 3321, 2976, 1711, 1662, 1169 cm⁻¹; HRMS (CI, M⁺) calcd for C₁₇H₂₆O₄N₂S *m/z* 354.1613, found *m/z* 354.1616.



3-Benzylthio-2-(N-*tert*-butyloxycarbonyl)aminopropionaldehyde (19). To a solution of *S*-benzyl-*N*-(*tert*-butyloxycarbonyl)-cysteine-*N*-methoxy-*N*-methylamide (18, 0.632 g, 1.78 mmol) in Et₂O (8 mL) was added LiAlH₄ (0.085 g, 2.23 mmol) at 0 °C. After stirring for 30 min, the mixture was diluted with Et₂O, washed with 1N HCl, brine, dried over MgSO₄, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 2:1) gave 19 as an oil (0.478 g, 91%); [α]_D²⁰ +3.47 (*c* 1.96, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.51 (s, 1H), 7.21-7.34 (m, 5H), 5.39 (m, 1H), 4.24-4.32 (m, 1H), 3.72 (s, 2H), 2.86 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.80 (dd, *J* = 14.1, 6.0 Hz, 1H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 199.2, 155.8, 138.0, 129.4, 129.1, 127.8, 80.8, 59.5, 37.3, 31.0, 28.7; IR (film) 3354, 2977, 1709, 1495 cm⁻¹.



3-Benzylthio-2-(N-*tert*-butyloxycarbonyl)amino-1-butene (20). To a suspension of methyltriphenylphosphonium bromide (1.27 g, 3.5 mmol) in THF (15 mL) was added KHMDS (0.5 M solution in toluene, 6.48 mL, 3.24 mmol). The resulting yellow suspension was stirred at room temperature for 1 h, and cooled to -78 °C. A solution of 19 (0.478 g, 1.62 mmol) in THF (10 mL) was added, the cooling bath was removed, and the mixture was allowed to reach room temperature. The mixture was diluted with Et₂O, washed with half-saturated Rochelle's salt, dried over MgSO₄, and concentrated. Purification of the residue by flash column chromatography (hexanes/ethyl acetate, 8:1) gave 20 (0.263 g, 55%); [α]_D²⁰ +12.7 (*c* 2.63, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.32 (m, 5H), 5.78 (ddd, *J* = 17.1, 10.5, 5.4 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.13 (d, *J* = 10.2 Hz, 1H), 4.80 (bs, 1H), 4.33 (bs, 1H), 3.73 (s, 2H), 2.58 (d, *J* = 6.0 Hz, 2H), 1.46 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.6, 138.4, 137.8, 129.4, 129.0, 127.5, 116.0, 80.0, 52.2, 37.0, 36.8, 28.8; IR (film) 3344, 2977, 1701, 1495 cm⁻¹; HRMS (CI, M⁺) calcd. for C₁₆H₂₃O₃NS *m/z* 293.1449, found *m/z* 293.1448.

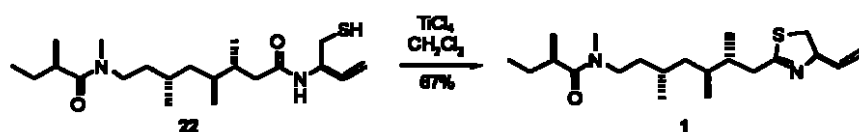


\$12

Supplementary Material (ESI) for Chemical Communications

This journal is © The Royal Society of Chemistry 2003

NMR (300 MHz, CDCl_3) δ 5.93 (d, $J = 8.1$ Hz, 1H, 1 rotamer), 5.82 (d, $J = 8.1$ Hz, 1H, 1 rotamer), 5.76 (ddd, $J = 16.2, 11.1, 5.1$ Hz, 1H), 5.20-5.26 (m, 2H), 4.72-4.83 (m, 1H), 3.21-3.45 (m, 2H), 3.01 (s, 3H, 1 rotamer), 2.92 (s, 3H, 1 rotamer), 2.51-2.85 (m, 3H), 2.25-2.30 (m, 1H), 1.88-2.04 (m, 2H), 1.61-1.75 (m, 2H), 1.28-1.57 (m, 6H), 1.12-1.16 (m, 1H), 1.10 (d, $J = 7.8$ Hz, 3H, 1 rotamer), 1.07 (d, $J = 6.9$ Hz, 3H, 1 rotamer), 0.80-0.94 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.9, 176.6, 172.8, 172.5, 136.32, 136.26, 117.2, 51.9, 51.7, 48.5, 46.5, 41.2, 41.1, 41.0, 40.5, 37.8, 37.6, 36.1, 35.9, 35.7, 34.7, 34.6, 34.1, 30.0, 29.7, 28.6, 27.8, 27.5, 19.7, 19.6, 18.2, 17.5, 16.9, 16.8, 16.6, 12.6, 12.4; IR (film) 3297, 2961, 1640, 1624 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{21}\text{H}_{40}\text{O}_2\text{N}_2\text{S}$ m/z 384.2810, found m/z 384.2811.



(+)-Kalkitoxin (1). To a solution of 22 (0.012 g, 0.031 mmol) in CH_2Cl_2 (1 mL) at room temperature was added freshly distilled TiCl_4 (0.034 mL, 0.31 mmol). The orange solution was stirred for 12 h. and the reaction was quenched with saturated NaHCO_3 . The mixture was extracted with CH_2Cl_2 , and the extract was dried over Na_2SO_4 , and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 1:1) gave (+)-kalkitoxin as a colorless oil (0.0076 g, 67%): $[\alpha]_D^{20} +11.5$ (c 0.34, CHCl_3); ^1H NMR (400 MHz, C_6D_6) δ 5.85 (ddd, $J = 16.8, 10.4, 6.0$ Hz, 1H), 5.24 (d, $J = 17.2$ Hz, 1H), 5.01 (d, $J = 10.4$ Hz, 1H), 4.75 (m, 1H), 3.35 (m, 1H), 2.94 (m, 1H), 2.93 (dd, $J = 10.8, 8.4$ Hz, 1H), 2.80 (s, 3H, 1 rotamer), 2.71 (dd, $J = 10.8, 8.4$ Hz, 1H), 2.46-2.55 (m, 1H), 2.42 (s, 3H, 1 rotamer), 2.20-2.37 (m, 2H), 2.06 (m, 1H), 1.84-1.99 (m, 1H), 1.21-1.59 (m, 5H), 1.18 (s, 3H, 1 rotamer), 1.10 (m, 1H), 1.09 (s, 3H, 1 rotamer), 0.69-0.96 (m, 13 H); ^{13}C NMR (100 MHz, C_6D_6) δ 175.5, 175.2, 170.1, 170.0, 138.5, 138.3, 115.5, 115.4, 79.4, 47.9, 46.1, 40.5, 40.4, 39.0, 38.8, 38.6, 38.2, 37.7, 37.6, 37.4, 36.1, 34.7, 34.6, 34.5, 33.6, 28.5, 28.1, 27.7, 19.6, 19.4, 18.4, 17.8, 16.6, 16.5, 12.6, 12.4; IR (film) 2961, 2874, 1643, 1463 cm^{-1} ; HRMS (FAB $\text{M}+\text{H}^+$) calcd for $\text{C}_{21}\text{H}_{38}\text{ON}_2\text{S}$ m/z 367.2783, found m/z 367.2793.



En la ciudad de Cali, Capital del Departamento del Valle del Cauca, República de Colombia, a los VEINTITRES (23) días - del mes de OCTUBRE del año DOS MIL UNO --

QUE CAICEDO... Nota
ulo de...
- 28 FEB 2007
- 14.949.56... de Cali, y dijo: ----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y representación de **TECNOQUIMICAS S.A.** sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de junio de 1957, reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali

Bogotá, identificado con C.C. # 79.152.473 de Isaquén, abogado en ejercicio, portador de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante

administrativos o contencioso-administrativos relacionados con estos derechos u otros de diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

EMERY CORP. C
RACION DE ESCRITURAS
Notaria 3^a de Cali

Proprietaria Veintitrés (E) de este Circuito
 Hacer constar que esta fotocopia coincide
 con la fotocopia autógrafa que ha tenido
 la sala.

11 ENE-2007

CHOCOLATE

ADDITIONAL QUESTIONS

~~NOTED BY: 2-201~~

Wash. D.C., Color

1994.01.15

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.

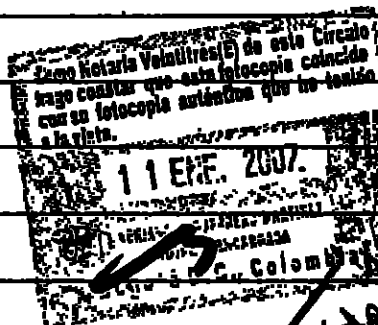
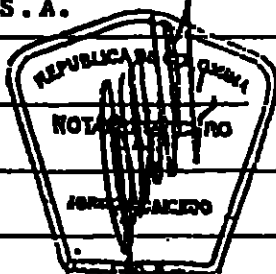
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.

Se agregan comprobantes. Derechos \$30.000,00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Juan m Barberi

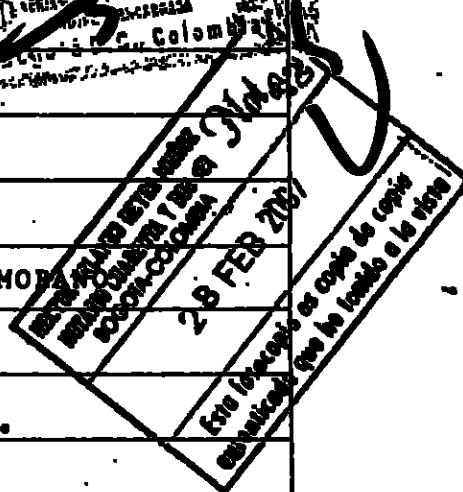
JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORA



CCC-1-1831951

EL SUSCRITO SEGRETAJO DE LA CAMARA DE COMERCIO DE CA

CHIFFRA

NONERESTENOUGHIMICSIMOTR
EDOWINGRENGICRUBSEVALUAT
IMPERFECTION,COMERCIAL
DIRECTION,NOTIFICATION,UN
CUDADONAL
GMAITRE,QUOTIENT,RENTAL,INNOV
HATH,PAIX

CERTIFICA

CERTIFIED

CERTIFICA

GERMÁNICA

आर्य समाज

Figure 1



— 11 —

Abstract

1000

下

ccc11831952

DE CUALQUIER NATURALEZA O TIPO LEGAL, DEDICADAS A LA EXPLOTACION DE CUALQUIER ACTIVIDAD ECONOMICA LICITA Y ENAJENARLAS O LA EXPLOTACION DEL NEGOCIO DE LA PUBLICIDAD Y EL ESTABLECIMIENTO DE OFICINAS DEDICADAS A ESTE NEGOCIO O A LA CREACION DE ORGANOS DE PUBLICIDAD HABLADOS O ESCRITOS Y EN GARANTIZAR LAS OBLIGACIONES PROPIAS DE LOS ACCIONISTAS O DE TERCEROS. 8) LA ADQUISICION DE BIENES MUEBLES, INMUEBLES Y DE TODA CLASE DE EQUIPO Y MAQUINARIA PARA SU ARRENDAMIENTO O PARA LA COMERCIALIZACION DE ELLOS EN DESARROLLO DEL OBJETO SOCIAL PARA OBTENER PRIVILEGIOS INDUSTRIALES, CONCESIONES, PATENTES DE INVENCION, DE MEJORAS O PROCEDIMIENTOS, MARCAS DE FABRICA O DE COMERCIO, YA SEA EN NOMBRE PROPIO O DE TERCEROS, OTORGAR A TERCEROS, DENTRO O FUERA DEL PAIS CONCESIONES O USOS DE EXPLOTACION SOBRE ESTOS DERECHOS, EJECUTAR TODA CLASE DE CONTRATOS DE COMPRAVENTA, DISTRIBUCION DE MATERIAS PRIMAS, DE PRODUCTOS SEMIELABORADOS O ELABORADOS EN EL MERCADO INTERNO O EN EL EXTERIOR Y EN GENERAL, LA CELEBRACION DE TODO ACTO O CONTRATO SOBRE BIENES MUEBLES O INMUEBLES DE COMERCIO INDUSTRIALES O DE OTRA ENDOLE QUE SE REFIERAN DIRECTAMENTE A LAS ACTIVIDADES QUE PERSIGUE LA SOCIEDAD.

CERTIFICA

ORGANOS DE DIRECCION Y ADMINISTRACION PARA LOS FINES DE SU DIRECCION, ADMINISTRACION Y REPRESENTACION, LA SOCIEDAD TIENE LOS SIGUIENTES ORGANOS: ASAMBLEA GENERAL DE ACCIONISTAS, EN JUNTA DIRECTIVA, UN PRESIDENTE, EJECUTIVO, TRES VICEPRESIDENTES ELEGUTIVOS, EN VICEPRESIDENCIAS ADMINISTRATIVAS.

LA DIRECCION DE LA SOCIEDAD CORRESPONDE, EN PRIMER TERMINO A LA ASAMBLEA GENERAL DE ACCIONISTAS Y EN SEGUNDO LUGAR A LA JUNTA DIRECTIVA COMO DELEGADA POR LA

REPRESENTACION LEGAL DE LA SOCIEDAD Y LA GESTION DE LOS NEGOCIOS SOCIALES, ESTARAN A CARGO DEL PRESIDENTE ELEGUTIVO Y DE LOS TRES VICEPRESIDENTES ELEGUTIVOS.

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS: ENTRE OTRAS, LAS SIGUIENTES: 1) ACORDAR LA FUSION DE LA SOCIEDAD, SU TRANSFORMACION, LA ENAJENACION O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCION O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACION O MODIFICACION DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICION DE ACCIONES PROPIAS CON SUCESSION A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE REGLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTERES DE LA SOCIEDAD.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLO MANDATO PARA ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TIENDE ATRIBUCIONES SEFICIENTES PARA ORDENAR QUE SE CUMPLA O CUMPLA CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TIENDE LAS SIGUIENTES FUNCIONES: ENTRE OTRAS: 1) NOMBRAR Y REMOVER GOBERNANTES, EL PRESIDENTE ELEGUTIVO, A LOS VICEPRESIDENTES ELEGUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS. 2) DISPONER EN EL ESTABLECIMIENTO O EN LA CAJAS DE SEGURANES O AGENCIAS, DENTRO O FUERA DEL DOMICILIO SOCIAL. 3) EMITIR BASES POLITICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECONOMICA Y LABORAL, APROBAR PLANES DE INVERSION Y DE PRODUCCION, DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCION Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE NEGOCIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIAS Y MAS ALGUNOS EN QUE FUELE NEGOCIO Y DIFERIR NORMAS Y REGLAMENTOS PARA LA ORGANIZACION Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD. 4) DETERMINAR LA PARTICIPACION QUE DEBA DARSE A LAS DEPENDENCIAS QUE, CON EL CARACTER DE RESERVAS DE INVERSION, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS. 5) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE PUEDAN POR OBJETO: 1) ADQUIRIR, HIPOTECAR, Y EN ADQUIRIR OTRA FORMA GRAVAR O CUMPLAR EL COMENIO DE BIENES RAICES, CUYA CUANTIA SEA SUPERIOR A \$500.000.000.00 MONEDA CORRIENTE. 2) CONTRIBUIR PRENDA SOBRE BIENES SOCIALES O BARRIOS EN ANTIGRESO PARA FACTOS O CONTRATOS CUYA CUANTIA SEA SUPERIOR A \$500.000.000.00 MONEDA CORRIENTE. 3) HACER INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS DE OTRAS EMPLEEN, EN CADA CASO, COSTOS O GASTOS EN CUANTIA SUPERIOR A \$500.000.000.00 MONEDA LEGAL. 6) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CUMPLIR LA SOCIEDAD POR REPRESENTANTES DELEGADOS CUANDO SU CUANTIA SEA SUPERIOR A \$500.000.000.00 MONEDA LEGAL. 7) COMPTAR, EN CASO QUE SE ADMITA A LA COMPTA A LA CELEBRACION DE CONCORDATOS PREVENTIVO CON SUS ACREEDORES, LA CONTRA DE ORGANO CONDUCTIVO Y ASOSOR DE LOS REPRESENTANTES DE LA COMPTA.

[illegible]

LOS AGRADOS DE LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN APLICACIÓN, SIN NINGUNA MODIFICACIÓN, PARA OBTENER AUTORIZACIÓN PREVIA DEL GOBIERNO BRITÁNICO PARA PAGAR, EN NOMBRE DE LA SOCIEDAD, EN LICITACIONES PÚBLICAS, CONVOCADAS POR EL GOBIERNO, LA MODALIDAD DE CONTRATACIÓN, PRESENTAR PROPUESTAS, ASISTIR A LA CONTRATACIÓN Y CONTRATAR, SIN LIMITACIÓN, EN MANEJOS DE LAS EMPRESAS PÚBLICAS, Y EN LOS SERVICIOS DE INGENIERÍA Y CONSTRUCCIÓN DE OBRAS PÚBLICAS, DE ECONOMÍA MIXTA, EN LAS QUE PARTICIPAN EMPRESAS NACIONALES, REGIONALES Y EXTRANJERAS, Y EN OTROS.

CERTIFICADO DE EFICIENCIA
 DEL PLAN DE DESARROLLO
 2013-2015 DEL INSTITUTO

ECONOMICALLY UNEMPLOYED
 URGENT, RUINED, DISTRESSING
 ANNOYANCE, UNEMPLOYED, UNEMPLOYED

FILE FRONT FROM REAR OF CAR
FRONT DOOR OPENED
FRANC 1980 VOLVO 740 GLE
1-800-441-6882

VICE PRESIDENT, CONCRETE
JOHN MANHILL, BARRE, VERMONT
800-345-9500

[illegible]

SECRET

CCC11831953

CERTIFICA

DOCUMENTO: ACTA No. 38 DEL 08 DE FEBRERO DE 1992
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 05 DE JUNIO DE 1992 No. 15016 DEL LIBRO IX

DOCUMENTO: ACTA No. 52 DEL 26 DE MARZO DE 1999
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 10 DE MAYO DE 1999 No. 1493 DEL LIBRO IX

DOCUMENTO: ACTA No. 54 DEL 31 DE MARZO DE 2000
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 24 DE MAYO DE 2000 No. 1622 DEL LIBRO IX

FUNCIONES NOMBRADOS

COMITÉ DIRECTIVA

PRIMER FONCIÓN

ANGELICO JOSÉ MARRERO OSPINA
C.C. 1445180

SEGUNDO FONCIÓN

JUAN MANUEL MARRERO OSPINA
C.C. 1749151

TERCER FONCIÓN

JUAN EDUARDO DE LOS RÍOS GILGARRÉZ
C.C. 1810021

CUARTO FONCIÓN

EMERSON ENRIQUE DÍAZ GILGARRÉZ
C.C. 1810021

QUINTO FONCIÓN

LUIS RAMIRO GILGARRÉZ
C.C. 1810021

SEXTO FONCIÓN

RAMIRO ADOLFO SANCHEZ TREMERO
C.C. 16623360

SEGUNDO FONCIÓN

VICTOR FERNANDO ROSA GARCÍA
C.C. 1810021

TERCER FONCIÓN

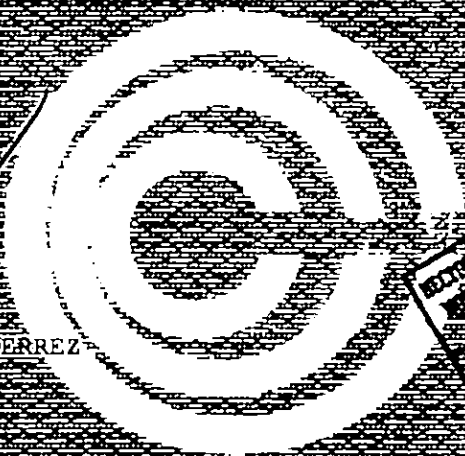
CARLOS ALBERTO RAMÍREZ GONZÁLEZ
C.C. 1810021

CUARTO FONCIÓN

FRANCISCO TRUJILLO GARCÍA
C.C. 1810021

QUINTO FONCIÓN

ANDRÉS MORALES GARCÍA
C.C. 1810021



**CAMARA
DE COMERCIO
DE CALI**

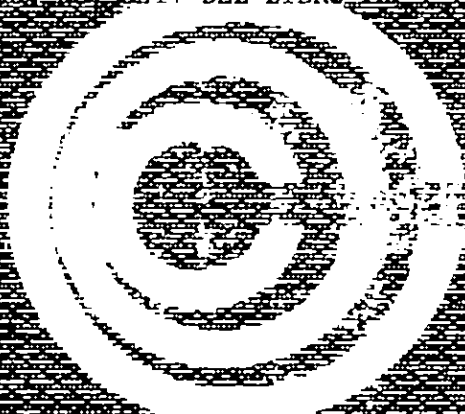
~~SECRET~~

01-160857-13

PROCESO DE DOCUMENTACIÓN PRÁCTICA DE LA ACERTEJADA-2006
 ESCRITA: ANTONIO E. FERNÁNDEZ-RODRÍGUEZ
 1997 DEL LIBRO

THE FRONT-NUMBERED CAR
WAS A SON-DISCARD PRIMOGENITURE
BORN OF THE FIRST OF TWO UN-RECORDED
MARRIAGES OF THE FATHER.

REVISOR EJC: SC# SUP# ENTER#
US# D# A# E# T# O# R# C# A# I# S# I#
C# E# 1# 2# 3# 4# 5# 6# 7# 8# 9# 0#

[illegible][illegible][illegible]

ccc11831954

ES MAS CONVENIENTE, DE MANERA QUE EN NINGUN CASO LA SOCIEDAD QUEDE SIN REPRESENTACION EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS.

CERTIFICA

QUE POR ESCRITURA NRO. 2719 DEL 15 DE JULIO DE 1999, NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE AGOSTO DE 1999 BAJO EL NRO. 323 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A SAMUEL GOMEZ UPEGUI, MAYOR DE EDAD Y VECINO DE CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 6633496, GERENTE DEL DISTRITO DE VENTAS DEL OCCIDENTE COLOMBIANO DE LA SOCIEDAD, CON SEDE EN CALI, UBICADO EN LA CALLE 23 NRO. 466, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS, PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES, DEL ORDEN JUDICIAL, ADMINISTRATIVO O POLICIVO, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES DE CARACTER LABORAL, CIVIL, COMERCIAL Y POLICIVO, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSULTA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESA FACULTAD PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESALES QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADOS DE PERSONA VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 4) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASILLO CONSIDERA NECESARIO, TENIENDO SUMA DE DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 5) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMITIR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE ALIQUOTOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ESTABLECIMIENTO QUE SE APODERA EN SU CONDICION DE GERENTE, ESTA FACULTAD PARA REVALUAR LA CARTERA SIN LIMITACION DE CUANTIA DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA PAGAR CHEQUES HASTA POR LA CANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 3403 DEL 21 DE NOVIEMBRE DE 1999, NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 09 DE DICIEMBRE DE 1999 BAJO EL NRO. 356 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE AL SEÑOR ALFONSO CHABLO GUTIERREZ BOTERO, MAYOR DE EDAD, VECINO DE MEDIOFON, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 8738529 DE MEDIOFON, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL DE ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDIOFON, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS, PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES, DEL ORDEN JUDICIAL, ADMINISTRATIVO O POLICIVO, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES DE CARACTER LABORAL, CIVIL, COMERCIAL Y POLICIVO, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSULTA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y

4000

1971

1972

1973

1974

1975

1976

1977

1978

1979

1980

1981

1982

1983

1984

1985

1986

1987

1988

1989

1990

1991

1992

1993

1994

1995

1996

1997

1998

1999

2000

2001

2002

2003

2004

2005

2006

2007

2008

2009

2010

2011

2012

2013

2014

2015

2016

2017

2018

2019

2020

2021

2022

2023

2024

2025

2026

2027

2028

2029

2030

2031

2032

2033

2034

2035

2036

2037

2038

2039

2040

2041

2042

2043

2044

2045

2046

2047

2048

2049

2050

2051

2052

2053

2054

2055

2056

2057

2058

2059

2060

2061

2062

2063

2064

2065

2066

2067

2068

2069

2070

2071

2072

2073

2074

2075

2076

2077

2078

2079

2080

2081

2082

2083

2084

2085

2086

2087

2088

2089

2090

2091

2092

2093

2094

2095

2096

2097

2098

2099

2100

2101

2102

2103

2104

2105

2106

2107

2108

2109

2110

2111

2112

2113

2114

2115

2116

2117

2118

2119

2120

2121

2122

2123

2124

2125

2126

2127

2128

2129

2130

2131

2132

2133

2134

2135

2136

2137

2138

2139

2140

2141

2142

2143

2144

2145

2146

2147

2148

2149

2150

2151

2152

2153

2154

2155

2156

2157

2158

2159

2160

2161

2162

2163

2164

2165

2166

2167

2168

2169

2170

2171

2172

2173

2174

2175

2176

2177

2178

2179

2180

2181

2182

2183

2184

2185

2186

2187

2188

2189

2190

2191

2192

2193

2194

2195

2196

2197

2198

2199

2200

2201

2202

2203

2204

2205

2206

2207

2208

2209

2210

2211

2212

2213

2214

2215

2216

2217

2218

2219

2220

2221

2222

2223

2224

2225

2226

2227

2228

2229

2230

2231

2232

2233

2234

2235

2236

2237

2238

2239

2240

2241

2242

2243

2244

2245

2246

2247

2248

2249

2250

2251

2252

2253

2254

2255

2256

2257

2258

2259

2260

2261

2262

2263

2264

2265

2266

2267

2268

2269

2270

2271

2272

2273

2274

2275

2276

2277

2278

2279

2280

2281

2282

2283

2284

2285

2286

2287

2288

2289

2290

2291

2292

2293

2294

2295

2296

2297

2298

2299

2300

2301

2302

2303

2304

2305

2306

2307

2308

2309

2310

2311

2312

2313

2314

2315

2316

2317

2318

2319

2320

2321

2322

2323

2324

2325

2326

2327

2328

2329

2330

2331

2332

2333

2334

2335

2336

2337

2338

2339

2340

2341

2342

2343

2344

2345

2346

2347

2348

2349

2350

2351

2352

2353

2354

2355

2356

2357

2358

2359

2360

2361

2362

2363

2364

2365

2366

2367

2368

2369

2370

2371

2372

2373

2374

2375

2376

2377

2378

2379

2380

2381

2382

2383

2384

2385

2386

2387

2388

2389

2390

2391

2392

2393

2394

2395

2396

2397

2398

2399

2400

2401

2402

2403

2404

2405

2406

2407

2408

2409

2410

2411

2412

2413

2414

2415

2416

2417

2418

2419

2420

2421

2422

2423

2424

[illegible]

[illegible][illegible]

ccc11831956

REPRESENTACION EN LA SALVAGUARDA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA UTILIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO LES ENTENDIDO QUE EL APODERADO EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA SIN LIMITACION DE CUANTIA DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 308 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALLI, INSCRITA EN LA CAMARA DE COMERCIO EN 04 DE MARZO DE 2002 BAJO EL NRO. 4378 DEL LIBRO V. MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A HERNANDO ANGELO MONO MAYOR DE EDAD, VECINO DE BOGOTA IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 19.342.319 DE BOGOTA GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL GUANO MANA DE LA SOCIEDAD CON SEDE EN BOGOTA PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE TRIBUNALES PUBLICAS NACIONALES O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DE ORDEN JUDICIAL ADMINISTRATIVO, PENAL O DE FISCALIA, VALSEAN PROCESOS, ACTUACIONES, ESTIMOS, ACTOS O DEFENSIONES Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALIANZAMIENTO Y CONCILIACION EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALIANZAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE GEORGE RODRIGUEZ MONO MANDATARIO PARA NEGOCIAR LAS ACCIONES COMERCIALES Y RENOVES TENDIENTES A LA RECUPERACION DE LA CARTERA SIN LIMITACION DE CUANTIA CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSGER, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVINGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORGA PODER Y CONSTITUYA MANDATARIOSE PARA HACERSE PARTE EN LOS PROCESOS CONCILIATORIOS, DE CONCILIACION OBLIGATORIA O RECONSTRUCCION ECONOMICA QUE SE PRAMANEAN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O EMPLEADOS CUANDO SE TRATE DE OTRA CLASE DE DEUDORES TENDIENTES A LA RECUPERACION DE LA CARTERA SIN LIMITACION DE CUANTIA CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSGER, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES.

4) PARA QUE EN NOMBRE DE RECLAMACIONES EXTRA PROCESO EN QUE INTERVINGA EN ASUNTOS DE RESPONSABILIDAD CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 5) PARA QUE SUSCRIBA LOS CONTRATOS DE TRABAJO Y OUVOS POR DETERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 6) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL. 7) ASISTIR O CONSIDERAR NECESARIO TENIENDO SUMA DE CUANTIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 8) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA UTILIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO LES ENTENDIDO QUE EL APODERADO EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA SIN LIMITACION DE CUANTIA DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR

EN NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXHIBIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 245202 DE 31 DE MAYO DE 1995 E NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO DE 24 DE SEPTIEMBRE DE 2003, LIBRO NRO. 134 DEL LIBRO IV SE CONFIERE PODER ESPECIAL AL ANTONIO JAIRO VILLANUEVA, ABOGADO TIENE EN EJERCICIO Y CONTINUA EN PROFESION EN EL OFICIO DEL MINISTERIO DE JUSTICIA IDENTIFICADO CON LA Cedula de Ciudadania Numero 9.944.004 DE CALI PARA QUE REPRESENTA A FARMACIAS ISLAS EN LOS SIGUIENTES ACTOS: 1.- PROMOVER Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES RELATIVOS A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL, DE TODOS LOS TRAMITES ANTE EL INVIMA RELATIVOS A LA OBTENCION DE REGISTROS SANITARIOS, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRAS LINEAS DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, GESTIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER A VECER, ASI COMO CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS A CADA OBJETO DE FACILITAR PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS REQUISITOS NECESARIOS, PRESENTAR MODELOS, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPEDIENTES, SOLICITAR PASAPORTES, RECIBIR DOCUMENTOS, COPIAR Y FOTOCOPIAR, ADOPTAR OTRAS Y PERCIBIR, ASI COMO DICHAS FOTOCOPIAS PARA LOS DICHOS ACTOS PARA EL CUMPLIMIENTO DEL NECESARIO ANTE LAS AUTORIDADES COMPETENTES PARA LOS DICHOS ACTOS, INCLUIDAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE PUEDAN SER NECESARIAS PARA SUSTITUIR Y DELEGAR EL PRESENTE PODER, PODER DELEGAR, PODER REVOCAR DICHAS SUSTITUCIONES, PODER ATENDER EN SU PROPIA CALIDAD, NOVELACIONES QUE DIRECTA O INDIRECTAMENTE SE DERIVEN DE LOS ACTOS Y DE LAS GESTIONES QUE TENGA RELACION CON LAS MISMAS, PODER PODER COORDINAR Y SUSCRIBIR EN GENERAL TODAS LAS ACTAS Y PERSONERIAS EN NOMBRE DE LA SOCIEDAD ISLAS, SIEMPRE QUE LO ESTE CORRESPONDIENDO, MANERA QUE EN NINGUN MOMENTO PUEDA SER IMPLICADO EN LA RESPONSABILIDAD DE SUS HECHOS Y OBLIGACIONES EN LAS MATERIAS DE QUE TRATA EL PRESENTE PODER, ANTONIO JAIRO VILLANUEVA, ABOGADO, EN FAVOR DE LOS TERMINOS Y PRONOMBROS QUE SE CONTIENEN EN EL PRESENTE PODER, CUALQUIER MODIFICACION O REVOCACION A SE PARA

CERTIFICA

QUE POR ESCRITURA NRO. 245202 DE 31 DE MAYO DE 1995 E NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO DE 24 DE SEPTIEMBRE DE 2003, LIBRO NRO. 134 DEL LIBRO IV SE CONFIERE PODER ESPECIAL AL ANTONIO JAIRO VILLANUEVA, ABOGADO TIENE EN EJERCICIO Y CONTINUA EN PROFESION EN EL OFICIO DEL MINISTERIO DE JUSTICIA IDENTIFICADO CON LA Cedula de Ciudadania Numero 9.944.004 DE CALI PARA QUE REPRESENTA A FARMACIAS ISLAS EN LOS SIGUIENTES ACTOS: 1.- PROMOVER Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES RELATIVOS A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL, DE TODOS LOS TRAMITES ANTE EL INVIMA RELATIVOS A LA OBTENCION DE REGISTROS SANITARIOS, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRAS LINEAS DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, GESTIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER A VECER, ASI COMO CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS A CADA OBJETO DE FACILITAR PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS REQUISITOS NECESARIOS, PRESENTAR MODELOS, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPEDIENTES, SOLICITAR PASAPORTES, RECIBIR DOCUMENTOS, COPIAR Y FOTOCOPIAR, ADOPTAR OTRAS Y PERCIBIR, ASI COMO DICHAS FOTOCOPIAS PARA LOS DICHOS ACTOS PARA EL CUMPLIMIENTO DEL NECESARIO ANTE LAS AUTORIDADES COMPETENTES PARA LOS DICHOS ACTOS, INCLUIDAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE PUEDAN SER NECESARIAS PARA SUSTITUIR Y DELEGAR EL PRESENTE PODER, PODER DELEGAR, PODER REVOCAR DICHAS SUSTITUCIONES, PODER ATENDER EN SU PROPIA CALIDAD, NOVELACIONES QUE DIRECTA O INDIRECTAMENTE SE DERIVEN DE LOS ACTOS Y DE LAS GESTIONES QUE TENGA RELACION CON LAS MISMAS, PODER PODER COORDINAR Y SUSCRIBIR EN GENERAL TODAS LAS ACTAS Y PERSONERIAS EN NOMBRE DE LA SOCIEDAD ISLAS, SIEMPRE QUE LO ESTE CORRESPONDIENDO, MANERA QUE EN NINGUN MOMENTO PUEDA SER IMPLICADO EN LA RESPONSABILIDAD DE SUS HECHOS Y OBLIGACIONES EN LAS MATERIAS DE QUE TRATA EL PRESENTE PODER, ANTONIO JAIRO VILLANUEVA, ABOGADO, EN FAVOR DE LOS TERMINOS Y PRONOMBROS QUE SE CONTIENEN EN EL PRESENTE PODER, CUALQUIER MODIFICACION O REVOCACION A SE PARA

CERTIFICA

QUE POR ESCRITURA NRO. 245202 DE 31 DE MAYO DE 1995 E NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO DE 24 DE SEPTIEMBRE DE 2003, LIBRO NRO. 134 DEL LIBRO IV SE CONFIERE PODER ESPECIAL AL ANTONIO JAIRO VILLANUEVA, ABOGADO TIENE EN EJERCICIO Y CONTINUA EN PROFESION EN EL OFICIO DEL MINISTERIO DE JUSTICIA IDENTIFICADO CON LA Cedula de Ciudadania Numero 9.944.004 DE CALI PARA QUE REPRESENTA A FARMACIAS ISLAS EN LOS SIGUIENTES ACTOS: 1.- PROMOVER Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES RELATIVOS A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL, DE TODOS LOS TRAMITES ANTE EL INVIMA RELATIVOS A LA OBTENCION DE REGISTROS SANITARIOS, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRAS LINEAS DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, GESTIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER A VECER, ASI COMO CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS A CADA OBJETO DE FACILITAR PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS REQUISITOS NECESARIOS, PRESENTAR MODELOS, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPEDIENTES, SOLICITAR PASAPORTES, RECIBIR DOCUMENTOS, COPIAR Y FOTOCOPIAR, ADOPTAR OTRAS Y PERCIBIR, ASI COMO DICHAS FOTOCOPIAS PARA LOS DICHOS ACTOS PARA EL CUMPLIMIENTO DEL NECESARIO ANTE LAS AUTORIDADES COMPETENTES PARA LOS DICHOS ACTOS, INCLUIDAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE PUEDAN SER NECESARIAS PARA SUSTITUIR Y DELEGAR EL PRESENTE PODER, PODER DELEGAR, PODER REVOCAR DICHAS SUSTITUCIONES, PODER ATENDER EN SU PROPIA CALIDAD, NOVELACIONES QUE DIRECTA O INDIRECTAMENTE SE DERIVEN DE LOS ACTOS Y DE LAS GESTIONES QUE TENGA RELACION CON LAS MISMAS, PODER PODER COORDINAR Y SUSCRIBIR EN GENERAL TODAS LAS ACTAS Y PERSONERIAS EN NOMBRE DE LA SOCIEDAD ISLAS, SIEMPRE QUE LO ESTE CORRESPONDIENDO, MANERA QUE EN NINGUN MOMENTO PUEDA SER IMPLICADO EN LA RESPONSABILIDAD DE SUS HECHOS Y OBLIGACIONES EN LAS MATERIAS DE QUE TRATA EL PRESENTE PODER, ANTONIO JAIRO VILLANUEVA, ABOGADO, EN FAVOR DE LOS TERMINOS Y PRONOMBROS QUE SE CONTIENEN EN EL PRESENTE PODER, CUALQUIER MODIFICACION O REVOCACION A SE PARA

CAPITAL FACTOR ZAPOR	\$27,200,000,000
NUMERO DE ACCIONES	51,400,000
VALOR NOMINAL	\$500
CAPITAL SOCIAL POC	\$27,123,804,000
NUMERO DE ACCIONES	51,247,608
VALOR NOMINAL	\$500
CAPITAL PAGADO	\$27,123,804,000
NUMERO DE ACCIONES	51,247,608
VALOR NOMINAL	\$500

QUE EM 27 DE MARÇO DE 2001, RÁTIOS DE NÚMERO 197/99 DO TRIBUNAL DE 1ª INSTÂNCIA INSCRIBIU EM SUA CAMARA DE COMERCIO UM DOCUMENTO PRIVADO DE 27 DE MARÇO DE 2001, EM QUE ACTUAL CONSTATAR A SITUAÇÃO DE CONJUNTO PERTENCIDA POR TAL SOCIEDADE E ANOQUE TAL ACTO

MATRIZ: TECNOQUIMICAS S.A.
DOMICILIO: SANTIAGO DE CALI
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: I+D+D ACTIVIDADES DE TECNOQUIMICAS (CORRESPONDEN A LA SUBSECTORIAL Y
COMERCIALIZACION DE PRODUCTOS BIOTECNICOS, QUIMICOS, MEDICAMENTOS, Y PRODUCTOS
FARMACEUTICOS, ANALISIS, PRODUCTOS VETERINARIO Y AGRICOLAS, ADORNOS, COSMETICOS Y DE
COCOR Y PRODUCTOS DE ASEO PARA EL HOGAR

COORDINADA ADHESIVOS INTERNACIONALES S.7A-ADHINTER S.A. DOMICILIO PRIMERA VUELTA VELO
NACIONAL 1940, COLOMBIANA
ACTIVIDADES DE ADHINTER S.A. SE DESARROLLAN EXCLUSIVAMENTE EN LA ZONA
FRANCA DEL PACIFICO CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION EN EL MERCADO
NACIONAL E INTERNACIONAL DE ADHESIVOS MEDICINALES, TAPAS, FOLIOS, CINTAS, VENDITAS,
ESPARTERAS, FROTIS, VENDAS, ADHESIVOS PARA USO EN COMBATE, TAPAS, CINTAS,
DEBILES, FROTIS, ADHESIVOS Y CINTAS ADHESIVAS PARA USO INTERIOR.

TRANSURSA TO (IN CONTROL) TECNOQUIMICAS S.A., TIENE SUSCRITAS EN LA SOCIEDAD ADHESIVOS INTERNACIONALES S.A. ADVENTER S.A. LA CANTIDAD DE DOS MILLONES CUATROCIENTOS TREINTA Y CINCO (2'435'000) ACCIONES ORDINARIAS DE VALOR NOMINAL DE CINCE PESOS (99'006'000) SOBRE UN TOTAL DE TRES MILLONES (3'000'000) DE ACCIONES ORDINARIAS SUSCRITAS QUE REPRESENTA UN PARTICIPACION DIRECTA DEL 81% SOBRE EL TOTAL DEL CAPITAL SUSCRITO Y PAGADO DE LA SOCIEDAD.

CAMARA

DE CERTICA

[illegible]

CERTIFICA

COUNCIL A NUMBER OF 177, SOCIETY FISCAL MANUSCRIPTS IN THE CHAMBER OF COMMERCE BATO IN
 NINO, FEBRUARY 22, ESTABLECIMIENTO DE LOS DIRECTORES TECNOCOMUNICAS
 PUBLICADO EN EL N.º 12, 12 DE JUNIO
 RECHAZA MANUSCRITO DE 22 DE ABRIL DE 1989
 RENOVACIÓN POR EL AÑO 2000

GERFICA

[illegible]

CERTIFICA

QUE EL NOMBRE DEL TAL SOCIEDAD SE HA REGISTRADO EN LA CAMARA DE COMERCIO, DADO EN
NRO. 5861070, DEPARTAMENTO DE COMERCIO, DE LA CIUDAD DE MANAGUA,
REPUBLICA DE NICARAGUA, EL DIA CINCO DE ABRIL DE 2005.
RENOVO EN LA FORMA ANEXA 2005.

CERTIFICA

QUE EL NOMBRE DE LA SOCIEDAD SE HA REGISTRADO EN LA CAMARA DE COMERCIO, DADO EN
NRO. 5861070, DEPARTAMENTO DE COMERCIO, DE LA CIUDAD DE MANAGUA,
REPUBLICA DE NICARAGUA, EL DIA CINCO DE ABRIL DE 2005.
RENOVO EN LA FORMA ANEXA 2005.

CERTIFICA

QUE EL NOMBRE DE LA SOCIEDAD SE HA REGISTRADO EN LA CAMARA DE COMERCIO, DADO EN
NRO. 5861070, DEPARTAMENTO DE COMERCIO, DE LA CIUDAD DE MANAGUA, DE 2005.

CERTIFICA

QUE NO EXISTEN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE LOS PRESENTES
OPUSCULOS.
LOS CUALES SE HAN REGISTRADO QUE QUEDAN EN FIRME CINCO (5) COTAS, HAY QUE REGISTRAR EN LA
CAMARA DE COMERCIO, EN EL BOLETIN NOTICIAS DE INSCRIPCIONES, SIEMPRE QUE QUEDAN
EN FIRME CINCO (5) COTAS, SIN SUJETO DE RECURSOS EN LA CAMARA DE COMERCIO.

RECONOCIDA EN LA CIUDAD DE MANAGUA, DE 1995 Y LA AUTENTICACION EMPADRONADA EN LA
CAMARA DE COMERCIO, EN LA FIRMA DE LA CAMARA DE COMERCIO, EN LA CAMARA DE COMERCIO,
CAMARA DE COMERCIO, EN LA CAMARA DE COMERCIO, EN LA CAMARA DE COMERCIO,
CAMARA DE COMERCIO, EN LA CAMARA DE COMERCIO, EN LA CAMARA DE COMERCIO.

**CAMARA
DE COMERCIO
DE NICARAGUA**



[Handwritten signature]

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-111045-00004-0000
Fec: 2007-02-28 16:35:47 Dep. 2020 NIJECREACIONE
Tra. 11 PATENTEYII
Eve: 379 FASENACIONALII
Act 400 OPOSNOBSERVTER Folios: 56

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 67 - 17,755
FECHA : FEBRERO 28 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54557463	28/02/2007	11,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-06110-6	54557404	28/02/2007	99,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	62243018	27/02/2007	984,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	62243019	27/02/2007	60,000.00

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

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEHAS COMERCIALES	256,000.00
	TOTAL :	\$ 256,000.00

SOM: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

48
225

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-111045- -00004-0000
Fec: 2007-02-26 16:56:47 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYI
Ere: 379 FASENACIONALI
Act: 400 OPOSIOBSERVTER Folio: 95

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 17,750
FEB : FEBRERO 28 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54557403	28/02/2007	11,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54557404	28/02/2007	99,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	62243018	27/02/2007	984,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	62243019	27/02/2007	60,000.00

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

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-08 PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	72,000.00
TOTAL :		\$ 72,000.00

SON: SETENTA Y DOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____