

ALVARO CASTELLANOS M. & CIA.
A B O G A D O S
Carrera 9 No. 93-09
Apartado 8349
Bogotá - COLOMBIA

SUPERINDUSTRIA Y COMERCIO
Radicación : 00091283 00000004 Folios: 2
Fecha (AMB): 2003-09-01 15:31:00
Trámite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

129

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. 00.091.283

Solicitud del examen de patentabilidad correspondiente a la Patente de Invención para:

**"COMPUESTO DE CARBAPENEM, USO DEL MISMO Y COMPUESTOS
INTERMEDIOS PARA EL MISMO"**

Solicitante: KYOTO PHARMACEUTICAL INDUSTRIES, LTD.

SOLICITUD EXAMEN DE PATENTABILIDAD

Yo, MARGARITA CASTELLANOS ABONDANO, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago No. 03 - 61.578 de Agosto 29 de 2003, correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente de Invención, y se continúe con su tramitación.

Señor Jefe,


Margarita Castellanos Abondano
C.C. No. 39.779.654 de Usaquén
T.P.A. No. 70.819 del Cons. Sup. de la Judicatura
Carrera 9ª. No. 93-09 - Bogotá, D.C.
Teléfono: 6107420 - 6107480

Bogotá, - 1 SET. 2003
MCA/gcb/4789

SUPERINDUSTRIA Y COMERCIO
Radacion : 00091283 00000004 Folios: 2
Fecha (AMB): 2003-09-01 15:31:00
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

130

135

28

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 61,578
FECHA : AGOSTO 29 DE 2003

***** CONSIGNACION *****

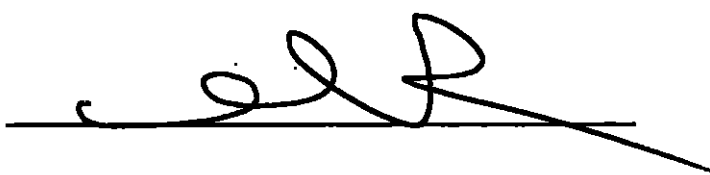
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
TERESA ESPINOSA	CONSIGNACION	BANCO POPULAR	050-00110-6	9931985	27/08/2003	5,717,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
		TOTAL :	\$ 335,000.00

SOM: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

131
~~79~~ 136

RADICACIÓN EXPEDIENTE No. 00- 91283

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION FUE PUBLICADO

EN LA GACETA DE PROPIEDAD INDUSTRIAL No 526, DE FECHA 31 DE MARZO DE 2003, EL

TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL 01 DE JULIO DE 2003.

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO **X**

137 132

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

2020/
Bogotá, D.C.,

**Doctor
Margarita Castellanos Abondano
Apoderado
KYOTO PHARMACEUTICAL INDUSTRIES, LTD**

Oficio N°: 2094

REFERENCIA	Radicación	00 91283
	Trámite	002
	Evento	001
	Actuación	430
	Folios	002

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 91283, realizado según el artículo 46 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El art. 46 de la Decisión 486 establece que "La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más documentos relativos a una o más solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ...b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera...Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente"

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existen en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- ALLSOP, A.; BROOKS, G.; EDWARDS, P.D.; KAURA, A.C.; SOUTHGATE, R., Inhibitors of bacterial signal peptidase: a series of 6-(substituted oxyethyl) penems, J. Antibiot., 1996, Vol.49, No.9, p. 921-928.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO 0140228, equivalente a la solicitud colombiana aquí estudiada, y no siendo viable la consecución de dicho artículo por este despacho, se requiere que el solicitante, en virtud de lo establecido en el art. 46

138 133
de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione la publicación completa, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001



Álix Carmona Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

23 FEB. 2006

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO Número 0226	EXAMINADOR TÉCNICO Código 202044
--	--

23-05-06



US005587474A

United States Patent [19]

Kondo et al.

[11] Patent Number: 5,587,474

[45] Date of Patent: Dec. 24, 1996

130

134

D₁

[54] METHOD FOR REMOVING THE PROTECTING GROUP FOR CARBOXYL GROUP

[75] Inventors: Kazuhiko Kondo, Osaka; Hiroshi Horikawa, Kawmishi; Tameo Iwasaki, Nishinomiya, all of Japan

[73] Assignee: Tanabe Selyaku Co., Ltd., Osaka, Japan

[21] Appl. No.: 77,383

[22] Filed: Jun. 17, 1993

[30] Foreign Application Priority Data

Jun. 18, 1992	[JP]	Japan	4-202866
Dec. 4, 1992	[JP]	Japan	4-325031

[51] Int. Cl.⁶ C07D 403/12

[52] U.S. Cl. 540/350

[58] Field of Search 540/350

[56] References Cited

U.S. PATENT DOCUMENTS

4,174,316 11/1979 Christensen et al. 260/239

FOREIGN PATENT DOCUMENTS

0013663	7/1980	European Pat. Off. .
0160876	4/1985	European Pat. Off. .
0215739	5/1986	European Pat. Off. .
0384732	2/1990	European Pat. Off. .
0410727	7/1990	European Pat. Off. .
0474243	9/1991	European Pat. Off. .
9202521	2/1992	European Pat. Off. .

55-105686	8/1980	Japan .
55-69586	9/1980	Japan .
58-103358	6/1983	Japan .
6058987	4/1985	Japan .
60-202886	10/1985	Japan .
61-5081	1/1986	Japan .
62-277389	12/1987	Japan .
3396	1/1991	Japan .
441489	of 1992	Japan .
2176478	6/1986	United Kingdom .

OTHER PUBLICATIONS

Journal Of Organic Chemistry; Homogenous, Palladium (0)-Catalyzed Exchange Deprotection of Allylic Esters, Carbonates, and Carbamates. 1982, vol. 47 No. 3, pp. 587-590.

Journal Of Organic Chemistry; Cephalosporin 3'-Quinolone Esters with a Dual Mode of Action. vol. 33, No. 1, pp. 77-86.

Primary Examiner—Mukund J. Shah

Assistant Examiner—King Lit Wong

Attorney, Agent, or Firm—Browdy and Neimark

[57] ABSTRACT

A method for removing substituted or unsubstituted allyl group from β -lactam compound having substituted or unsubstituted allyl group-protecting carboxyl group, which comprises treating said β -lactam compound with palladium catalyst in the presence of allyl-scavenger in aqueous organic solvent, by which the substituted or unsubstituted group can be easily and effectively removed under moderate conditions so that the desired compound can be obtained in high yield at low cost.

16 Claims, No Drawings

1

METHOD FOR REMOVING THE PROTECTING GROUP FOR CARBOXYL GROUP

The present invention relates to a novel method for removing the protecting group for carboxyl group.

Prior Art

β -Lactam compounds having a carboxyl group have been known to be useful as an antimicrobial agent having excellent antimicrobial activity or a useful intermediate thereof. For instance, there are disclosed various β -lactam antimicrobials such as penem antimicrobials [cf. Japanese Patent Second Publication (Kokoku) No. 396/1991, Japanese Patent First Publication (Kokai) No. 105686/1980, Japanese Patent First Publication (Kokai) No. 58987/1985], carbapenem antimicrobials [cf. Japanese Patent First Publication (Kokai) No. 202886/1985, Japanese Patent First Publication (Kokai) No. 5081/1986, Japanese Patent First Publication (Kokai) No. 233077/1985, Japanese Patent First Publication (Kokai) No. 69586/1980, EP-A-474243], oxapenem antimicrobials [cf. Japanese Patent First Publication (Kokai) No. 103358/1983], cephem antimicrobials [cf. Japanese Patent First Publication (Kokai) No. 277389/1987], carbacephem antimicrobials (cf. U.S. Pat. No. 4,174,316), and the like.

In the processes for preparing these conventional β -lactam antimicrobials, there are used intermediates having a protected carboxyl group, and such protecting groups for carboxyl group are a substituted or unsubstituted allyl group such as allyl group, 3-methylallyl group, 3-phenylallyl group, and the like.

On the other hand, there have been known various methods for removing the above mentioned substituted or unsubstituted allyl groups, for example, 1) treating with tetrakis(triphenylphosphine) palladium (0) in the presence of 2-ethylhexanoic acid potassium salt in a mixture of ethyl acetate/methylene chloride [cf. The Journal of Organic Chemistry, Vol. 47, pp 587-590 (1982)], or 2) treating with palladium diacetate and triethyl phosphite in the presence of 2-ethylhexanoic acid sodium salt in a mixture of ethyl acetate/methylene chloride [cf. Journal of Medicinal Chemistry, Vol. 33, pp. 77-86 (1990)], and the like.

However, in case that above mentioned substituted or unsubstituted allyl group are removed from compounds having an unstable structure such as β -lactam compounds, the above mentioned conventional methods have various defects, for example, the yield of the product is low because the desired compound are decomposed during the reaction, or the removal of the protecting group is not completely accomplished, or the efficiency of catalytic cycle is bad so that a large amount of catalyst is required.

BRIEF DESCRIPTION OF THE INVENTION

An object of the present invention is to provide a novel method for removing the protecting groups for carboxyl group. More particularly, the present invention provides a novel method for removing effectively a substituted or unsubstituted allyl group from a compound having a substituted or unsubstituted allyl group-protecting carboxyl group without decomposition of the desired product, even though the such compound has an unstable structure, such as β -lactam compound.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, the removal of the protecting group from a β -lactam compound having a sub-

2

stituted or unsubstituted allyl group-protecting carboxyl group is carried out by treating said β -lactam compound with a palladium catalyst in the presence of an allyl-scavenger in an aqueous organic solvent. The organic solvent in the "aqueous organic solvent" may be any one being able to mix with water which does not disadvantageously affect the reaction, especially a polar organic solvent is more preferable. The polar organic solvent includes, for example, lower alkanols, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide, acetonitrile, acetone, hexamethylphosphoric triamide (HMPA), and the like. Among these solvents, ethanol, tetrahydrofuran and dioxane are more preferable.

Besides, the content of water in these aqueous organic solvents are preferably in the range of 5%-50%, more preferably in the range of 10%-20%.

The palladium catalyst may be any palladium complex (0), for example, tetrakis(triphenylphosphine)palladium (0), di[1,2-bis(diphenylphosphino)ethane]palladium (0), bis(dibenzylidenacetone)palladium (0), and the like, and tetrakis(triphenylphosphine)palladium (0) is more preferable.

Besides, instead of using the above mentioned palladium complex (0), it is possible to use a palladium compound (II) and a phosphine compound which react to form a palladium complex (0) in the reaction system. The palladium compound (II) includes, for example, palladium di-lower alkanates (e.g. palladium diacetate) and palladium dihalides (e.g. palladium dichloride), and the phosphine compound includes, for example, tri-lower alkyl phosphites (e.g. trimethyl phosphite, triethyl phosphite), and triphenylphosphine. Particularly, a combination of a palladium di-lower alkanate and a tri-lower alkyl phosphite is preferable.

The allyl-scavenger may be any conventional ones such as ones disclosed in Japanese Patent First Publication (Kokai) No. 79180/1989, for example, alicyclic β -dicarbonyl compounds (e.g. dimedone, 1,3-cyclohexanedione), aliphatic β -dicarbonyl compounds (e.g. acetylacetone, ethyl acetoacetate), aromatic amines (e.g. N-lower alkylamine, aniline), alkanolic acids having 2-9 carbon atoms (e.g. acetic acid, propionic acid, 2-ethylhexanoic acid) and alkali metal salts thereof, and di-lower alkylamines (e.g. dimethylamine, diethylamine). Among these compounds, alicyclic β -dicarbonyl compounds, aliphatic β -dicarbonyl compounds and aromatic amines are more preferable. Besides, said allyl-scavengers may be used not only for removing unsubstituted allyl groups but also for removing substituted allyl groups as well.

The reaction of the present invention can more preferably be carried out by using as an aqueous organic solvent a mixture of ethanol and water, a mixture of tetrahydrofuran and water, or a mixture of dioxane and water, and as a palladium catalyst tetrakis(triphenylphosphine)palladium (0) or a palladium complex (0) obtained by reacting a palladium diacetate and triethyl phosphite in the reaction system, and as an allyl-scavenger dimedone.

The reaction of the present invention can preferably be carried out under cooling, at room temperature or with heating, for example, at a temperature from -30° C. to 100° C., more preferably at a temperature from 20° C. to 40° C.

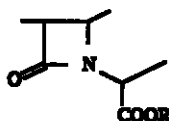
The reaction of the present invention is preferably carried out in the presence of an inorganic or-organic base, and the base includes, for example, alkali metal compounds (e.g. alkali metal hydrogen carbonates, alkali metal carbonates, alkali metal hydroxides, alkali metal hydrides, etc.), organic amines, and the like. These bases are usually used in an amount of 0.1 to 10 equivalents, preferably 1 to 4 equivalents.

3

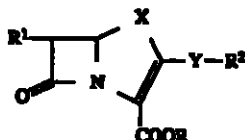
lents to the starting compound, which is sufficient amount for keeping the pH value of the reaction system at pH 5-9, especially at pH 6-8, so that the β -lactam ring is not cloven.

In the reaction of the present invention, the substituted or unsubstituted allyl group may be groups of the formula: $-\text{CH}_2-\text{CH}=\text{CHR}^0$ (wherein R^0 is hydrogen atom, a lower alkyl group or aryl group), more particularly allyl group, 3-methylallyl group, 3-phenylallyl group, and the like.

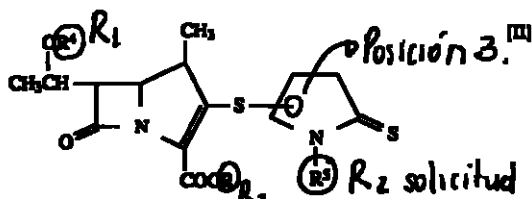
The β -lactam compound having a substituted or unsubstituted allyl-protecting carboxyl group may be any conventional ones, for example, compounds having a partial structure of the following formula:



wherein R is a substituted or unsubstituted allyl group, more particularly, compounds of the following formula [I]:



wherein R is a substituted or unsubstituted allyl group, each of R^1 and R^2 is independently an organic group, X is a group of the formulae: $-\text{CH}_2\text{CH}_2-$, $-\text{S}-\text{CH}_2-$, $-\text{O}-\text{CH}_2-$, $-\text{CH}_2-$, $-\text{CH}(\text{R}^3)-$, $-\text{S}-$ or $-\text{O}-$, R^3 is a lower alkyl group, and Y is sulfur atom, oxygen atom or a single bond. More preferable β -lactam compounds having a substituted or unsubstituted allyl-protecting carboxyl group are compounds of the formula [II]:



wherein R is a substituted or unsubstituted allyl group, R^4 is hydrogen atom or a protecting group for hydroxy group, and R^5 is hydrogen atom or a lower alkyl group.

The above mentioned β -lactam compounds are useful as an antimicrobial agent, a prodrug thereof, or a synthetic intermediate thereof.

In the formula [I], the organic group for R^1 may be any conventional ones which are used in the conventional β -lactam antimicrobials. Suitable examples of the organic groups are hydrogen atom, amino group, azide group, mercapto group, a lower alkyl group, a lower alkoxy group, a lower alkoxythio group, aryl group (e.g. phenyl, naphthyl, etc.), a carbonyl group substituted by a heterocyclic group (e.g. pyrrolidinyl, piperidyl, furyl, thienyl, imidazolynyl, pyridyl, etc.), a lower alkanoyl group substituted by a heterocyclic group (e.g. pyrrolidinyl, piperidyl, furyl, thienyl, imidazolynyl, pyridyl, etc.). Moreover, these groups may have one or more substituents, and the suitable examples of the substituent are amino group, hydroxy group, a lower alkyl group, a lower alkoxy group, a lower alkanoyl group, a lower alkanoylamino group, a lower alkoxy-lower alkanoyl group, mercapto group, a lower alkylthio group, an aralkyl group, an aralkyloxycarbonyl group, a heterocyclic group (e.g. tetrahydropyranyl, etc.), and a lower alkanoyl group substituted by a heterocyclic group (e.g. thienyl).

4

The organic groups for R^2 may be any conventional ones which are used in the conventional β -lactam antimicrobials as well as R^1 , and the suitable examples of the organic groups are a lower alkyl group, a cycloalkyl group, an aryl group (e.g. phenyl, etc.), and a heterocyclic group having at least one nitrogen atom, oxygen atom or sulfur atom as a heteroatom (e.g. pyrrolidinyl, piperidyl, furyl, thienyl, imidazolynyl, pyridyl, etc.), and the like. Besides, these groups may have one or more substituents, such as hydroxy group, a lower alkyl group, an amino-lower alkyl group, a lower alkoxy group, amino group, a lower alkylamino group, mercapto group, a lower alkylthio group, amidino group, guanidino group, carbamoyl group, thiocarbamoyl group, sulfamoyl group, carbamoyloxy group, cyano group, carboxyl group, a lower alkoxy-carbonyl group, a lower alkanoyloxy group, an aralkyloxycarbonyl group, oxo group, thio group, a halogeno group, a cycloalkyl group, an aryl group (e.g. phenyl, etc.), a heterocyclic group (e.g. pyrrolidinyl, piperidyl, furyl, thienyl, imidazolynyl, pyridyl, etc.), and the like.

The organic groups for R^1 or R^2 may optionally be protected by a protecting group, and the protecting group may be any conventional protecting groups.

The protecting groups for hydroxy group represented by R^4 are, for example, a lower alkoxy-carbonyl group, a halogeno-lower alkoxy-carbonyl group, a substituted or unsubstituted phenyl-lower alkyl group (e.g. benzyl group optionally being substituted by a nitro group or a lower alkoxy group), a tri-lower alkylallyl group, a tri(substituted or unsubstituted phenyl)allyl group, a substituted or unsubstituted phenyl-lower alkoxy-carbonyl group (e.g. benzyloxycarbonyl group optionally being substituted by a nitro group or a lower alkoxy group), and the like.

Throughout the present disclosure and claims, the lower alkyl group, the lower alkoxy group and the lower alkanol are ones having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, respectively. The lower alkanoyl group is ones having 2 to 7 carbon atoms, preferably 2 to 5 carbon atoms, and the cycloalkyl group is ones having 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms. The lower alkanate is ones wherein the lower alkanoyl moiety is alkanoyl groups having 2 to 7 carbon atoms, preferably 2 to 5 carbon atoms.

EXAMPLES

The present invention is illustrated in more detail by the following Examples and Reference Example, but should not be construed to be limited thereto.

Example 1

A mixture of sodium hydrogen carbonate (0.84 g) in water (10 ml), dimedone (0.84 g) and tetrahydrofuran (80 ml) is treated with ultrasonics, and thereto is added palladium diacetate (0.11 g) and triethyl phosphite (0.58 g) under nitrogen atmosphere, and the mixture is stirred for three minutes. To the mixture is added (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-carbapen-2-em-3-carboxylic acid allyl ester (3.83 g), and the mixture is stirred at 35°-37° C. for 45 minutes. The mixture is stirred at 5° C. for 30 minutes, and the precipitated crystals are collected by filtration, washed with tetrahydrofuran, and dried under reduced pressure to give (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-carbapen-2-em-3-carboxylic acid sodium salt (3.28 g).

Yield: 90%

5

NMR (D_2O) δ : 1.22 (3H, d, $J=7$ Hz), 1.31 (3H, d, $J=6$ Hz), 2.87–3.07 (1H, m), 3.20–3.60 (3H, m), 3.55–3.72 (1H, m), 4.05–4.35 (4H, m)

Example 2

(1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid allyl ester (400 mg) is dissolved in tetrahydrofuran (16 ml), and thereto are added a solution of potassium hydrogen carbonate (105 mg) in water (4 ml) and dimedone (660 mg), and then further added thereto tetrakis(triphenylphosphine)palladium (0) (42 mg) under nitrogen atmosphere, and the mixture is stirred at 25° C. in the dark for 30 minutes. After the reaction is completed, the mixture is evaporated under reduced pressure to remove the solvent, and to the residue is added water (15 ml), and the mixture is washed with methylene chloride.

To the aqueous layer is added active charcoal (40 mg), and the mixture is filtered on celite (2 g). The residue is washed, and the washing and the aqueous layer are combined, and washed twice with chloroform. The resulting aqueous solution is concentrated under reduced pressure to remove the dissolved organic solvent, and subjected to lyophilization to give (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid potassium salt (328 mg).

Yield: 82%

NMR (D_2O) δ : 1.20 (3H, d), 1.29 (3H, d), 2.94 (1H, dd), 3.28–3.67 (4H, m), 4.06–4.27 (4H, m)

Example 3

To a solution of sodium hydrogen carbonate (84 mg) in water (1 ml) is added dimedone (84 mg), and the mixture is dissolved by treating with ultrasonics. Thereto is added ethanol (8 ml), and further treated with ultrasonics for five minutes. To the mixture are added palladium diacetate (11 mg), triethyl phosphite (0.06 ml) and (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid allyl ester (383 mg) under nitrogen atmosphere, and the mixture is stirred at 35°–38° C. for one hour, and stirred at 20° C. for 10 minutes, and then stirred at 5° C. for 20 minutes. The precipitated crystals are collected by filtration to give (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid sodium salt (157 mg). The mother liquor is concentrated under reduced pressure to remove the ethanol, and thereto is added water (20 ml). The mixture is washed five times with chloroform (20 ml), and the aqueous layer is subjected to lyophilization to give the above sodium salt (168 mg).

6

The NMR data of this product are the same as those of the product obtained in Example 1.

Example 4

Dimedone (169 mg) is dissolved in a solution of sodium hydrogen carbonate (169 mg) in water (2 ml) by ultrasonic treatment, and thereto are added dioxane (16 ml), palladium diacetate (23 mg) and triethyl phosphite (0.12 ml) under nitrogen atmosphere, and further added thereto (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-t-butyldimethylsilyloxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid allyl ester (1.03 g). The mixture is stirred at 30° C. for 30 minutes, and thereto is added diethyl ether (32 ml), and the mixture is stirred at 25° C. for 15 minutes, and further stirred at 5° C. for 30 minutes. The precipitated crystals are collected by filtration, washed with diethyl ether, and dried under reduced pressure at 25° C. for 17 hours to give (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-t-butyldimethylsilyloxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid sodium salt (885 mg).

M.p. 133°–136° C. (decomposed)

Examples 5–8

The compounds listed in Table 1 are treated in the same manner as in Examples 1–4 to remove a substituted or unsubstituted allyl group ($-\text{CH}_2\text{CH}=\text{CHR}^0$) to give the corresponding de-allylated compounds.

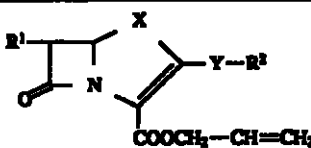
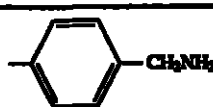
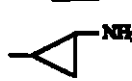
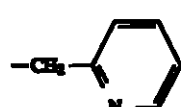
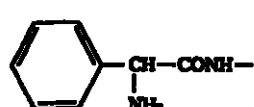
TABLE 1

Ex. No.	R ⁴	R ⁰
5	Hydrogen atom	Methyl group
6	Hydrogen atom	Phenyl group
7	t-Butyldimethylsilyl group	Methyl group
8	t-Butyldimethylsilyl group	Phenyl group

Examples 9–19

The compounds listed in Table 2 are treated in the same manner as in Examples 1–4 to remove an allyl group to give the corresponding de-allylated compounds.

TABLE 2

				
Ex. No.	R ¹	X	Y	R ²
9	CH ₂ CH(OH)-	-CH(CH ₂)-	Single bond	
10	CH ₂ CH(OH)-	-CH(CH ₂)-	Single bond	
11	CH ₂ CH(OH)-	-CH(CH ₂)-	Single bond	
12	CH ₂ CH(OH)-	-CH ₂ -	S	-CH ₂ CH ₂ NH ₂
13	CH ₂ CH(OH)-	-S-	S	-CH ₂ CH ₂ OH
14	CH ₂ CH(OH)-	-O-	S	-CH ₂ CH ₂ NH ₂
15	CH ₂ CH(OH)-	-CH ₂ CH ₂ -	S	-CH ₂ CH ₂ NH ₂
16		-S-CH ₂ -	Single bond	-CH ₂ OCOCH ₃
17		-S-CH ₂ -	Single bond	-CH ₃
18	HOOCCH(NH ₂)- -(CH ₂) ₃ CONH-	-S-CH ₂ -	Single bond	-CH ₂ OCOCH ₃
19	CH ₂ CH ₂ -	-CH ₂ -	S	-CH ₂ CH ₂ NHCOCH ₃

Reference Example 1

(1) To a mixture of (3S,4S)-3-[(1R)-1-t-butylidimethylsilyloxyethyl]-4-[(1R)-1-carboxyethyl]-2-azetidinone (10 g) and acetonitrile (50 ml) are added 4-dimethylaminopyridine (400 mg), t-butylmercaptane (5.98 g) and 1,3-dicyclohexylcarbodiimide (8.22 g) at -5° C. The mixture is stirred at room temperature for 17 hours, and the insoluble materials are removed by filtration, and the filtrate is concentrated under reduced pressure. To the residue is added ethyl acetate, and the mixture is washed, dried and concentrated under reduced pressure. The residue is purified by silica gel column chromatography to give (3S,4S)-3-[(1R)-1-t-butylidimethylsilyloxyethyl]-4-[(1R)-1-t-butylthiocarbonyl-ethyl]-2-azetidinone (11.7 g).

(2) To a mixture of the above compound (320 mg), bromoacetic acid allyl ester (169 mg) and tetrahydrofuran (1 ml) is added dropwise a 1M solution of sodium bis(trimethylsilyl)amide (0.94 ml) in tetrahydrofuran at -65° C. to -60° C., and the mixture is warmed to -30° C. The reaction solution is poured into water, and extracted with diethyl ether. The extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography to give (3S,4S)-3-[(1R)-1-t-butylidimethylsilyloxyethyl]-4-[(1R)-1-t-butylthiocarbonyl-ethyl]-1-(allyloxycarbonylmethyl)-2-azetidinone (538 mg).

(3) To a mixture of the above product (1 g) and tetrahydrofuran (6 ml) is added a 1M solution of sodium bis(trimethylsilyl)amide (4.24 ml) in tetrahydrofuran at -40° C. to

-30° C. The mixture is stirred at -30° C. for five minutes, and thereto is added trimethylchlorosilane (230 mg) at -60° C. The mixture is stirred for five minutes, and thereto is added diphenylphosphoryl chloride (598 mg). The mixture is stirred at 0° C. for one hour, and the reaction solution is poured into a phosphate buffer (pH 7.0), and extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. The resulting residue is purified by reversed phase rubber column (RP-8, manufactured by E. Merck) (solvent; acetonitrile:water=3:1) to give (1R,5R,6S)-6-[(1R)-1-t-butylidimethylsilyloxyethyl]-1-methyl-2-diphenylphosphoryloxycarbapen-2-em-3-carboxylic acid allyl ester (1.1 g) as oil.

(4) To a mixture of the above product (100 mg) and acetonitrile (0.5 ml) are added (4R)-4-mercaptopyrrolidine-2-thion (22 mg) and diisopropylethylamine (21 mg) at 0° C. The mixture is stirred at 0° C. for one hour, and poured into a phosphate buffer (pH 7.0), and extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; n-hexane:chloroform:ethyl acetate=5:5:4) to give (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-t-butylidimethylsilyloxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid allyl ester (57 mg).

(5) To a mixture of the above product (50 mg), tetrahydrofuran (0.5 ml) and acetic acid (6.0 mg) is added a 1M solution of tetra-n-butylammonium fluoride in tetrahydro-

furan (0.35 ml) under ice-cooling, and the mixture is stirred at room temperature for two hours. To the reaction solution is added ethyl acetate, and the mixture is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:ethanol=20:1) to give (1R,5S,6S)-2-[(4R)-pyrrolidine-2-thion-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-carbapen-2-em-3-carboxylic acid allyl ester (13 mg).

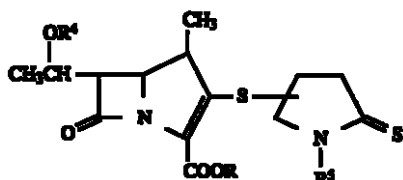
M.p. 139°-141° C.

Effects of the Invention

According to the present invention, substituted or unsubstituted allyl groups are effectively removed under moderate conditions from a compound having substituted or unsubstituted allyl group-protecting carboxyl group, even though said compound has an unstable structure such as β -lactam compound, so that the desired compound can be obtained easily and in high yield without decomposition of the desired compound. Accordingly, the method of the present invention is industrially useful as a method for removing a substituted or unsubstituted allyl group from a carboxyl group.

What is claimed is:

1. A method for removing the protecting group of the carboxyl group from a compound of the formula II:



wherein R is the formula: $-\text{CH}_2-\text{CH}=\text{CHR}^0$, R^0 is a hydrogen atom, a lower alkyl group or a phenyl group, R^4 is a hydrogen atom or a protecting group for a hydroxy group, and R^5 is a hydrogen atom or a lower alkyl group comprising:

reacting said compound II with an alkyl-scavenger selected from the group consisting of dimedone, 1,3-cyclohexadione, acetylacetone, ethylacetoacetate, an N-lower alkyl aniline and aniline in the presence of a palladium (II) compound and a compound selected from the group consisting of a tri-lower alkyl phosphate and a triphenyl phosphine in an aqueous organic solvent.

2. The method according to claims 1, wherein R^4 is a hydrogen atom, a lower alkoxy carbonyl group, a halogeno-lower alkoxy carbonyl group, a phenyl-lower alkyl group, a phenyl lower alkyl group in which the phenyl group is substituted by a member selected from the group consisting of a nitro group and a lower alkoxy group, a tri-lower alkylsilyl group, a triphenylsilyl group, and a phenyl-lower alkoxy carbonyl group or a phenyl-lower alkoxy carbonyl group in which the phenyl group is substituted by a member selected from the group consisting of a nitro group and a lower alkoxy group.

3. The method according to claim 1, wherein R^4 is a hydrogen atom or a t-butyldimethylsilyl group, and R^5 is a hydrogen atom.

4. The method according to claim 1, wherein the palladium compound is a palladium (II) di-lower alkanate or a palladium dihalide.

5. The method according to claim 4, wherein the reaction is carried out in the presence of an alkali metal hydrogen carbonate, an alkali metal carbonate, an alkali metal hydroxide, an alkali metal hydride or an organic amine.

6. The method according to claim 1, wherein the palladium compound is a palladium (II) di-lower alkanate.

7. The method according to claim 1, wherein the compound selected from the group consisting of a tri-lower alkyl phosphite and a triphenylphosphine is a tri-lower alkyl phosphite.

8. The method according to claim 1, wherein the palladium compound is a palladium (II) di-lower alkanate and the compound selected from the group consisting of a tri-lower alkyl phosphite and a triphenylphosphine is a tri-lower alkyl phosphite.

9. The method according to claim 1, wherein the palladium compound is palladium (II) diacetate and the compound selected from the group consisting of a tri-lower alkyl phosphite and a triphenylphosphine is triethyl phosphite.

10. The method according to claim 1, wherein the aqueous organic solvent is a mixture of water and a polar organic solvent or a mixture of water and polar organic solvents, said organic solvent being selected from the group consisting of a lower alkanol, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide, acetonitrile, acetone, and hexamethylphosphoric triamide.

11. The method according to claim 10, wherein the polar organic solvent is selected from the group consisting of ethanol, tetrahydrofuran and dioxane.

12. The method according to claim 10, wherein the reaction is carried out in the presence of an alkali metal hydrogen carbonate, an alkali metal carbonate, an alkali metal hydroxide, an alkali metal hydride or an organic amine.

13. The method according to claim 1, wherein the alkyl-scavenger is dimedone.

14. The method according to claim 13, wherein the reaction is carried out in the presence of an alkali metal hydrogen carbonate, an alkali metal carbonate, an alkali metal hydroxide, an alkali metal hydride or an organic amine.

15. The method according to claim 1, wherein the palladium compound is palladium (II) diacetate, the compound selected from the group consisting of a tri-lower alkyl phosphite and a triphenylphosphine is triethyl phosphite, the aqueous organic solvent is a mixture of water and a polar organic solvent which is selected from the group consisting of ethanol, tetrahydrofuran and dioxane, and the alkyl-scavenger is dimedone.

16. The method according to claim 1, wherein the reaction is carried out in the presence of an alkali metal hydrogen carbonate, an alkali metal carbonate, an alkali metal hydroxide, an alkali metal hydride or an organic amine.

* * * * *

245/140

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

2020/
Bogotá, D.C.,

Doctora
Margarita Castellanos Abondano
Apoderado
KYOTO PHARMACEUTICAL INDUSTRIES, LTD.

Oficio N° 2.293

REFERENCIA	Radicación	00 91283
	Trámite	002
	Evento	001
	Actuación	430
	Folios	006

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 91283, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

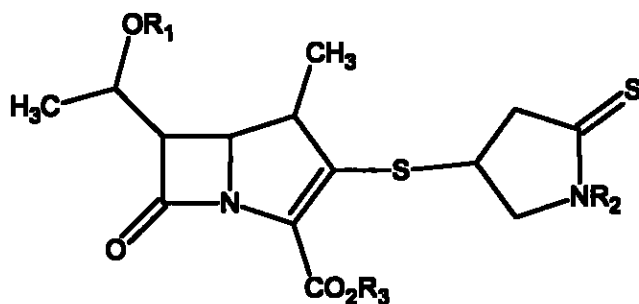
- El resumen y el capítulo descriptivo de la solicitud que se encuentra en los folios 5 y 6 a 28 respectivamente.
- Los ejemplos que ilustran la solicitud y que se encuentran en los folios 28 a 46.
- Las cláusulas 1 a 7 relacionadas en el capítulo reivindicatorio de la solicitud que se encuentran en los folios 47 a 50.
- El primer examen de forma realizado a la solicitud que se encuentra en el folio 57.
- La respuesta al primer examen de forma realizado a la solicitud, allegada mediante memorial de fecha 28/02/2001 en los folios 58 a 127 y que contiene la copia de la solicitud original mediante la cual se reivindica prioridad.
- La copia de la solicitud original mediante la cual se reivindica prioridad de Japón No. 345535/1999 del 03/12/1999 en los folios 67 a 119 junto con su traducción correspondiente en los folios 120 a 127.
- La solicitud de examen de patentabilidad que se encuentra en los folios 134 y 135.

2. OBJETO DE LA INVENCION:

La invención hace referencia a: **"Compuesto de carbapenem, uso del mismo y compuestos intermedios para el mismo"**

• **Reivindicaciones 1 a 5:**

Se reivindica un compuesto de carbapenem de fórmula (I):



Tal es el caso de:

Fenil éster del ácido (1R,5S,6S)-6-[(1R)-1-(L-alaniloxy)etil]-2-[(4R)-pirrolidin-2-tion-4-iltio]-1-metilcarbapen-2-em-3-carboxílico

5-indanil éster del ácido (1R,5S,6S)-6-[(1R)-1-(L-alaniloxy)etil]-2-[(4R)-pirrolidin-2-tion-4-iltio]-1-metilcarbapen-2-em-3-carboxílico

3,4-metilendioxifenil éster del ácido (1R,5S,6S)-6-[(1R)-1-(L-alaniloxy)etil]-2-[(4R)-pirrolidin-2-tion-4-iltio]-1-metilcarbapen-2-em-3-carboxílico

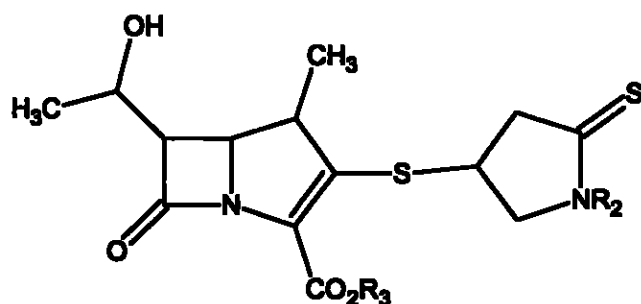
Fenil éster de ácido (1R,5S,6S)-6-[(1R)-1-(L-valiloxi)etil]-2-[(4R)-pirrolidin-2-tion-4-iltio]-1-metilcarbapen-2-em-3-carboxílico

Entre otros...

Además se reivindica un agente antibacteriano que comprende el compuesto de carbapenem de la cláusula 1, definido por la fórmula (I) o una sal farmacéuticamente aceptable del mismo como ingrediente activo y que se destina para uso oral.

• **Reivindicaciones 6 y 7:**

Se reivindica un compuesto de carbapenem de fórmula (II):



Tal es el caso de:

Fenil éster del ácido (1R,5S,6S)-6-[(1R)-1-hidroxietil]-2-[(4R)-pirrolidin-2-tion-4-iltio]-1-metilcarbapen-2-em-3-carboxílico

5-indanil éster del ácido (1R,5S,6S)-6-[(1R)-1-hidroxietil]-2-[(4R)-pirrolidin-2-tion-4-iltio]-1-metilcarbapen-2-em-3-carboxílico

3,4-metilendioxifenil éster del ácido (1R,5S,6S)-6-[(1R)-1-hidroxietil]-2-[(4R)-pirrolidin-

2-tion-4-iltio]-1-metilcarbapen-2-em-3-carboxílico

Una vez catalogada la solicitud ésta se clasificó en la sección A 61 K ³¹/40 // ³¹/095 de la Clasificación Internacional de Patentes.

3. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontró el siguiente documento, anterior a la fecha de presentación de la solicitud – 03/12/1999 – y que se relaciona directamente con la materia objeto de estudio:

Nº	Documento	Título	Fecha de Publicación
D1	US5587474	"Method for removing the protecting group for carboxyl group"	24/12/1996

Ver copia de la anterioridad en los folios 139 a 144.

4. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

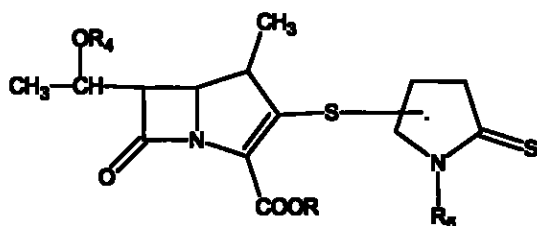
El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

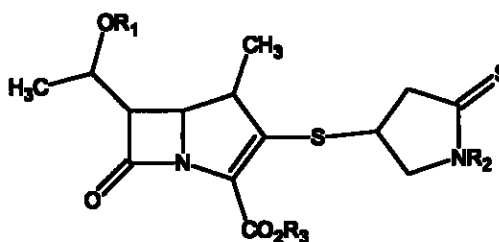
4.1 Evaluación del NIVEL INVENTIVO:

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

La anterioridad D1 señala un método para remover un grupo alilo de un compuesto β-lactámico sustituido o insustituido, en particular en la columna 3 líneas 33 a 46 muestra la estructura de un compuesto beta-lactámico de fórmula (III), de estructura similar a aquella reivindicada por la fórmula (I) en la cláusula independiente 1 de la presente solicitud:

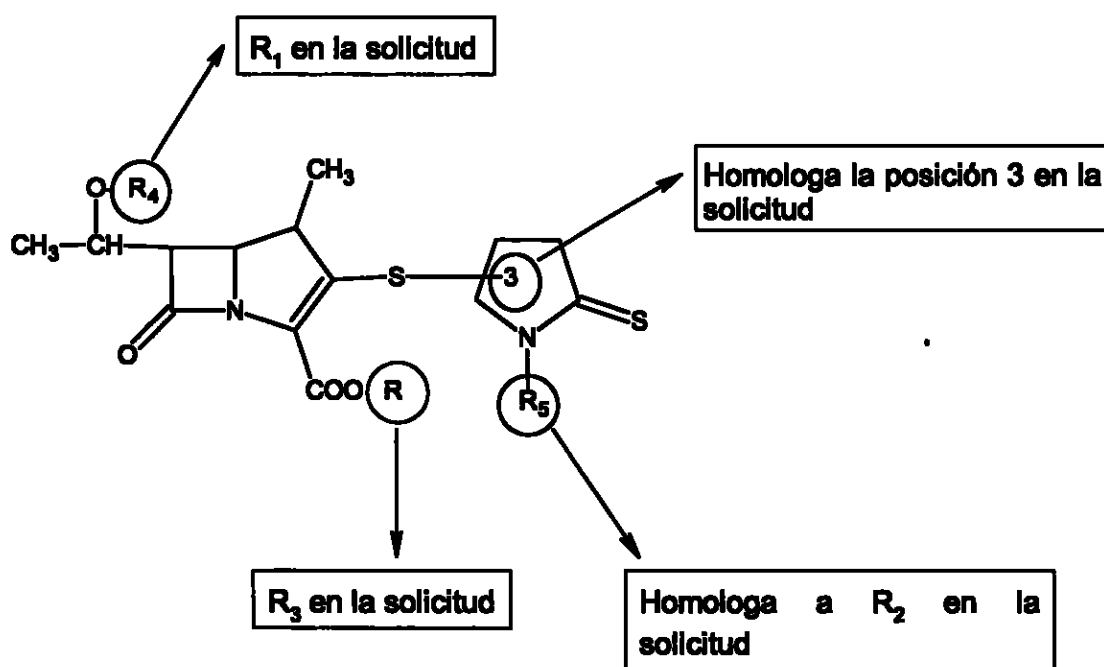


Fórmula (III) de la Anterioridad D1



Fórmula (I) reivindicada

Así las cosas, al realizar la comparación estructural punto a punto de cada uno de los radicales y sustituyentes que comprenden las fórmulas en mención se encuentran las siguientes analogías estructurales:



R_4 de la anterioridad D1 toma las siguientes connotaciones: es hidrógeno o un grupo protector del radical hidroxilo como: alcóxicarbonilo, alcóxicarbonilo halogenado, fenil sustituido por un grupo alquilo o insustituido, un grupo trialkylsilo entre otros. En el caso de la solicitud R_1 puede ser un grupo acilo de un α -aminoácido como: alaniloxi, valiloxi, leuciloxi, isoleuciloxi, gliciloxi, lisiloxi, proliloxi, fenilalaniloxi y glicilgliciloxi en configuración L.

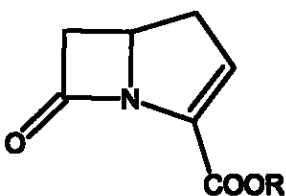
R_5 de la anterioridad D1 toma las siguientes connotaciones: hidrógeno o alquilo. En el caso de la solicitud R_2 puede ser hidrógeno o alquilo inferior.

R es un grupo alilo sustituido o no sustituido. En el caso de la solicitud R_3 es un fenilo opcionalmente sustituido.

Y la posición de enlace al anillo de pirrol por el azufre puede ser 2 ó 3 con respecto al heteroátomo (N). En el caso de la solicitud (fórmula I) la posición de enlace al azufre es 3 con respecto al heteroátomo del pirrol.

En consecuencia, para un técnico de nivel medio, versado en la materia técnica resulta derivable del arte la inclusión de radicales como los que se presentan en la anterioridad D1. Lo anterior se ratifica aún más cuando al comparar la estructura (III) de la anterioridad con la fórmula (II) reclamada se encuentra que existe mayor similitud debido a que se tiene un grupo hidroxilo para la sustitución éter en el anillo

del ácido 1-carbapen-2-em-3-carboxílico y R_4 según la anterioridad puede ser hidrógeno para formar el correspondiente hidroxilo.

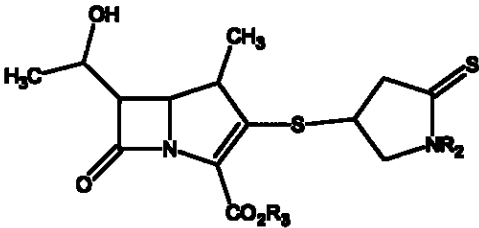
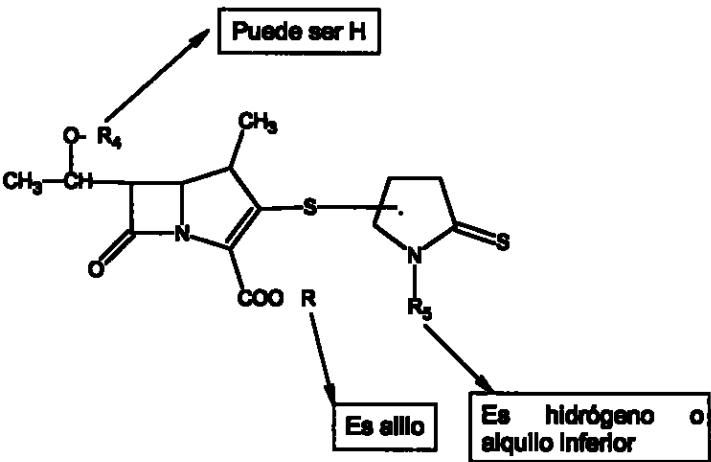


En el caso de R_2 puede ser hidrógeno o alquilo inferior como en la anterioridad D1.

R_3 que es fenilo opcionalmente sustituido en la solicitud puede ser, en el caso de la anterioridad, alilo (R en D1).

Y la posición de enlace al anillo de pirrol por el azufre puede ser 2 ó 3 con respecto al heteroátomo (N). En el caso de la solicitud (fórmula II) la posición de enlace al azufre es 3 con respecto al heteroátomo del pirrol.

De esta forma se encuentra la siguiente analogía estructural entre la fórmula (II) reclamada en la cláusula 6 y la de la anterioridad D1:



Fórmula (II) reivindicada

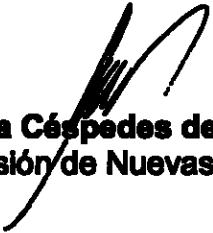
Fórmula (III) de la anterioridad D1

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US5587474	1 a 7	Nivel Inventivo

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

150 145
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha: 23 FEB. 2006

CONCEPTO TÉCNICO Número 0231	EXAMINADOR TÉCNICO Código 202044
--	--

24-05-06

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

146

RADICACIÓN: 0-91283

EDICTO No. 9376

**LA SECRETARÍA GENERAL AD-HOC
HACE SABER:**

Que esta Superintendencia profirió Resolución No. 14249 de 31-MAY-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

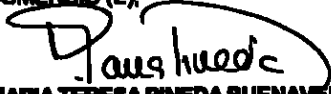
ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPUESTO DE CARBAPENEM, USO DEL MISMO Y COMPUESTOS INTERMEDIOS PARA EL MISMO".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Margarita Castellanos Abondano, o a quien haga sus veces, en su calidad de apoderada de Kyoto Pharmaceutical Industries, Ltd., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los **31 MAY 2006**

LA SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E).


MARIA TERESA PINEDA BUENAVENTURA

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 20-JUN-2006  Este edicto se desflja hoy 05-JUL-2006 a las cinco (5:00 p.m.) 
Secretaría General Ad-Hoc
EDICTO No. 9376