Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2379650 C 2008/09/02

(11)(21) 2 379 650

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2000/07/27
(87) Date publication PCT/PCT Publication Date: 2001/02/08
(45) Date de délivrance/Issue Date: 2008/09/02
(85) Entrée phase nationale/National Entry: 2002/01/16
(86) N° demande PCT/PCT Application No.: JP 2000/005031
(87) N° publication PCT/PCT Publication No.: 2001/009135
(30) Priorités/Priorities: 1999/07/30 (JP11/216807);
1999/07/30 (JP11/216806)

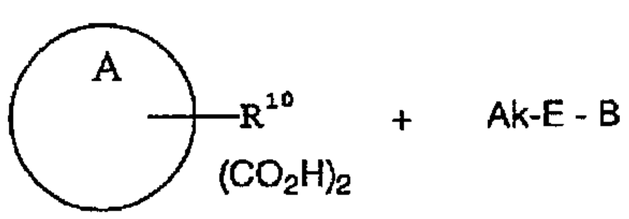
(51) Cl.Int./Int.Cl. *C07D 477/20* (2006.01),
C07D 463/02 (2006.01), *C07D 463/22* (2006.01),
C07D 477/08 (2006.01), *C07D 499/04* (2006.01),
C07D 499/21 (2006.01), *C07D 499/68* (2006.01),
C07D 501/02 (2006.01), *C07D 501/22* (2006.01),
C07D 501/34 (2006.01), *C07D 501/36* (2006.01),
C07D 501/38 (2006.01), *C07D 519/06* (2006.01)

(72) Inventeurs/Inventors:
KAYANO, AKIO, JP;
CHIBA, HIROYUKI, JP;
NAKAMURA, TAIJU, JP;
SAKURAI, SHIN, JP;
...

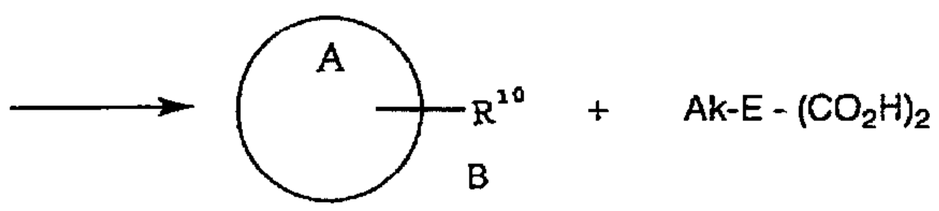
(73) Propriétaire/Owner:

(54) Titre : PROCEDE DE PREPARATION DE SELS D'ADDITION ACIDES INORGANIQUES D'ANTIBIOTIQUES DE BASE ET OXALATES INTERMEDIAIRES

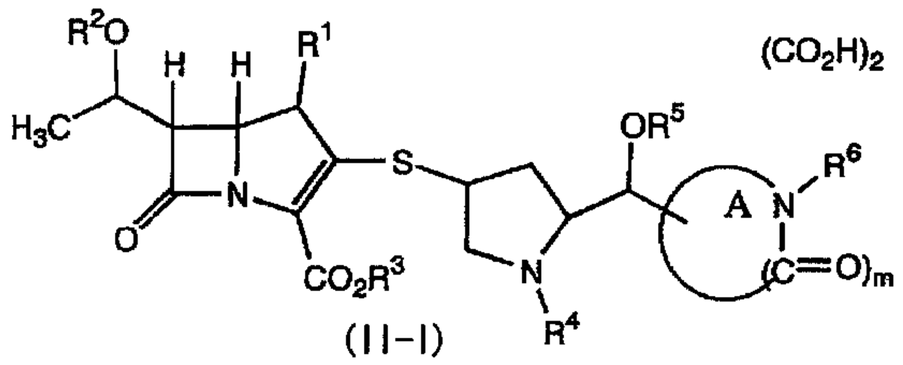
(54) Title: PROCESS FOR PRODUCING A BASIC ANTIBIOTIC INORGANIC ACID SALT, AND OXALATE INTERMEDIATE



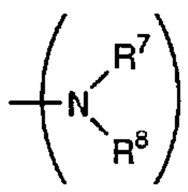
(II) (III)



(I)



(II-1)



(IV)

(57) Abrégé/Abstract:
The present invention provides: an industrially-excellent and novel process for producing a basic antibiotic inorganic acid salt, for example, an excellent production process for producing a hydrochloride thereof industrially, that is, a production process which

CA 2379650 C 2008/09/02

(11)(21) 2 379 650

(13) C

(72) Inventeurs(suite)/Inventors(continued): ISHIZUKA, HIROYUKI, JP; SAITO, HIROYUKI, JP; KOMATSU, YUUKI, JP; SASHO, MANABU, JP; SATO, NOBUAKI, JP; NEGI, SHIGETO, JP

(73) Propriétaires(suite)/Owners(continued):EISAI R&D MANAGEMENT CO., LTD., JP

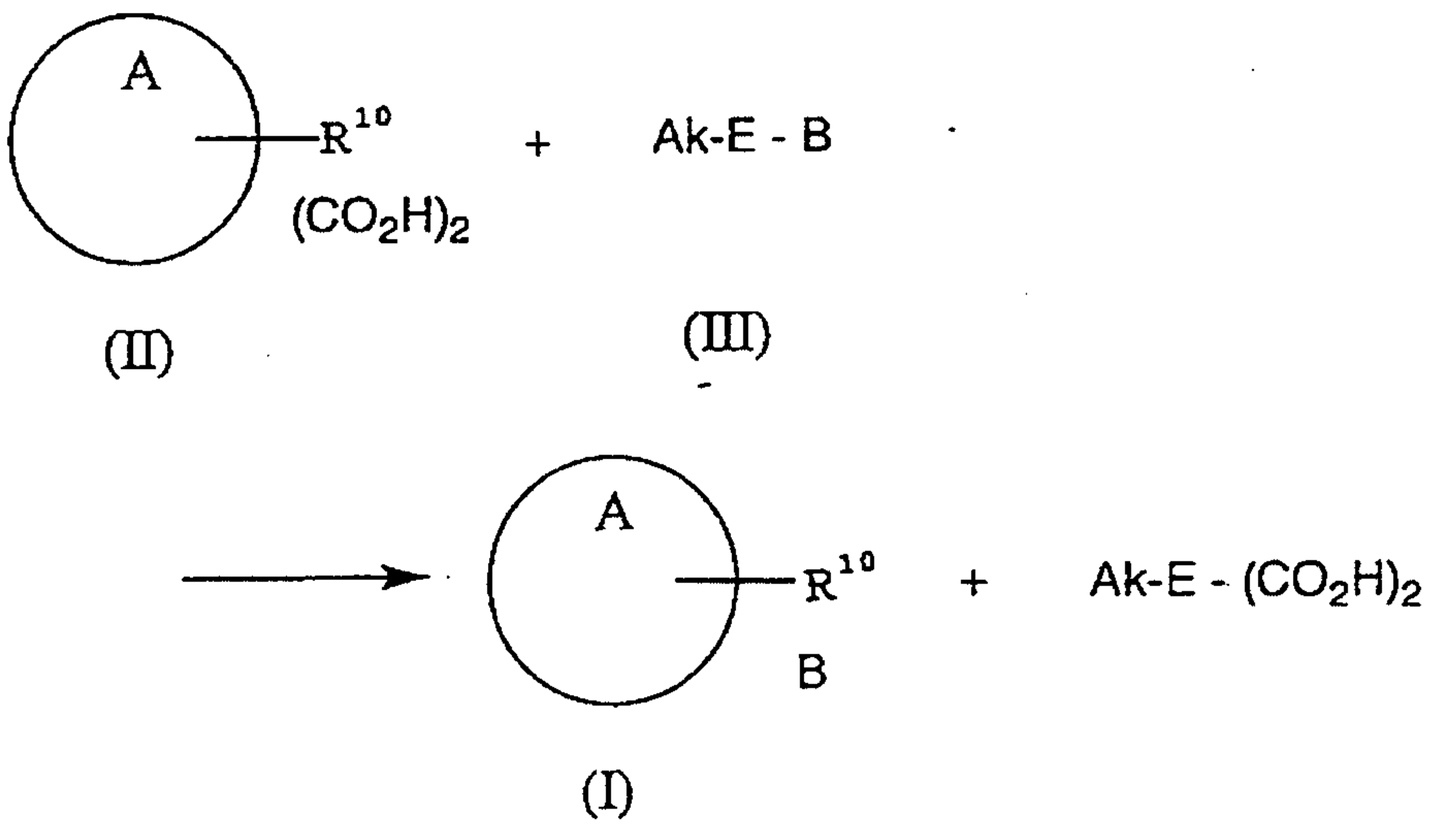
(74) Agent: SMART & BIGGAR

(57) Abrégé(suite)/Abstract(continued):
comprises subjecting a basic antibiotic oxalate (II) to salt-exchange with an alkali earth metal salt (III) of an inorganic acid: (see formula II) (see formula III) (wherein the ring A means the basic antibiotic; R^{10} means a protected functional group used in organic synthesis; Ak-E means the alkali earth metal; and B means the inorganic acid, respectively); a novel oxalate useful as a production intermediate for producing an antibiotic hydrochloride industrially, that is, an oxalate (II-I) of a carbapenem compound represented by the following formula: (see formula II-I) (wherein the ring A represents a 3- to 7-membered ring having at least one nitrogen atom, and the ring A may be substituted with other than R^6; R^1 represents hydrogen or methyl group; R^2 and R^5 are the same as or different form each other and each represents hydrogen or a hydroxyl-protecting group; R^3 represents a carboxyl-protecting group; R^4 represents hydrogen, a lower alkyl group or an amino-protecting group; R^6 represents (1) hydrogen, (2) an optionally protected hydroxyl group, carbamoyl, formimidoyl, acetoimidoyl or a lower alkyl group which may be substituted with a substituent represented by the formula: (see formula IV) (wherein R^7 and R^8 are the same as or different from each other and each represents hydrogen, a lower alkyl group or an amino-protecting group) or (3) an amino-protecting group or an imino-protecting group; and m is 0 or 1); and a process for producing its.

Abstract

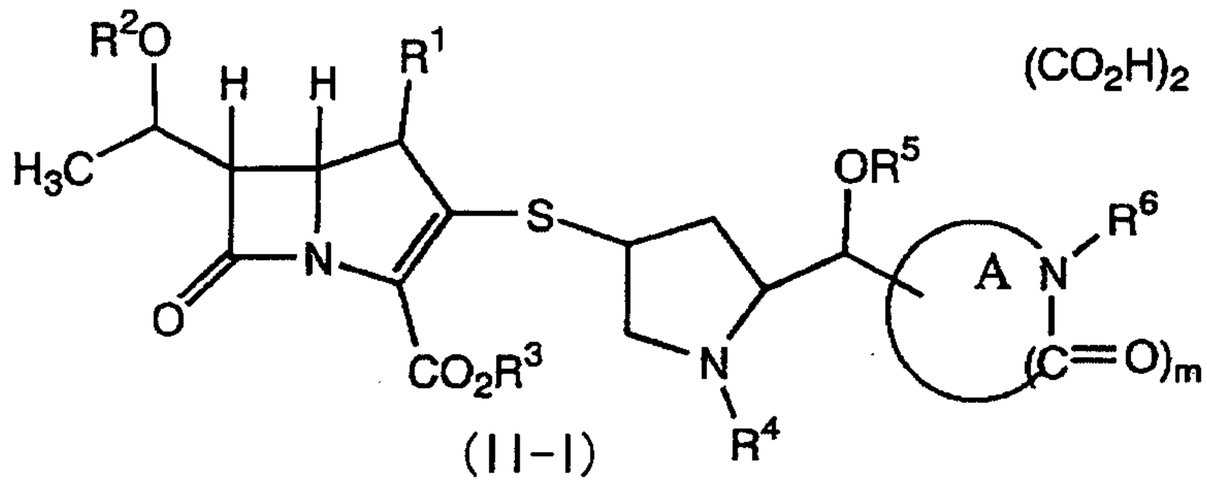
The present invention provides:

an industrially-excellent and novel process for producing a basic antibiotic·inorganic acid salt, for example, an excellent production process for producing a hydrochloride thereof industrially, that is, a production process which comprises subjecting a basic antibiotic·oxalate (II) to salt-exchange with an alkali earth metal salt (III) of an inorganic acid:



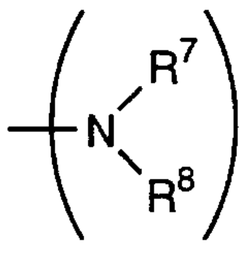
(wherein the ring A means the basic antibiotic; R^{10} means a protected functional group used in organic synthesis; Ak-E means the alkali earth metal; and B means the inorganic acid, respectively);

a novel oxalate useful as a production intermediate for producing an antibiotic·hydrochloride industrially, that is, an oxalate (II-I) of a carbapenem compound represented by the following formula:



(II-I)

(wherein the ring A represents a 3- to 7-membered ring having at least one nitrogen atom, and the ring A may be substituted with other than R^6; R^1 represents hydrogen or methyl group; R^2 and R^5 are the same as or different form each other and each represents hydrogen or a hydroxyl-protecting group; R^3 represents a carboxyl-protecting group; R^4 represents hydrogen, a lower alkyl group or an amino-protecting group; R^6 represents (1) hydrogen, (2) an optionally protected hydroxyl group, carbamoyl, formimidoyl, acetoimidoyl or a lower alkyl group which may be substituted with a substituent represented by the formula:



(wherein R^7 and R^8 are the same as or different from each other and each represents hydrogen, a lower alkyl group or an amino-protecting group) or (3) an amino-protecting group or an imino-protecting group; and m is 0 or 1); and

a process for producing its.

Description

Process for producing a basic antibiotic·inorganic acid salt, and oxalate intermediate

Field of the Invention

The present invention relates to a novel and industrially-excellent process for producing a basic antibiotic·inorganic acid salt, for example, an industrially-excellent production process for producing an inorganic acid salt of an excellent antimicrobial agent having strong antimicrobial action on gram-positive bacteria and gram-negative bacteria, disclosed in JP-A 8-73462. More specifically, it relates to industrially-excellent production process for producing, for example, (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid·hydrochloride, a novel oxalate useful as a production intermediate, and a process for producing it.

Prior Art

In order to produce a basic antibiotic·inorganic acid salt, it is general to produce a free form, purify by column chromatography etc., and react the product with an inorganic acid.

For example, in the process disclosed in JP-A 8-73462,

WO96/01261 or Example 9 of EP-A 773222 as a process for producing (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid·hydrochloride etc., the objective product is obtained by subjecting a p-nitrobenzyl ester compound to catalytic reduction, purifying by reversed-phase silica gel chromatography, conversing the product to a hydrochloride, and subjecting it to freeze-drying.

In the above-mentioned process in the prior art, the purification by chromatography is performed. Thus, a solvent is used in a large amount. Therefore, costs for the production rise to a considerable degree. Additionally, many problems as follows arise: difficulty in industrial processing in large amount, the possibility of the generation of thermal cruelty (thermal decomposition) at the time of concentrating fractions, a problem of the remaining of the solvent in the final product, a problem about disposal of waste liquid and environment pollution by transpiration of the solvent. Thus, it cannot be said that the process is a process suitable for industry.

Moreover, it is necessary to perform subtle adjustment of pH when the free form is produced (neutralized) or converted to the hydrochloride. Thus, the process requires much labor and cost in industrial production. Moreover, freeze-drying is required in the last step, and results additional problems as follows: a further rise in the production costs, unsuitability thereof for processing in large amount and necessity of much

time.

Disclosure of the Invention

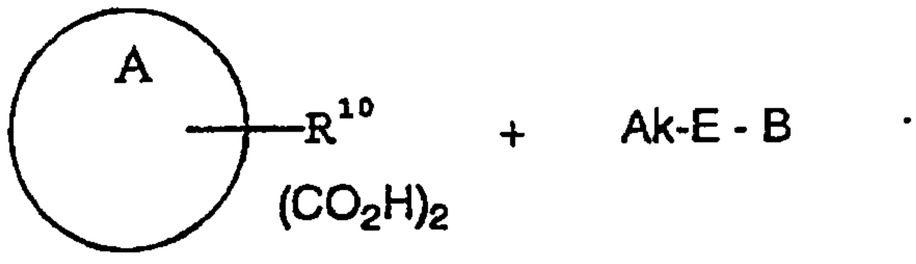
Thus, the present inventors made eager investigations to pursue a novel production process excellent in viewpoints such as production costs, operability (workability, safety and non-toxicity), the purity of final products, and the protection of the environment.

As a result, they have found out that the above-mentioned problems can be overcome at a stroke by using a novel oxalate which will be in detail described below as a production intermediate and subjecting the oxalate to salt-exchange with an alkali earth metal salt of an inorganic acid. Thus, they have accomplished the present invention.

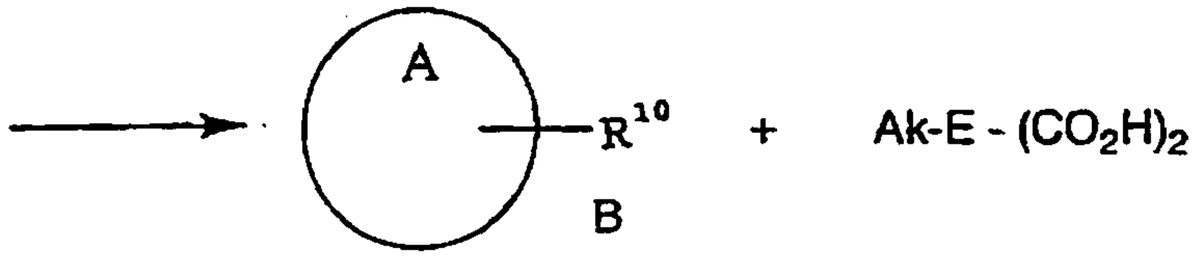
Therefore, an object of the present invention is to provide a novel production process useful for producing a basic antibiotic·inorganic acid salt industrially, and a novel production intermediate useful for producing antimicrobial agents, and a process for producing it.

The present invention is a process for producing a basic antibiotic·inorganic acid salt (I), which comprises subjecting a basic antibiotic·oxalate (II) to salt-exchange with an alkali earth metal salt (III) of an inorganic acid.

65702-503



(II) (III)



(I)

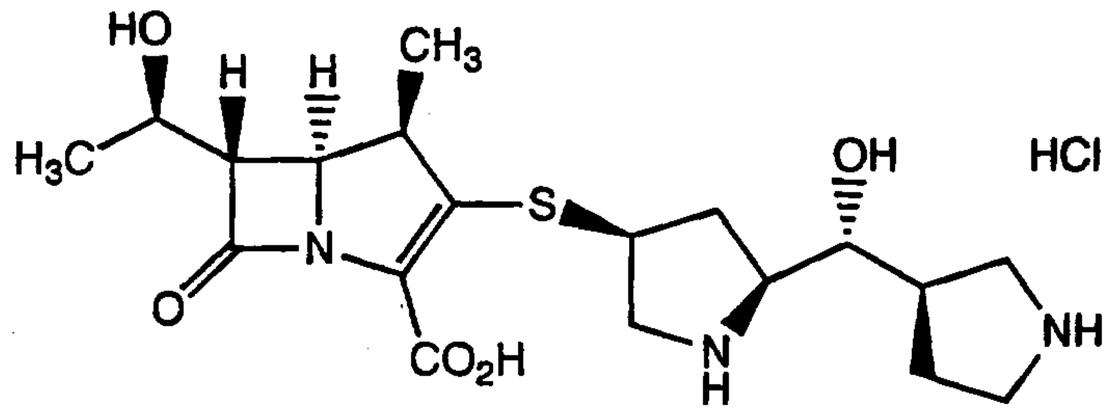
wherein the ring A means the basic antibiotic; R^{10} means a protected functional group used in organic synthesis; Ak-E means the alkali earth metal; and B means the inorganic acid.

An embodiment relates to a process for producing a basic antibiotic·inorganic acid salt (I), which comprises subjecting a basic antibiotic protector·oxalate (VI) to deprotection reaction; and then subjecting to salt-exchange with an alkali earth metal salt (III) of an inorganic acid. An embodiment relates to a process for producing a basic antibiotic inorganic acid salt (I), which comprises subjecting a basic antibiotic protector·oxalate (VI) to deprotection reaction; then subjecting to salt-exchange with an alkali earth metal salt (III) of an inorganic acid; and then crystallizing the resultant by adding a poor solvent thereto.

An embodiment relates to a process for producing (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid·hydrochloride

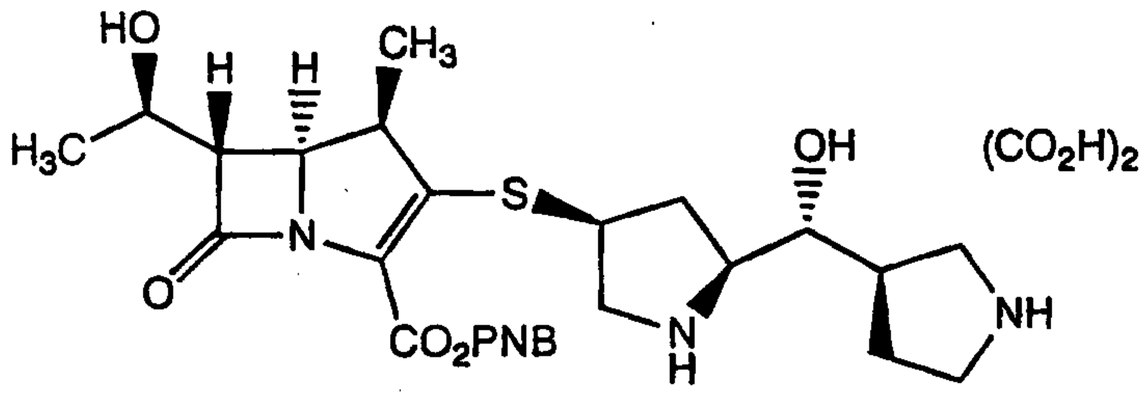
65702-503

(VIII) represented by the following formula:



(VIII)

which comprises subjecting p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate·oxalate (VII) represented by the following formula:

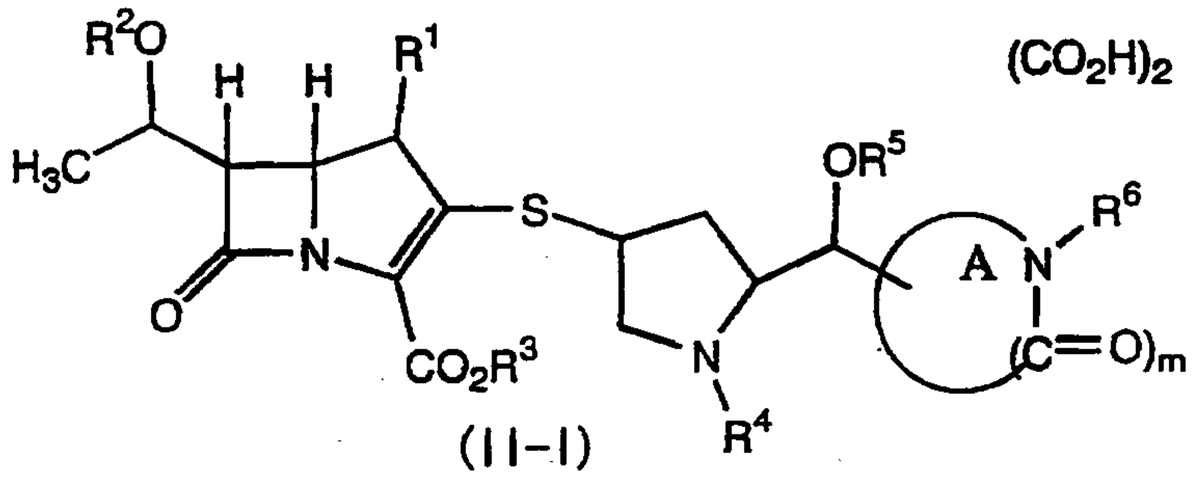


(VII)

(wherein PNB represents p-nitrobenzyl group) to deprotection reaction; then subjecting to salt-exchange with calcium chloride; and then crystallizing the resultant by adding methanol and/or isopropanol thereto.

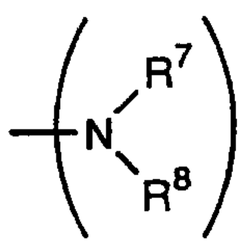
An embodiment relates to a process for producing a basic antibiotic·inorganic acid salt (I), in which the oxalate (II-I) of a carbapenem compound represented by the following formula is a basic antibiotic·oxalate (II), and which comprises subjecting the basic antibiotic·oxalate (II) to salt-exchange with an alkali earth metal salt (III) of an inorganic acid.

65702-503



(II-I)

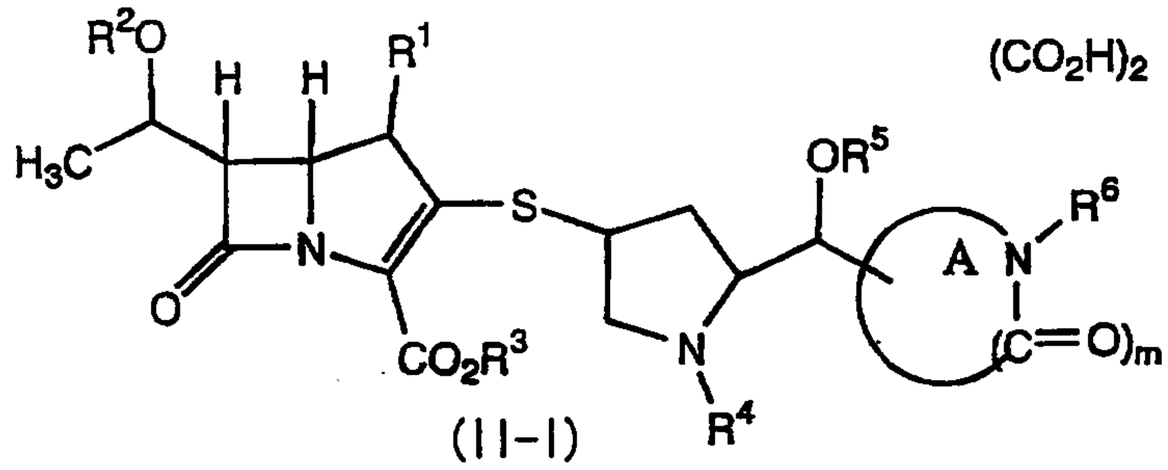
Wherein the ring A represents a 3- to 7-membered ring having at least one nitrogen atom, and the ring A may be substituted with other than R^6; R^1 represents hydrogen or methyl group; R^2 and R^5 are the same as or different from each other and each represents hydrogen or a hydroxyl-protecting group; R^3 represents a carboxyl-protecting group; R^4 represents hydrogen, a lower alkyl group or an amino-protecting group; R^6 represents (1) hydrogen, (2) an optionally protected hydroxyl group, carbamoyl, formimidoyl, acetoimidoyl or a lower alkyl group which may be substituted with a substituent represented by the formula:



(wherein R^7 and R^8 are the same as or different from each other and each represents hydrogen, a lower alkyl group or an amino-protecting group) or (3) an amino-protecting group or an imino-protecting group; and m is 0 or 1.

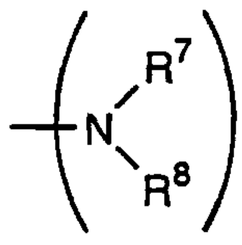
An aspect provides an oxalate (II-I) of a carbapenem compound represented by the following formula:

65702-503



(II-I)

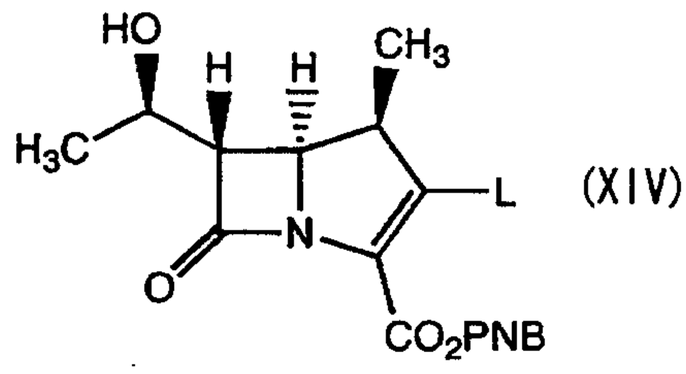
wherein the ring A represents a 3- to 7-membered ring having at least one nitrogen atom, and the ring A may be substituted with other than R^6; R^1 represents hydrogen or methyl group; R^2 and R^5 are the same as or different from each other and each represents hydrogen or a hydroxyl-protecting group; R^3 represents a carboxyl-protecting group; R^4 represents hydrogen, a lower alkyl group or an amino-protecting group; R^6 represents (1) hydrogen, (2) an optionally protected hydroxyl group, carbamoyl, formimidoyl, acetoimidoyl or a lower alkyl group which may be substituted with a substituent represented by the formula:



(wherein R^7 and R^8 are the same as or different from each other and each represents hydrogen, a lower alkyl group or an amino-protecting group) or (3) an amino-protecting group or an imino-protecting group; and m is 0 or 1.

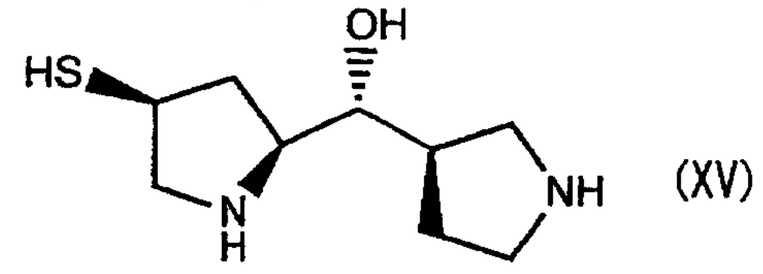
Further, an embodiment relates to a process for producing p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-

hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate·oxalate (II-III), which comprises reacting p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate-2-active compound (XIV) represented by the following formula:



(XIV)

(wherein PNB has the same meaning as described above; and L means a leaving group) with (2S,4S)-2-{[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}-4-mercaptopyrrolidine·dihydrochloride (XV) represented by the following formula:



(XV) · 2HCl

and then converting the resultant into to an oxalate.

Herein, the basic antibiotic·inorganic acid salt (I) according to the present invention is an antibiotic having a basic salt in the molecule thereof, and is not limited so long as the antibiotic is combined with an inorganic acid to form a salt. Preferred examples thereof include the following:

(1) cefotiam (CAS Res.No.: 66309-69-1) hydrochloride;

(2) cefmenoxime (CAS Res.No.: 75738-58-8) hydrochloride;

(3) cefozopran(CAS Res.No.: 113981-44-5) hydrochloride;

(4) cefpirome(CAS Res.No.: 98753-19-6) sulfate;

(5) cefepime (CAS Res.No.: 123171-59-5) hydrochloride;

(6) cefoselis (CAS Res.No.: 122841-10-5) sulfate;

(7) cefotiam hexetil (CAS Res.No.: 95789-30-3) hydrochloride;

(8) cefetamet pivoxil (CAS Res.No.: 65052-63-3) hydrochloride;

(9) cefcapene pivoxil (CAS Res.No.: 135889-00-8) hydrochloride;

(10) talampicillin (CAS Res.No.: 39878-70-1) hydrochloride;

(11) bacampicillin (CAS Res.No.: 37661-08-8) hydrochloride

(12) lenampicillin (CAS Res.No.: 80734-02-7) hydrochloride;

(13) pivmecillinam (CAS Res.No.: 32886-97-8) hydrochloride;

and

(14) (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid·hydrochloride (JP-A 8-73462, Example 9).

Next, the basic antibiotic·oxalate (II) according to the present invention is a starting material for producing the above-mentioned basic antibiotic·inorganic acid salt (I) by salt-exchange, and specific examples thereof include an oxalate of the above-mentioned basic antibiotic.

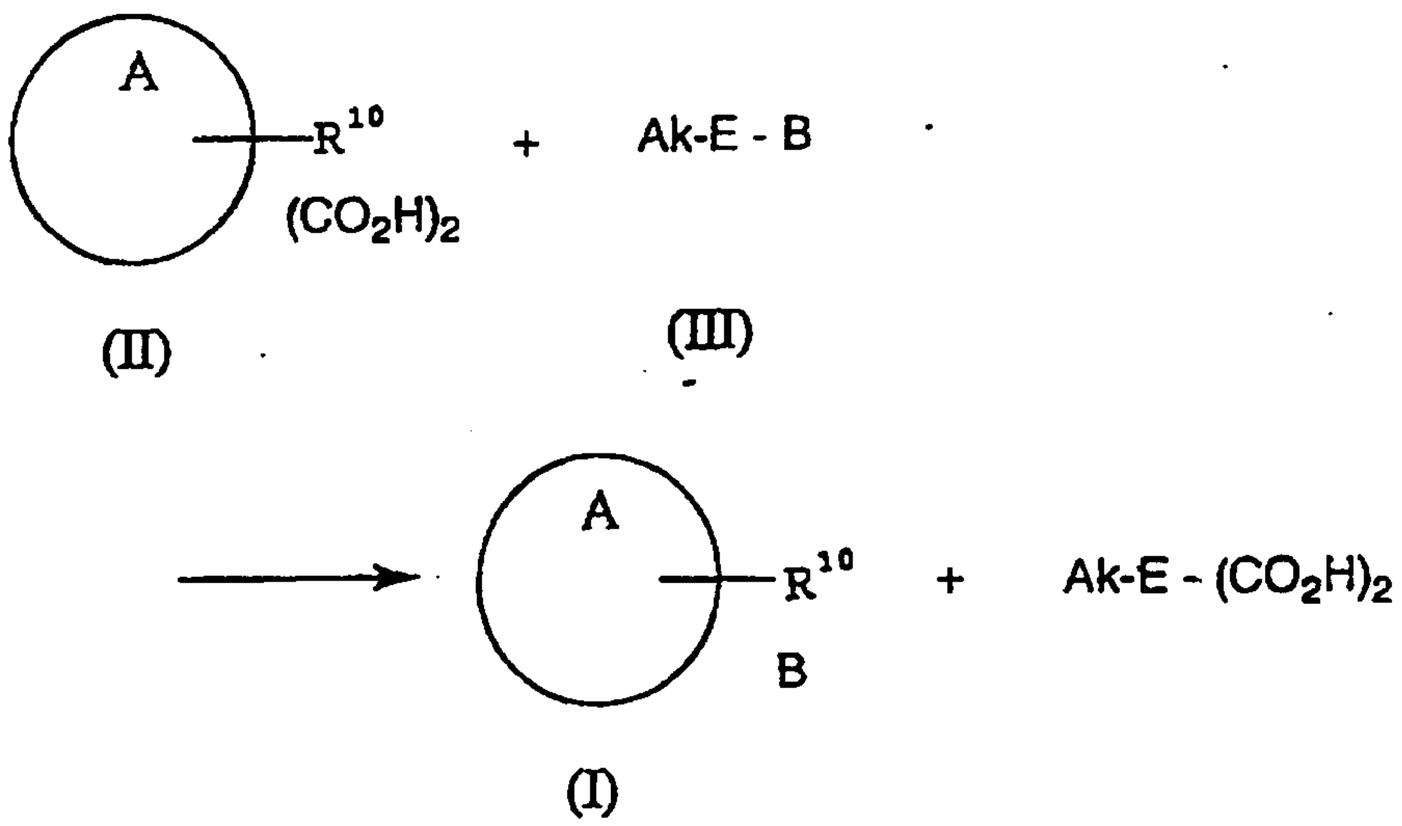
Next, the alkali earth metal salt (III) of the inorganic acid according to the present invention is not limited so long as it is an adduct salt made from the inorganic acid and an alkali earth metal such as beryllium, magnesium, calcium, strontium and barium. Preferred are alkali earth metal halide (IV) and alkali earth metal sulfides (V).

More specific examples of the alkali earth metal halides (IV) include beryllium fluoride, magnesium fluoride, calcium fluoride, strontium fluoride, barium fluoride, beryllium chloride, magnesium chloride, calcium chloride, strontium chloride, barium chloride, beryllium bromide, magnesium bromide, calcium bromide, strontium bromide, barium bromide, beryllium iodide, magnesium iodide, calcium iodide, strontium iodide, barium iodide etc.

Among these, magnesium chloride, calcium chloride, magnesium bromide, calcium bromide etc. are more preferred.

Examples of the alkali earth metal sulfates (V) include beryllium sulfate, magnesium sulfate and calcium sulfate.

The following will describe an preferred embodiment of the present invention in more detail. (See the following chemical reaction formula, wherein the ring A means a basic antibiotic; R^{10} means a protected functional group used in organic synthesis; Ak-E means an alkali earth metal; and B means an inorganic acid.)



(1) Step 1

The present step is a step of conducting deprotection reaction in the case that a basic antibiotic·oxalate has a protected functional group in the molecule thereof.

The protected function group herein means a group obtained by protecting a functional group such as a hydroxyl group, an amino group or a carboxyl group and used in organic synthesis. The deprotection reaction can be conducted in an ordinary manner such as hydrolysis or reduction.

(2) Step 2

The present step is a step of subjecting the basic antibiotic·oxalate (II) to salt-exchange with an alkali earth metal salt (III) of an inorganic acid, to give the target basic antibiotic·inorganic acid salt (I).

Herein, the amount of the alkali earth metal salt (III) of the inorganic acid used is not limited and is usually from 0.7 to 2.0 equivalents, preferably from 0.8 to 1.5 equivalent, and more preferably from 0.9 to 1.3 equivalent.

Herein, the solvent used is not limited. Specific examples thereof include water, lower alcohols, ketone solvents, ester solvents, ether solvents, formamide solvents and dimethylsulfoxide. These may be used alone or in the form of a mixture thereof. Among these, water and lower alcohols are preferred.

The manner of carrying out (operating) the salt-exchange is not limited. Usually, a solution wherein a necessary amount

of the alkali earth metal salt (III) of the inorganic acid is dissolved is dropwise added to a solution of the basic antibiotic·oxalate (II).

Herein, a solvent wherein an alkali earth metal·oxalate which is by-produced by the salt-exchange is insoluble is selected at this time, the alkali earth metal·oxalate is precipitated and can easily be by filtration. Therefore, this case is more suitable for industry.

The target basic antibiotic·inorganic acid salt (I) is in a solution state at this stage. Accordingly, extracting operation is necessary. However, by concentration of the solvent or addition of a poor solvent (solvent having low solubility), it can easily be precipitated as crystal.

In the case of concentrating the solvent, it may be completely dried. It is however allowable to concentrate it partially into a small-amount solution, cool the resultant solution or cause the resultant solution to stand still, thereby precipitating the target crystals.

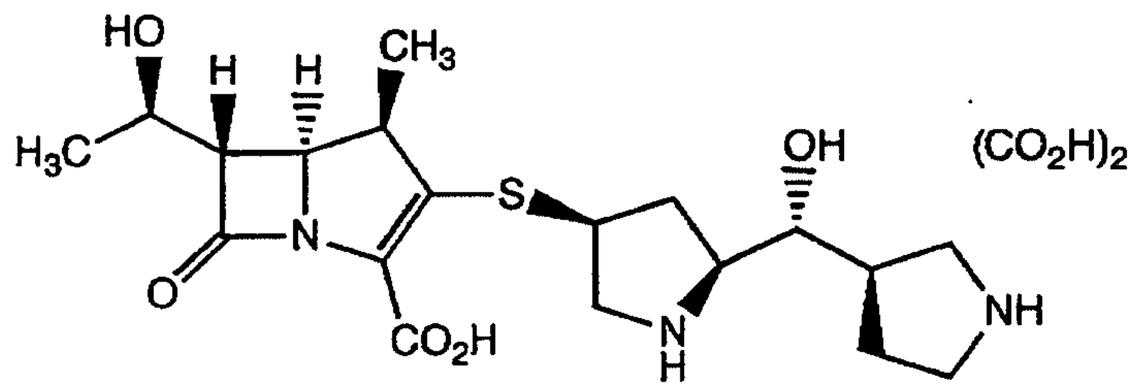
In the case of using the poor solvent, the kind thereof is not limited. In general, methanol, n-propanol, isopropanol etc. are preferred.

In the present invention, the step 2 may be performed after the step 1 is performed to isolate and/or purify the basic antibiotic·oxalate (II). However, the steps 1 and 2 may be continuously performed by the so-called one-spot reaction.

In this case, the deprotection reaction solution can be

used, as it is, for the salt-exchange. As a result, column chromatography, pH adjustment and freeze-drying become unnecessary. Therefore, this case is excellent in industrial operability, reduction in production costs, processing in large amount and environment protection.

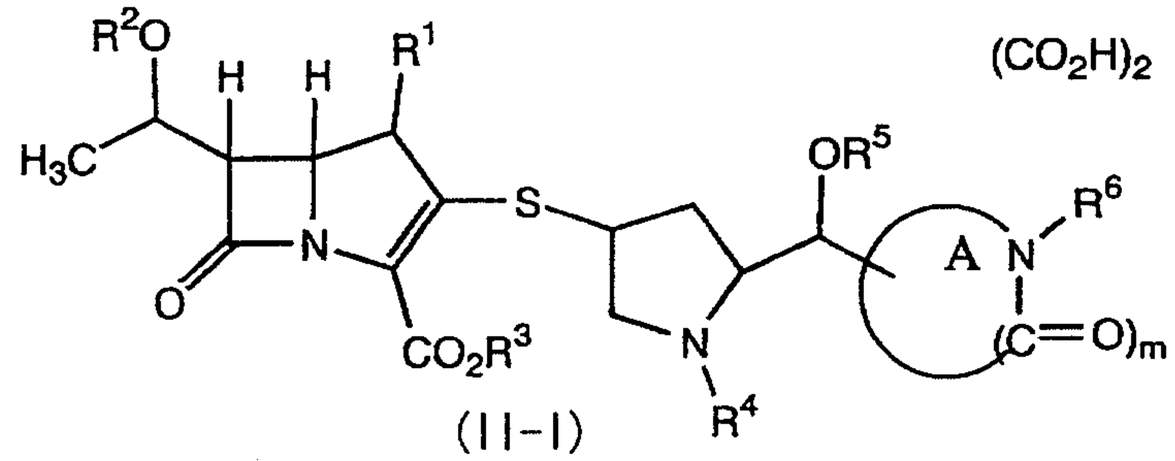
(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid·oxalate (II-IX) according to the present invention, which is represented by the following formula:



(II-IX)

is a novel compound and is useful for a production intermediate.

Herein, the oxalate (II-I) of the carbapenem compound according to the present invention is represented by the following formula.

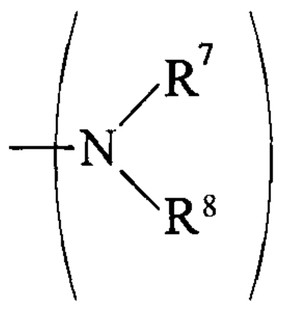


(II-I)

Wherein the ring A represents a 3- to 7-membered ring having at least one nitrogen atom, and the ring A may be substituted

65702-503

with other than R^6; R^1 represents hydrogen or methyl group; R^2 and R^5 are the same as or different from each other and each represents hydrogen or a hydroxyl-protecting group; R^3 represents a carboxyl-protecting group; R^4 represents hydrogen, a lower alkyl group or an amino-protecting group; R^6 represents (1) hydrogen, (2) an optionally protected hydroxyl group, carbamoyl, formimidoyl, acetoimidoyl or a lower alkyl group which may be substituted with a substituent represented by the formula:



(wherein R^7 and R^8 are the same as or different from each other and each represents hydrogen, a lower alkyl group or an amino-protecting group) or (3) an amino-protecting group or an imino-protecting group; and m is 0 or 1.

In the above-mentioned definition, the hydroxyl-protecting group, the carboxyl-protecting group, the lower alkyl group, the amino-protecting group, the optionally protected hydroxyl, the imino-protecting group etc. are not limited so long as they are groups which are usually used in organic synthesis. The "lower alkyl group" means a C_{1-6} alkyl group, as well-understood in organic chemistry. More specific examples thereof include the same groups as described in JP-A 8-73462.

The oxalate (II-I) of the carbapenem compound according to the present invention has an asymmetric carbon atom or a double bond in the molecule thereof, and is in the form of an

optically active substance, a diastereomer, or a racemic body. In the present invention, it is not limited and may be any one. About geometrical isomers thereof, the same matter is true.

More specific examples of the oxalate (II-I) of the carbapenem compound according to the present invention include the following compounds, though it is not limited thereto.

(1) p-Nitrobenzyl 6-(1-hydroxyethyl)-1-methyl-2-{[2-(azetidin-3-yl)hydroxymethylpyrrolidine-4-yl]thio}-1-carbapen-2-em-3-carboxylate·oxalate;

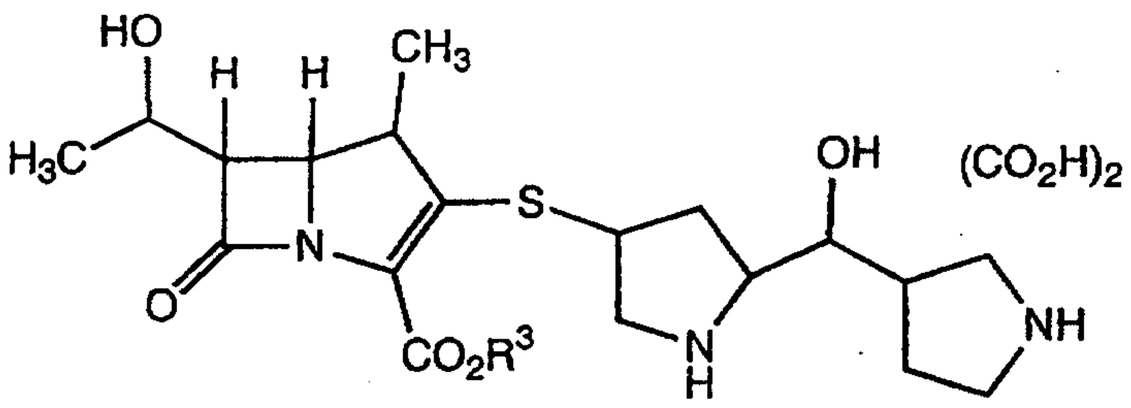
(2) p-nitrobenzyl 6-(1-hydroxyethyl)-1-methyl-2-{[2-(pyrrolidine-3-yl)hydroxymethylpyrrolidine-4-yl]thio}-1-carbapen-2-em-3-carboxylate·oxalate;

(3) p-nitrobenzyl 6-(1-hydroxyethyl)-1-methyl-2-{[2-(piperidine-3-yl) hydroxymethylpyrrolidine-4-yl]thio}-1-carbapen-2-em-3-carboxylate·oxalate;

(4) p-nitrobenzyl 6-(1-hydroxyethyl)-1-methyl-2-{[2-(piperidine-4-yl)hydroxymethylpyrrolidine-4-yl]thio}-1-carbapen-2-em-3-carboxylate·oxalate; and

(5) p-nitrobenzyl 6-(1-hydroxyethyl)-1-methyl-2-{[2-(azepin-3-yl)hydroxymethylpyrrolidine-4-yl]thio}-1-carbapen-2-em-3-carboxylate·oxalate.

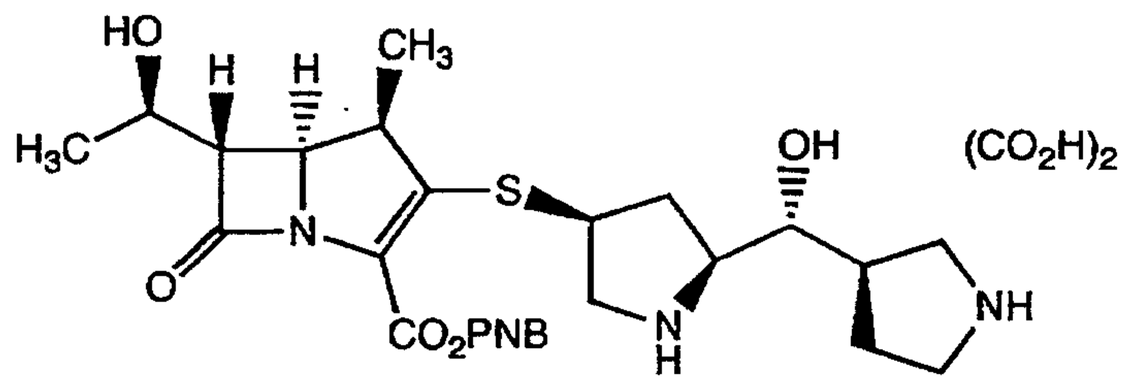
Next, 6-(1-hydroxyethyl)-1-methyl-2-{[2-(pyrrolidine-3-yl)hydroxymethylpyrrolidine-4-yl]thio}-1-carbapen-2-em-3-carboxylate·oxalate (II-II) according to the present invention is represented by the following formula:



(II-II)

wherein R^3 represents a carboxyl-protecting group.

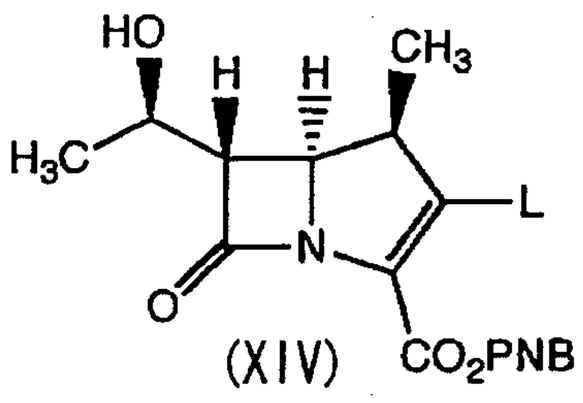
Lastly, p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate·oxalate (II-III) according to the present invention is represented by the following formula:



(II-III)

wherein PNB represents p-nitrobenzyl group.

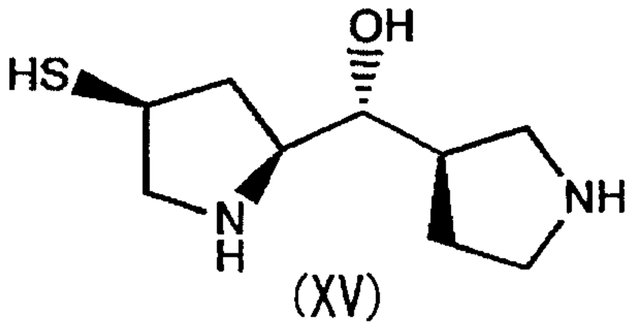
Sequentially, p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate-2-active compound (XIV) which is a starting material for p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate·oxalate (II-III) according to the present invention, is represented by the following formula:



(XIV)

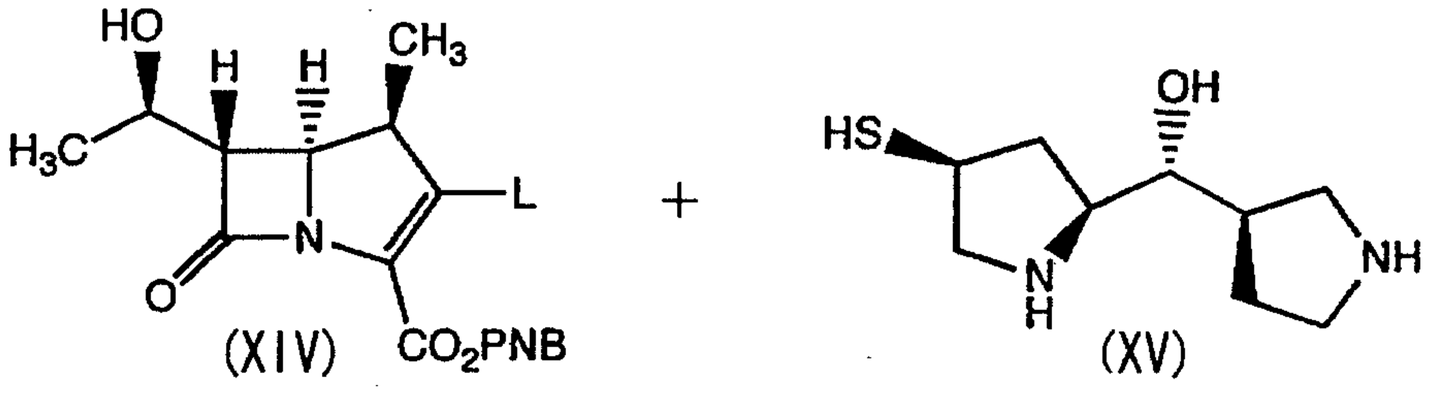
(wherein PNB has the same meaning as described above; L represents a leaving group which is usually used in organic synthesis, and specific examples thereof include trifluoroacethoxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy and diphenoxyphosphoryloxy), and can be produced by the process ([0069] - [0076]) described in JP-A 8-73462.

Furthermore, (2S,4S)-2-[[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl]-4-mercaptopyrrolidine·dihydrochloride (XV), which is a reaction reagent, is represented by the following formula, and can be produced by the process described in Example 3 of JP-A 8-73462 etc.

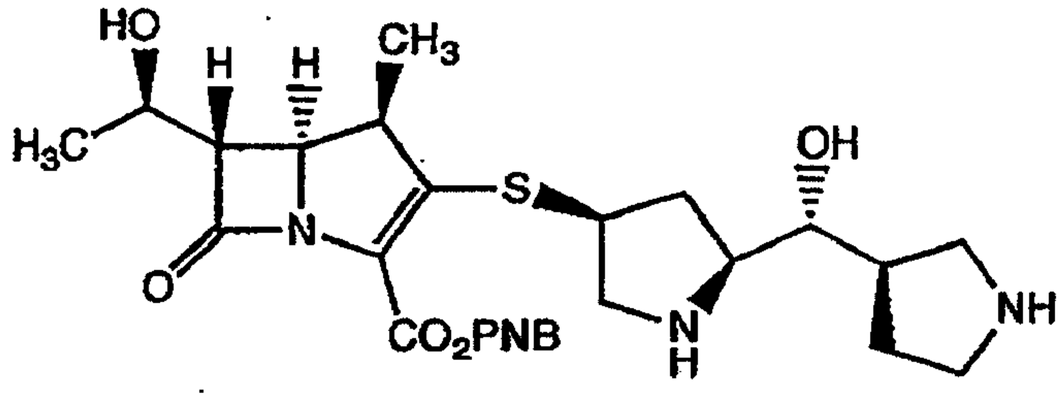


(XV)

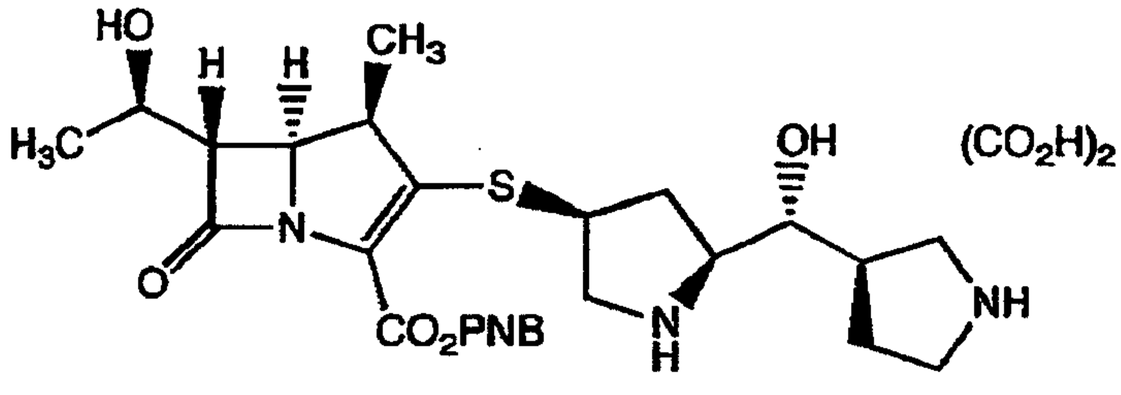
The following will describe the process for producing the compound of the present invention in more detail. (See the following chemical reaction formula, wherein PNB and L have the same meanings as described above.)



Step 1 →



Step 2 →



(II-III)

(1) Step 1

The present step is a step of reacting p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate-2-active compound (XIV) with (2S,4S)-2-[[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl]-4-mercaptopyrrolidine·dihydrochloride (XV), to give a free compound or p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate.

The present reaction is not limited so long as it is a thioether-synthesizing process which is usually conducted in organic synthesis. The process can easily be conducted in the

presence of a base so as to give a high yield.

The kind of the base used herein is not limited. Specific examples thereof include alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; alkali earth metal hydroxides such as barium hydroxide and calcium hydroxide; alkali metal carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrogencarbonates such as sodium hydrogencarbonate and potassium hydrogencarbonate; inorganic bases such as alkali metal hydrides, for example, sodium hydride; primary to tertiary organic amines such as triethylamine, diethylamine, N,N-diisopropylamine and ethylamine; aromatic amines such as pyridine; and aniline derivatives such as N,N-dimethylaniline. Among these, N,N-diisopropylamine is more preferred.

(2) Step 2

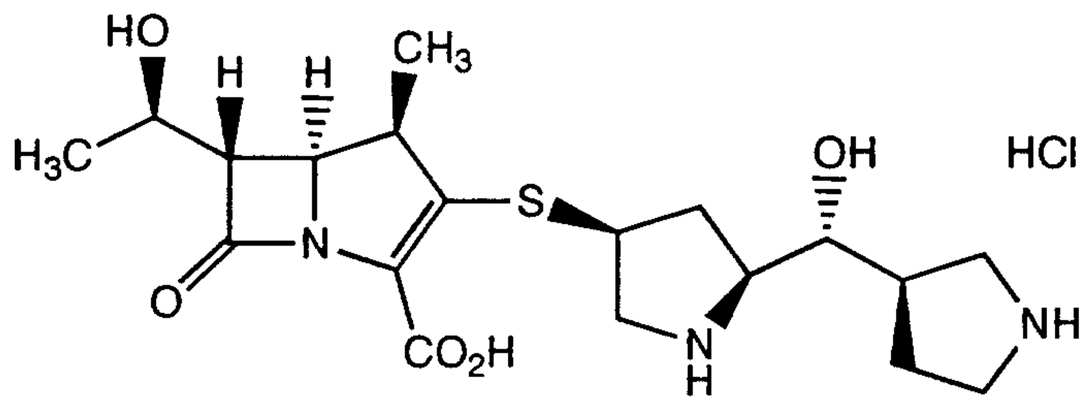
The present step is a step of converting the free compound of p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate into an oxalate thereof, to give the target p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate·oxalate (II-III).

The present step can be conducted in a conventional way for conversion to oxalates. Usually, 0.7 to 2.0 equivalents

of oxalic acid, preferably 0.8 to 1.5 equivalent of oxalic acid, and more preferably 0.9 to 1.2 equivalent of oxalic acid is dissolved into a solvent such as dimethylsulfoxide (DMSO), and then the resulting crystals were collected by filtration. Though the resulting crystals have sufficient purity by only air-drying, a higher-purity product can be obtained by solvent-washing, recrystallization etc.

Now, Examples are shown below to describe the present invention specifically. However, it is needless to say that the present invention is not limited thereto.

Example 1: Production of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·hydrochloride (calcium chloride: 1 equivalent)



1-1) Deprotection (reduction)

Into a reaction vessel having a pH-stat were charged p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylate·1 oxalate (26.0 g, 38.3 mmol), 20% palladium hydroxide-carbon (5.24 g, a 50% wet body) and water (598 ml), and then the mixture was suspended and stirred under cooling

in an ice bath. The pH of the suspension was 3.81. After purge with nitrogen was performed 5 times, a 1 N sodium hydroxide solution was dropwise added thereto from a constant rate pump connected to a pH-stat under the atmosphere of hydrogen (normal pressure, supply of hydrogen from a balloon). The reaction solution was vigorously stirred for 3.5 hours while the pH thereof was adjusted to 5.5. The advance of the reaction was confirmed by HPLC. When the consumption (about 124 mL) of the 1 N sodium hydroxide stopped, purge with nitrogen was performed. Celite (26 g) was charged therein under stirring. The reaction solution was stirred for 7 minutes. The reaction solution was subjected to filtration under reduced pressure through Buchner funnel, on the bottom of which celite (78 g) was laid. The cake was washed with water (169 mL), to give an aqueous solution (790.7 g) of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·oxalate. The quantitative analysis by HPLC demonstrated that the resultant aqueous solution contained 13.08 g of the free form of the title compound (yield: 82.9%).

1-2) Salt-exchange

To a part (28 g, containing 0.421 g of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·oxalate) of this aqueous solution was dropwise added 1.6 g (about 1 equivalent) of 7.5%

(w/w) calcium chloride solution (solution wherein 7.5 g of calcium chloride was dissolved in 100 g of ion-exchanged water). The reaction solution immediately became whitely turbid. The precipitation was filtered off, to give a clear solution. Isopropanol (IPA, 120 mL) was added thereto so as to yield crystals. The precipitated crystals were collected by filtration and dried in a nitrogen stream for about 1 hour, to give the title compound as crystals (0.30 g, 0.248 g in terms of the free form).

^{1}H-NMR(400MHz,D_2O) ; δ (ppm) 1.18(3H,d,J=7Hz), 1.24(3H,d,J=6Hz), 1.73(1H,td,J=9,13Hz), 1.84(1H,ddd,J=7,10,12Hz), 2.07-2.18(1H,m), 2.44(1H,qd,J=9,18Hz), 2.58(1H,td,J=8,14Hz), 3.15(1H,dd,J=10,12Hz), 3.21-3.37(3H,m), 3.39-3.47(2H,m), 3.51(1H,dd,J=8,12Hz), 3.64(1H,dd,J=7,12Hz), 3.83(1H,ddd,J=3,8,11Hz), 3.92-4.01(2H,m), 4.15-4.23(2H,m).

Example 2: Production of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·hydrochloride (calcium chloride: 1.15 equivalent)

2-1) Deprotection (reduction)

Into a reaction vessel having a pH-stat were charged p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylate·1 oxalate (4.0 g, 6.02 mmol), 20% palladium hydroxide-carbon (0.82 g, a 50% wet body) and water (92 ml),

and then the mixture was suspended and stirred, under cooling in an ice bath. The pH of the suspension was 3.77. After purge with nitrogen was performed 5 times, a 1N sodium hydroxide solution was dropwise added thereto from a constant rate pump connected to a pH-stat under the atmosphere of hydrogen (normal pressure, supply of hydrogen from a balloon). The reaction solution was vigorously stirred for 3 hours while the pH thereof was adjusted to 5.5. The advance of the reaction was confirmed by HPLC. When the consumption (about 8.6 mL) of the 1 N sodium hydroxide stopped, purge with nitrogen was performed. Celite (4 g) was charged therein under stirring. The reaction solution was stirred for 7 minutes. The reaction solution was subjected to filtration under reduced pressure through Buchner funnel, on the bottom of which Celite (12 g) was laid. The cake was washed with water (26 mL) to give an aqueous solution (109.9 g) of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·oxalate. The quantitative analysis by HPLC demonstrated that the resultant aqueous solution contained 1.88 g of the free form of the title compound (yield: 75.7%).

2-2) Salt-exchange

To a part (75 g, containing 1.193 g of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·oxalate) of this solution was

dropwise added 5.287 g (about 1.15 equivalent) of 7.5% (w/w) calcium chloride solution (solution wherein 7.5 g of calcium chloride was dissolved in 100 g of ion-exchanged water). The reaction solution became whitely turbid rapidly. The resulting precipitates were filtered off, to give a clear solution. The solution was concentrated into about 1/2 of the original volume thereof. Isopropanol (88 mL) was added thereto so as to give crystals. The precipitated crystals were collected by filtration and dried in a nitrogen stream for about 1 hour, to give the title compound as crystals (1.222 g, 1.0416 g in terms of the free form).

Example 3: Production of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·hydrochloride (calcium chloride: 1.25 equivalent)

3-1) Deprotection (reduction)

Into a reaction vessel having a pH-stat were charged p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylate·oxalate (5.0 g, 7.31 mmol), 20% palladium hydroxide-carbon (0.99 g, a 50% wet body) and water (115 ml), and then the mixture was suspended and stirred, under cooling in an ice bath. The pH of the suspension was 3.75. After purge with nitrogen was performed 5 times, an 1 N sodium hydroxide

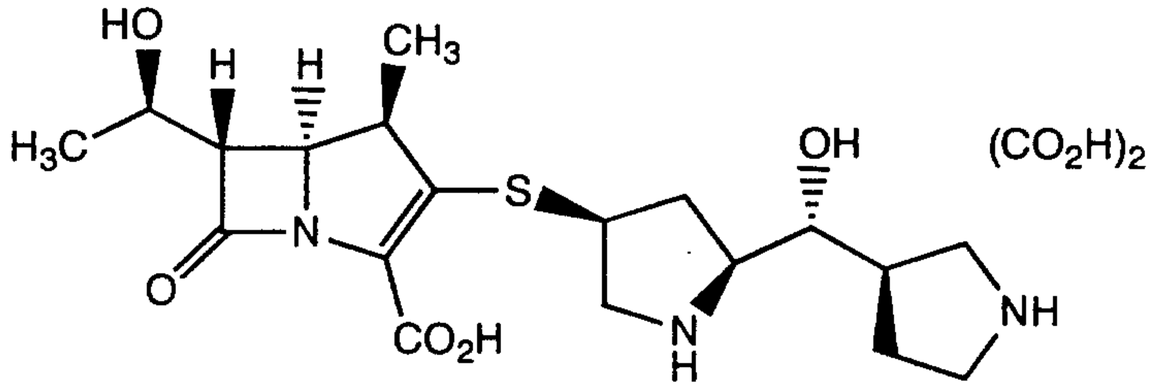
solution was dropwise added thereto from a constant rate pump connected to a pH-stat under the atmosphere of hydrogen (normal pressure, supply of hydrogen from a balloon). The reaction solution was vigorously stirred for 2.5 hours while the pH thereof was adjusted to 5.5. The advance of the reaction was confirmed by HPLC. When the consumption (about 8.3 mL) of the 1N sodium hydroxide stopped, purge with nitrogen was performed. Celite (5 g) was charged therein under stirring. The reaction solution was stirred for 7 minutes, and then subjected to filtration under reduced pressure through Buchner funnel, on the bottom of which Celite (15 g) was laid. The cake was washed with water (32.5 mL), to give an aqueous solution (147.8 g) of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid/oxalate. The quantitative analysis by HPLC demonstrated that the resultant aqueous solution contained 2.36 g of the free form of the title compound (yield: 78.4%).

3-2) Salt-exchange

To a part (112.9 g, containing 1.73 g of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·oxalate) of this solution was dropwise added 7.78 g (about 1.25 equivalent) of 7.5% (w/w) calcium chloride solution (solution wherein 7.5 g of calcium chloride was dissolved in 100 g of ion-exchanged water). The

reaction solution became whitely turbid rapidly. The precipitation was filtered off to give a clear solution. This solution was concentrated into about 1/2 of the original volume thereof. Isopropanol (75.3 mL) was added thereto so as to give crystals. The precipitated crystals were collected by filtration, and dried in a nitrogen stream for about 1 hour, to give the title compound as crystals (1.925 g, 1.562 g in terms of the free form).

Example 4: Production of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylic acid·oxalate



4-1) Deprotection (reduction)

Into a reaction vessel having a pH-stat were charged p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methylpyrrolidine-4-yl}thio-1-carbapen-2-em-3-carboxylate·oxalate (5.0 g, 7.12 mmol), 20% palladium hydroxide-carbon (0.97 g, a 50% wet body) and water (115 ml). Then the mixture was suspended and stirred under cooling in an ice bath. The pH of the suspension was 3.7. After purge with nitrogen was performed 5 times, an 1 N sodium hydroxide solution

was dropwise added thereto from a constant rate pump connected to a pH-stat under the atmosphere of hydrogen (normal pressure, supply of hydrogen from a balloon). The reaction solution was vigorously stirred for 2 hours while the pH thereof was adjusted to 5.5. The advance of the reaction was confirmed by HPLC. When the consumption (about 8.3 mL) of the 1 N sodium hydroxide stopped, purge with nitrogen was performed. Celite (5 g) was charged therein under stirring. The reaction solution was stirred for 7 minutes. The reaction solution was subjected to filtration under reduced pressure with a Buchner funnel, on the bottom of which celite (15 g) was laid. The cake was washed with water (32.5 mL), to give an aqueous solution (154.7 g) of the title compound. The quantitative analysis by HPLC demonstrated that the resulting aqueous solution contained the title compound in a free form (2.43g, yield: 82.9%).

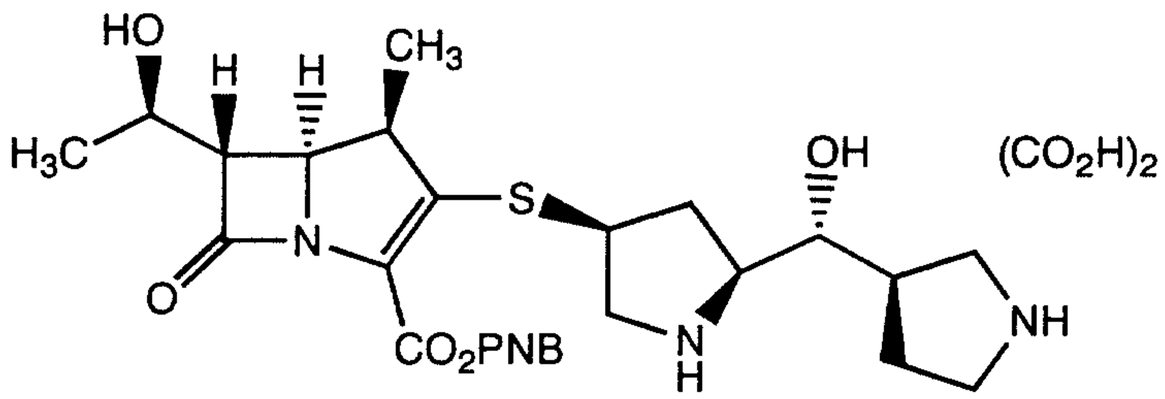
4-2) Crystallization

To a part (25 g) of this solution were dropwise added methanol (200 mL) and isopropanol (30 mL) under stirring. The reaction solution was stirred under ice-cooling for 3 hours. The precipitated solid was filtered under reduced pressure, washed with methanol (10 mL) and dried under reduced pressure, to give the title compound as a slightly-yellowish white powder (the free form content: 67.9%, gradient HPLC purity: 98.9%).

^{1}H-NMR(400MHz,D_2O) ; δ (ppm) 1.10(d,3H,J=7.3 Hz), 1.17(d,3H,J=6.4 Hz), 1.58-1.73(m,1H), 1.72-1.85(m,1H), 1.98-2.14(m,1H), 2.36(q-like,1H,J=8.3 Hz), 2.51(dt,1H,J=7.8,6.8 Hz), 3.09(dd,1H,J=9.0,12 Hz), 3.14-3.25(m,3H), 3.25-

3.40(m,2H), 3.43(dd,1H,J=8.0,12 Hz), 3.55-3.65(m,1H), 3.72-3.83(m,2H), 4.08-4.17(m,2H).

Example 5: p-Nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate·monooxalate



Wherein PNB represents p-nitrobenzyl group.

p-Nitrobenzyl (1R,5S,6S)-2-dipnenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (50.0 g, 84.1 mmol) was dissolved in N,N-dimethylformamide (150 mL) and dimethylsulfoxide (300 mL) in a nitrogen stream, under stirring. After cooling to 10°C, N,N-diisopropylamine (36.6 mL, 210.3 mmol) was added thereto. Further, (2S,4S)-2-{[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}-4-mercaptopyrrolidine·dihydrochloride (25.46 g, 92.5 mmol) was added thereto, followed by stirring for 2 hours. A solution of oxalic acid (7.8 g, 86.6 mmol) in dimethylsulfoxide (30 mL) was added to the reaction solution, so that a solid was precipitated. Furthermore, 2-propanol (1750 mL) was added thereto, followed by stirring at the same temperature for 4 hours. The reaction solution in a slurry form was subjected to filtration under reduced pressure through Buchner funnel,

and air-dried in a nitrogen stream for 1 hour, to give 117.4 g of a wet product. This product was suspended into methanol (333 mL) and ethanol (667 mL) under stirring at 14°C for 15 hours. The solid was collected by filtration and dried under reduced pressure for 20hr, to give the title compound (52.3 g, yield: 92%).

^{1}H-NMR(400MHz,DMSO-d_6) ; δ (ppm) 1.15(d,1H,J=6.3Hz), 1.46(d,1H,J=7.6Hz), 1.52(dt,1H,J=13,8.8Hz), 1.64(dq,1H,J=12,9Hz), 1.87-1.98(m,1H), 2.23-2.40(m,2H), 2.80(dd,1H,J=6,12Hz), 2.92-3.10(m,2H), 3.12-3.30(m,3H), 3.30-3.56(m,3H), 3.73(quintet-like,1H,J=6.6Hz),3.97(quintet-like,1H,J=6.3Hz), 4.22(dd,1H,J=5.4,9.5Hz), 5.36(ABq,2H,J=14Hz), 7.71(d,2H,J=8.5Hz), 8.23(d,2H,J=8.5Hz).

65702-503

CLAIMS:

1. A process for producing a salt of a basic antibiotic with an inorganic acid, the salt being selected from the group consisting of:

(1) cefotiam hydrochloride;

(2) cefmenoxime hydrochloride;

(3) cefozopran hydrochloride;

(4) cefpirome sulfate;

(5) cefepime hydrochloride;

(6) cefoselis sulfate;

(7) cefotiam hexetil hydrochloride;

(8) cefetamet pivoxil hydrochloride;

(9) cefcapene pivoxil hydrochloride;

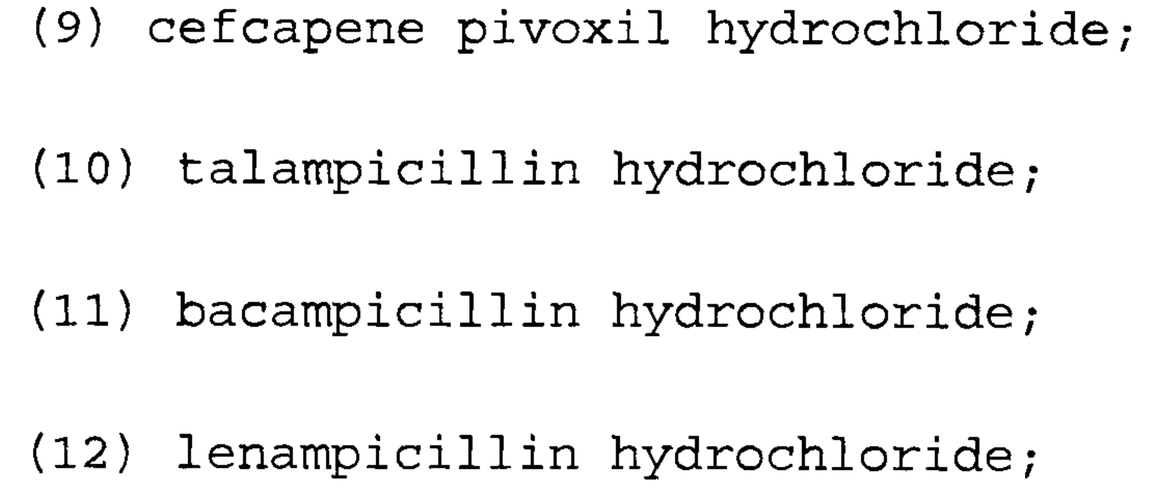
(10) talampicillin hydrochloride;

(11) bacampicillin hydrochloride;

(12) lenampicillin hydrochloride;

(13) pivmecillinam hydrochloride; and

(14) a hydrochloride of a carbapenem compound of the formula:



65702-503

wherein:

the ring A means a 3- to 7-membered ring having at least one nitrogen atom;

R^1 represents hydrogen or a methyl group;

R^2 and R^5 are the same as or different from each other and each represents hydrogen or a hydroxyl-protecting group;

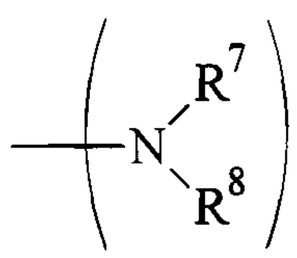
R^3 represents a carboxyl-protecting group;

R^4 represents hydrogen, a C_{1-6} alkyl group or an amino-protecting group;

R^6 represents:

(1) hydrogen,

(2) an optionally protected hydroxyl group, carbamoyl, formimidoyl, acetoimidoyl or a C_{1-6} alkyl group which may be substituted with a substituent represented by the formula:



(wherein R^7 and R^8 are the same as or different from each other and each represents hydrogen, a C_{1-6} alkyl group or an amino-protecting group) or

(3) an amino-protecting group or an imino-protecting group; and

m is 0 or 1,

which process comprises subjecting an oxalate of the basic antibiotic to a salt-exchange with an alkaline earth metal salt of the inorganic acid.

2. The process according to claim 1, in which the alkaline earth metal in the alkaline earth metal salt is beryllium, magnesium or calcium.

3. The process according to claim 1, in which the salt of the basic antibiotic to be produced is as defined in claim 1 other than cefpirome sulfate and cefoselis sulfate; and the alkaline earth metal salt is selected from the group consisting of beryllium chloride, magnesium chloride, calcium chloride, strontium chloride and barium chloride.

4. The process according to claim 1, in which the salt of the basic antibiotic to be produced is cefpirome sulfate or cefoselic sulfate; and the alkaline earth metal salt is selected from the group consisting of beryllium sulfate, magnesium sulfate and calcium sulfate.

5. The process according to any one of claims 1 to 4, in which the alkaline earth metal salt is used in an amount of from 0.7 to 2.0 equivalents relative to the oxalate.

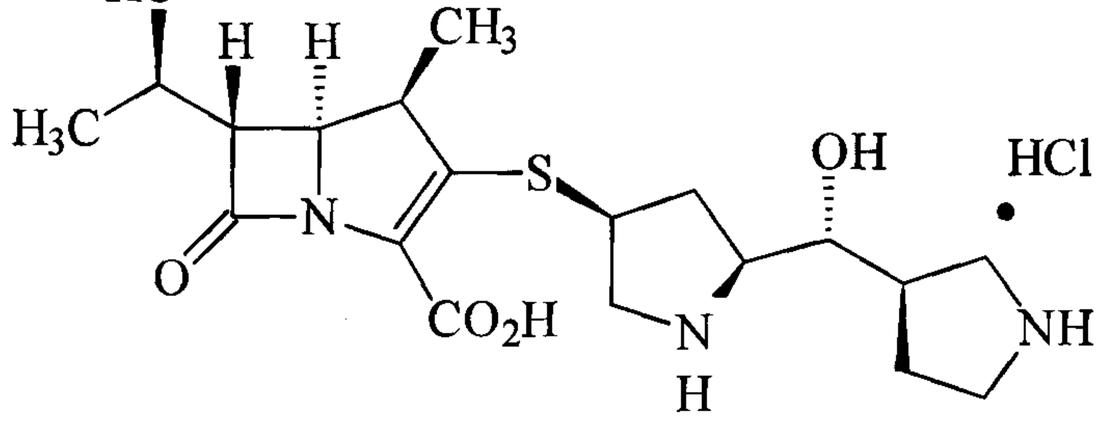
6. The process according to any one of claims 1 to 5, in which water is used as a solvent.

7. The process according to any one of claims 1 to 6, wherein the salt of the basic antibiotic is the hydrochloride of the carbapenem.

8. The process according to claim 7, wherein the hydrochloride of the carbapenem is (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid hydrochloride.

65702-503

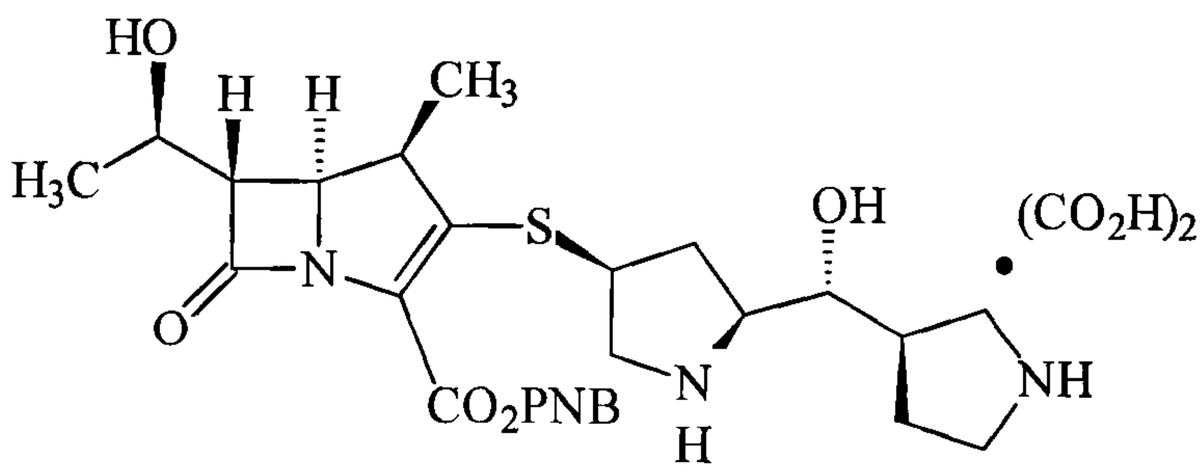
9. A process for producing (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid hydrochloride represented by the following formula (VIII):



(VIII)

which comprises:

subjecting p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate oxalate represented by the following formula (VII):



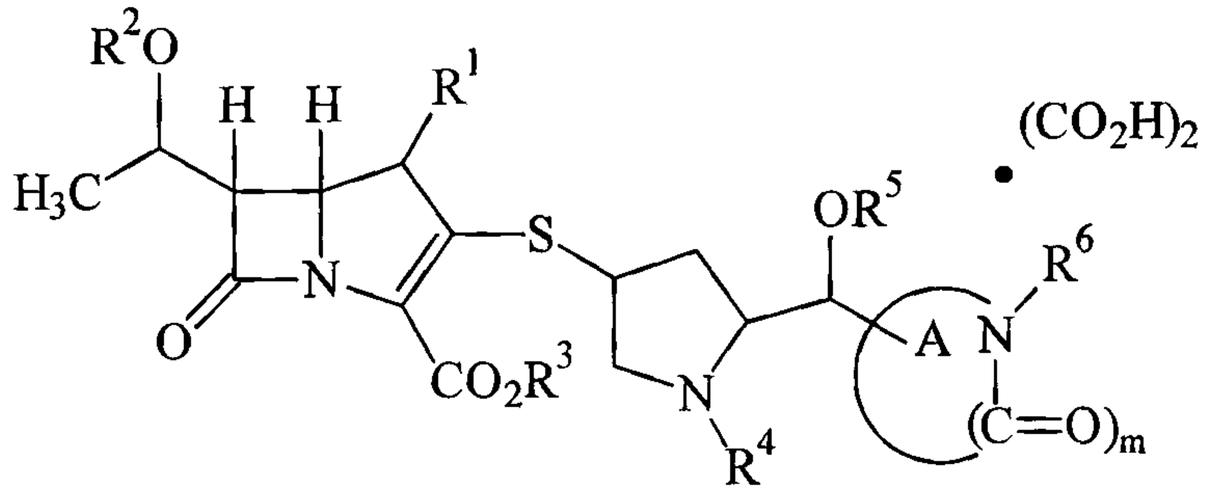
(VII)

(wherein PNB represents p-nitrobenzyl group) to a deprotection reaction to obtain an oxalate of (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylic acid;

subjecting the obtained oxalate to a salt-exchange with calcium chloride in water to obtain the hydrochloride dissolved in water; and

then crystallizing the resultant hydrochloride by adding methanol or isopropanol thereto.

10. An oxalate of a carbapenem compound represented by the following formula (II-I):



(II-I)

wherein:

the ring A represents a 3- to 7-membered ring having at least one nitrogen atom;

R^1 represents hydrogen or a methyl group;

R^2 and R^5 are the same as or different from each other and each represents hydrogen or a hydroxyl-protecting group;

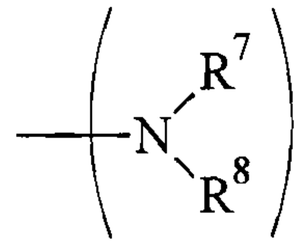
R^3 represents a carboxyl-protecting group;

R^4 represents hydrogen, a C_{1-6} alkyl group or an amino-protecting group;

R^6 represents:

(1) hydrogen,

(2) an optionally protected hydroxyl group, carbamoyl, formimidoyl, acetoimidoyl or a C_{1-6} alkyl group which may be substituted with a substituent represented by the formula:

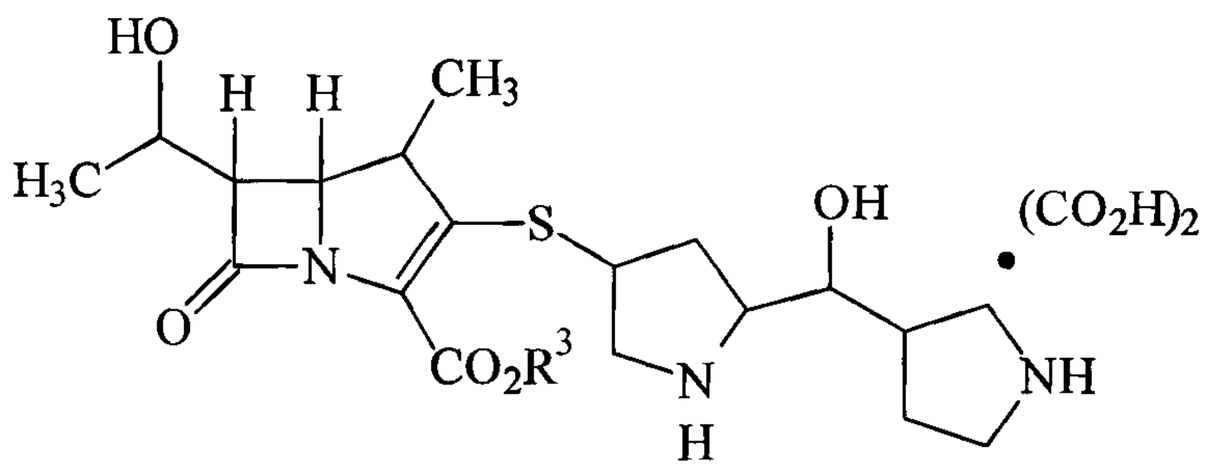


(wherein R^7 and R^8 are the same as or different from each other and each represents hydrogen, a C_{1-6} alkyl group or an amino-protecting group) or

(3) an amino-protecting group or an imino-protecting group; and

m is 0 or 1.

11. 6-(1-Hydroxyethyl)-1-methyl-2-{[2-(pyrrolidine-3-yl)hydroxymethylpyrrolidine-4-yl]thio}-1-carbapen-2-em-3-carboxylic acid derivative oxalate represented by the following formula (II-II):



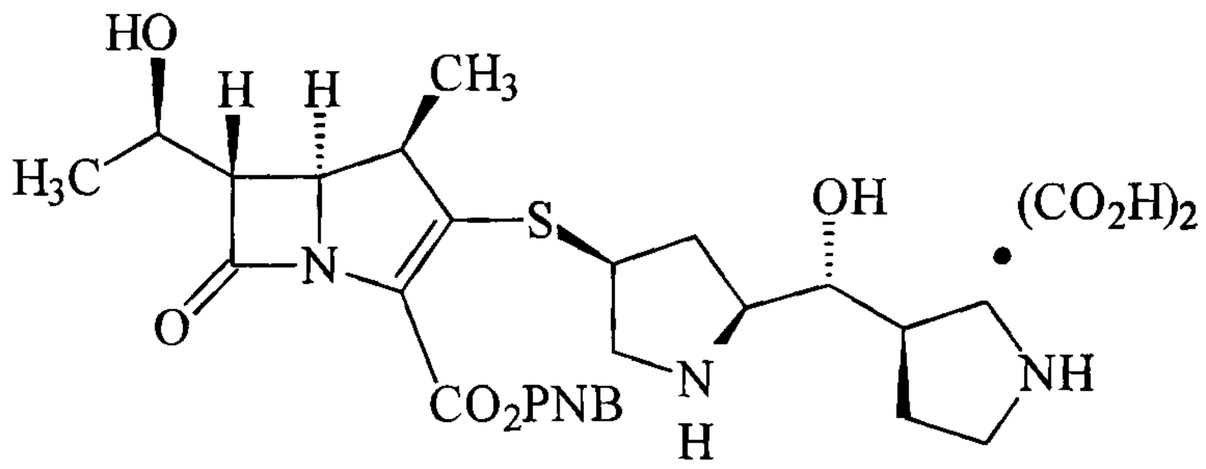
(II-II)

wherein R^3 represents a carboxyl-protecting group.

12. p-Nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-

65702-503

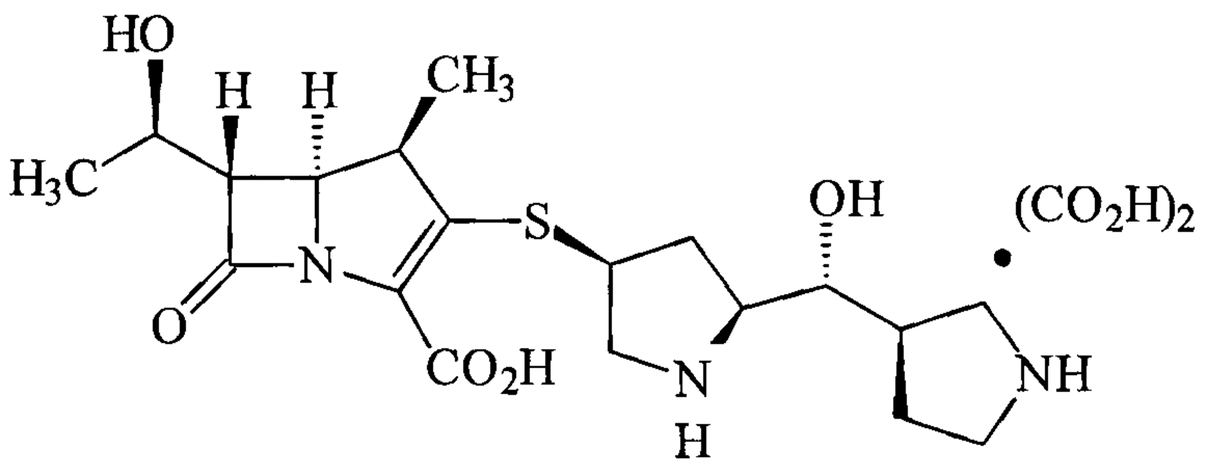
carboxylate oxalate represented by the following formula (II-III):



(II-III)

wherein PNB represents a p-nitrobenzyl group.

13. (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate oxalate represented by the following formula (II-IX):

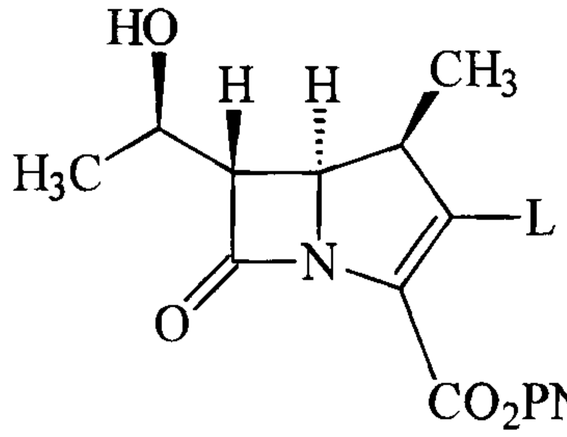


(II-IX).

14. The process according to claim 9, which, for producing p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate oxalate, further comprises reacting p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-1-

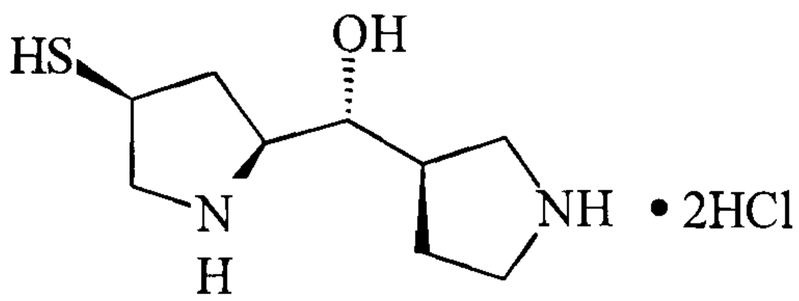
65702-503

carbapen-2-em-3-carboxylate-2-active compound represented by the following formula (XIV):



(XIV)

(wherein PNB represents a p-nitrobenzyl group; and L represents a leaving group) with (2S,4S)-2-{[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}-4-mercaptopyrrolidine dihydrochloride represented by the following formula (XV):

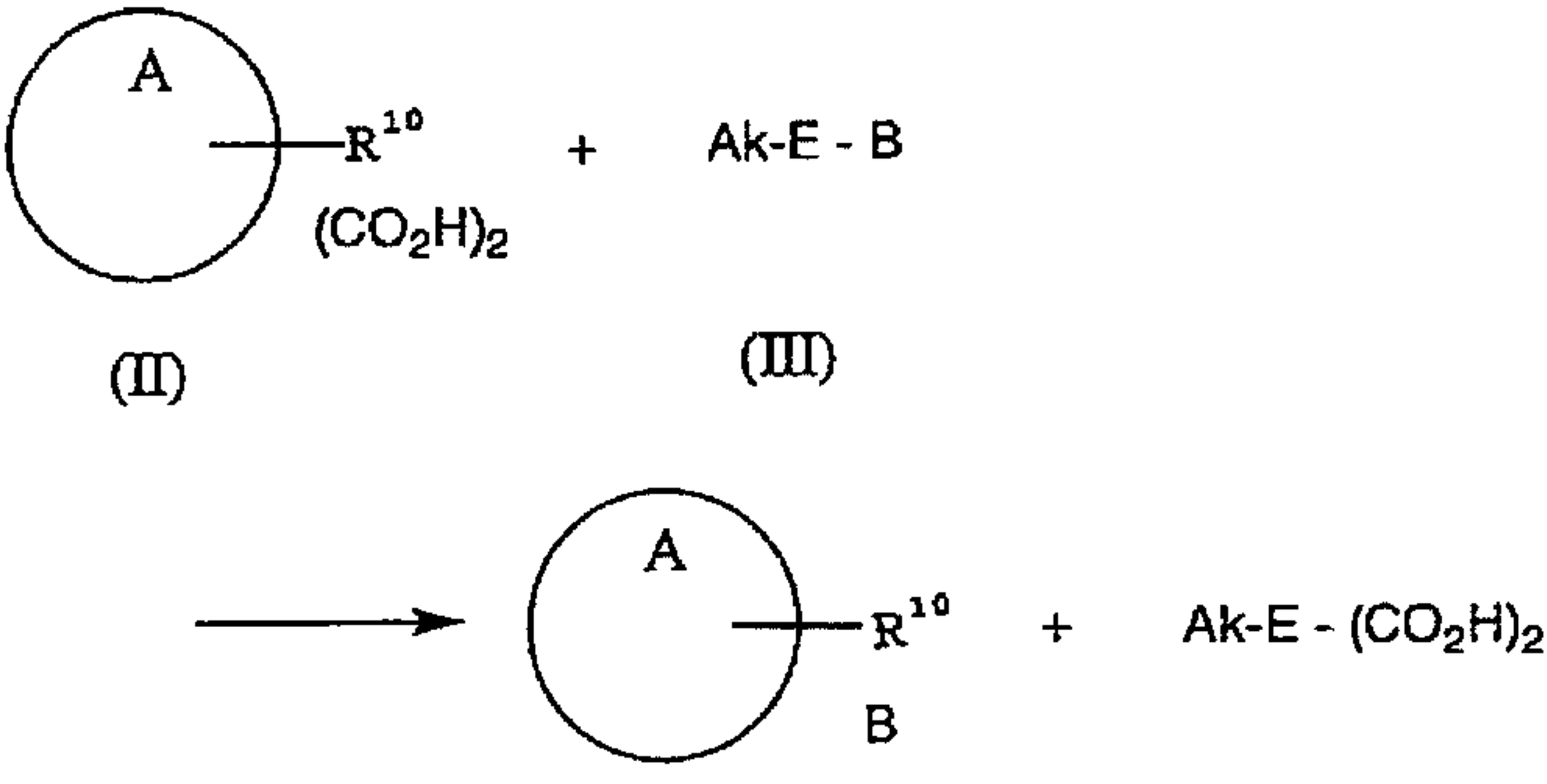


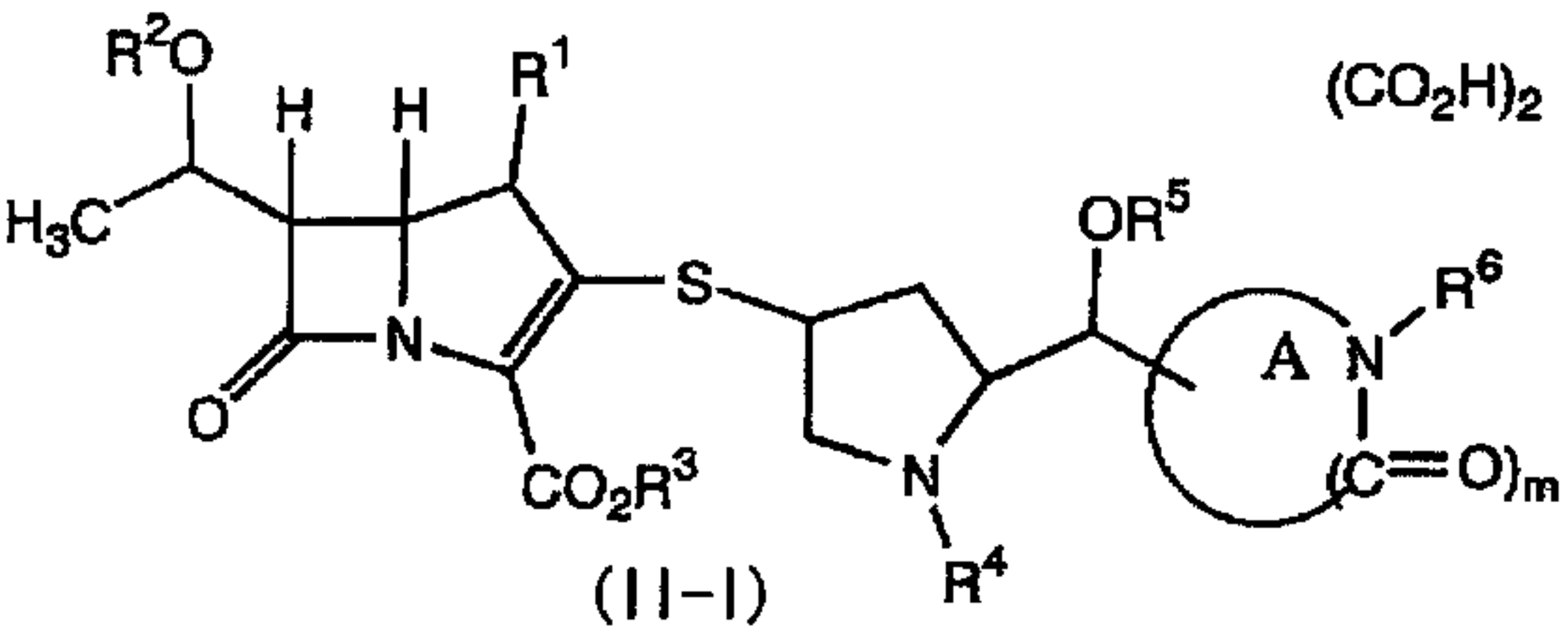
(XV)

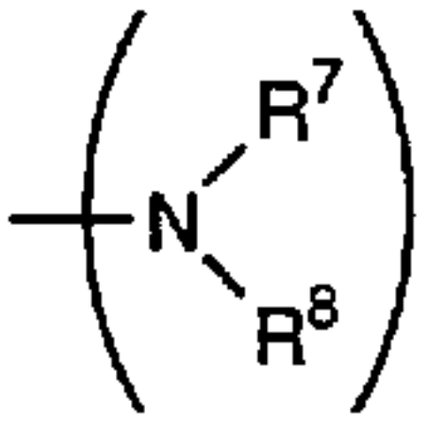
to produce p-nitrobenzyl (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[{(2S,4S)-2-[(3R)-pyrrolidine-3-yl-(R)-hydroxy]methyl}pyrrolidine-4-ylthio]-1-carbapen-2-em-3-carboxylate, and

then converting the resultant into an oxalate.

SMART & BIGGAR
OTTAWA, CANADA
PATENT AGENTS


A
R10
(CO2H)2
+
Ak-E - B
(II)
(III)
A
R10
B
+
Ak-E - (CO2H)2
(I)


R2O
H
H
R1
(CO2H)2
H3C
OR5
S
R6
A
N
O
N
CO2R3
N
(C=O)m
R4
(II-1)


R7
N
R8

(IV)