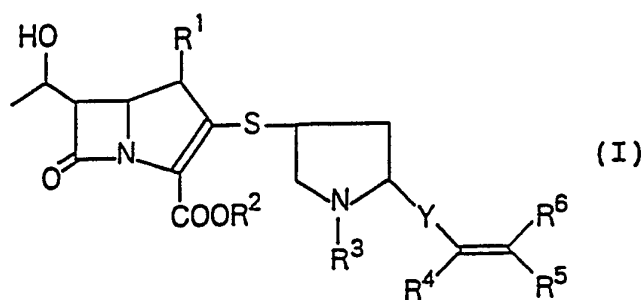




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(54) Title: 2-(2-SUBSTITUTED PYRROLIDINYLTHIO)CARBAPENEM DERIVATIVES



(57) Abstract

A compound of formula (I), wherein R¹ is a hydrogen atom or a methyl group, R² is a hydrogen atom or a negative charge, R³ is a hydrogen atom or lower alkyl group, each of R⁴, R⁵ and R⁶ is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula -X-N(R⁷)R⁸ {wherein each of R⁷ and R⁸ which may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R⁷ and R⁸ form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8-membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents}, provided that at least one of R⁴, R⁵ and R⁶ is the group of the formula -X-N(R⁷)R⁸ wherein R⁷, R⁸ and X are as defined above, and Y is a lower alkylene group or a single bond; or a pharmaceutically acceptable salt or ester thereof.

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DESCRIPTION

TITLE OF THE INVENTION

2-(2-SUBSTITUTED PYRROLIDINYLTIO)CARBAPENEM DERIVATIVES

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TECHNICAL FIELD

The present invention relates to novel carbapenem (7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylic acid) compounds, antibacterial agents containing such compounds as active ingredients, and a process for producing such
10 compounds.

BACKGROUND ART

In recent years, new β -lactam antibiotic substances have been found in nature which have the same β -lactam rings as penicillin derivatives and as cephalosporin
15 derivatives, but which have different basic structures.

For example, naturally derived carbapenem compounds such as thienamycin isolated from the fermentation of Streptomyces cattleya (J. Am. Chem. Soc., vol. 100, p.6491 (1978)), may be mentioned. Thienamycin has an
20 excellent antibacterial spectrum and strong antibacterial activities over a wide range against gram positive bacteria and gram negative bacteria. Therefore, its development as a highly useful β -lactam agent has been expected. However, thienamycin itself is chemically
25 unstable, and it has been reported that it is likely to be decomposed by a certain enzyme in vivo such as renal dehydropeptidase I (hereinafter referred to simply as

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DHP-I), whereby the antibacterial activities tend to decrease, and the recovery rate in the urine is low (Antimicrob. Agents Chemother., vol. 22, p.62 (1982); ditto, vol. 23, p.300 (1983)).

5 Merck & Co., Inc. have synthesized many thienamycin analogues with an aim to maintain the excellent antibacterial activities of thienamycin and to secure chemical stability. As a result, imipenem, (5R,6S,8R)-3-
[[2-(formimidoylamino)ethyl]thio]-6-(1-hydroxyethyl)-7-
10 oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylic acid monohydrate, obtained by formimidation of the amino group of thienamycin, has been practically developed as a pharmaceutical product (J. Med. Chem., vol. 22, p. 1435 (1979)). Imipenem has antibacterial activities of an
15 equal or higher level than thienamycin against various types of bacteria and has β -lactamase resistance. Especially against Pseudomonas aeruginosa, its antibacterial activities are superior to thienamycin by from 2 to 4 times. Further, the stability of imipenem in
20 the solid form or in an aqueous solution is remarkably improved over thienamycin.

However, like thienamycin, imipenem is likely to be decomposed by DHP-I in the human kidney. Therefore, it can not be used for treatment of the urinary-tract
25 infection. Further, it presents toxicity against the kidney due to the decomposition products. Therefore, imipenem can not be administered alone and is required to

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be used in combination with a DHP-I inhibitor like
cilastatin (J. Antimicrob. Chemother., vol. 12 (Suppl.
D), p. 1 (1983)). In recent years, imipenem has been
frequently used for the treatment and prevention of
5 infectious diseases. Consequently, highly methicillin
resistant Staphylococcus aureus which is resistant to
imipenem and imipenem resistant Pseudomonas aeruginosa
are increasing in the clinical field. Imipenem does not
show adequate treating effects against these resistant
10 bacteria.

As the prior art closest to the present invention, EP
411664A may be mentioned. This publication discloses
carbapenem compounds having a 2-[2-
(aminocarbonyl)vinyl]pyrrolidin-4-ylthio group at the 2-
15 position of the carbapenem structure, represented by
(1R,5S,6S)-2-[(2S,4S)-2-[(E)-2-
(aminocarbonyl)vinyl]pyrrolidin-4-ylthio]-6-[(R)-1-
hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid
(Compound No. 145, compound of Example 3; hereinafter
20 referred to simply as BO-2171), as a typical compound.

β -Lactam antibiotics exhibit selective toxicity
against bacteria and show no substantial effects against
animal cells. Therefore, they are widely used for
treatment of infectious diseases caused by bacteria, as
25 rare antibiotics having little side effects, and thus are
highly useful drugs.

However, in recent years, highly methicillin

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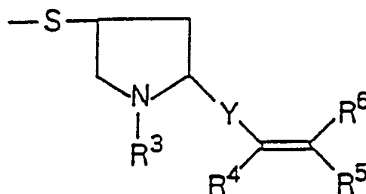
resistant Staphylococcus aureus and resistant Pseudomonas aeruginosa have been isolated frequently from patients with the immunity decreased, as bacteria causing hardly curable infectious diseases. This is regarded as a clinically serious problem. Accordingly, it is strongly desired to develop an antibacterial agent having improved antibacterial activities against such resistant bacteria. Especially with respect to carbapenem compounds, it is desired to improve the antibacterial activities, to improve the stability against DHP-I, to reduce the toxicity against the kidney and to reduce side effects against the central nervous system.

The compounds disclosed in EP 411664A, have a certain level of stability against DHP-I. However, the antibacterial activities against the above-mentioned highly methicillin resistant Staphylococcus aureus and the stability against DHP-I are not adequate, and a carbapenem compound having superior antibacterial activities and stability against DHP-I, is desired.

20 DISCLOSURE OF THE INVENTION

The present inventors have made extensive researches with an aim to provide novel carbapenem compounds which have excellent antibacterial activities and which are resistant against DHP-I. As a result, they have found that carbapenem compounds of the present invention having, at the 2-position of the carbapenem structure, a group of the formula:

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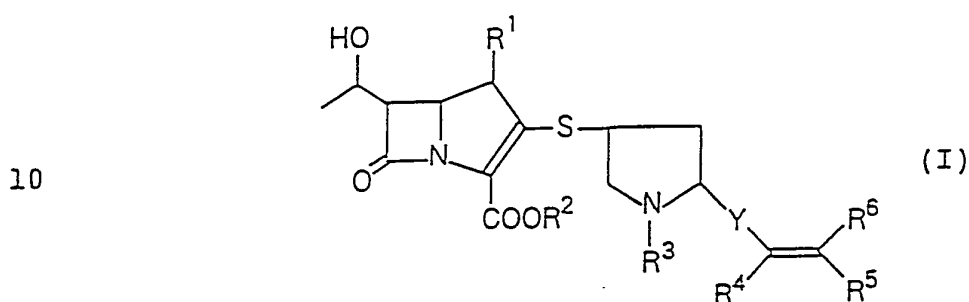


5 wherein R³ is a hydrogen atom or a lower alkyl group, each of R⁴, R⁵ and R⁶ is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula -X-N(R⁷)R⁸ {wherein each of R⁷ and R⁸ which may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R⁷ and R⁸ form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8-membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents}, provided that at least one of R⁴, R⁵ and R⁶ is the group of the formula -X-N(R⁷)R⁸ wherein R⁷, R⁸ and X are as defined above, and Y is a lower alkylene group or a single bond, are novel compounds not disclosed any literatures, and that such compounds have strong antibacterial activities

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against gram positive bacteria such as Staphylococcus aureus and against gram negative bacteria including Pseudomonas aeruginosa and further exhibit excellent stability against DHP-I. The present invention has been
 5 accomplished on the basis of this discovery.

The present invention provides a compound of the formula (I):

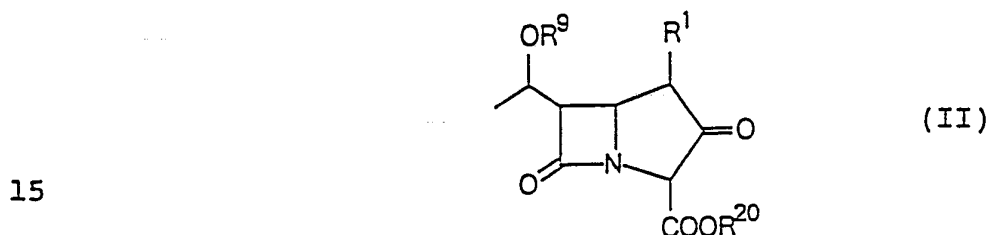


wherein R¹ is a hydrogen atom or a methyl group, R² is a hydrogen atom or a negative charge, R³ is a hydrogen atom
 15 or a lower alkyl group, each of R⁴, R⁵ and R⁶ is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula -X-N(R⁷)R⁸ {wherein each of R⁷ and R⁸ which
 20 may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R⁷ and R⁸ form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a
 25 sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8-membered heterocyclic group which may be substituted (provided that either the nitrogen atom

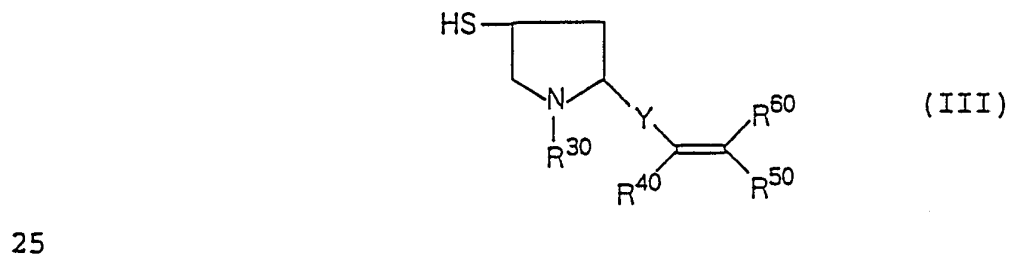
- 7 -

adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents}, provided that at least one of R^4 , R^5 and R^6 is the group of the
 5 formula $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined above, and Y is a lower alkylene group or a single bond; or a pharmaceutically acceptable salt or ester thereof.

The present invention also provides a process for producing the compound of the formula (I) or a
 10 pharmaceutically acceptable salt or ester thereof, which comprises reacting a compound of the formula (II):



wherein R^1 is as defined above, R^9 is a hydrogen atom or a hydroxyl-protecting group, and R^{20} is a hydrogen atom or a carboxyl-protecting group, or a reactive derivative
 20 thereof, with a compound of the formula (III):

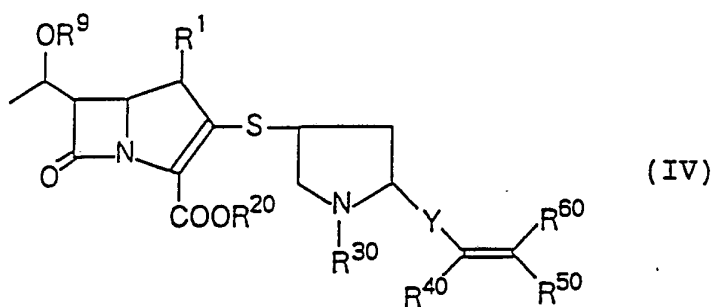


wherein R^{30} is a hydrogen atom, a lower alkyl group or an imino-protecting group, each of R^{40} , R^{50} and R^{60} is a

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hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula $-X^1-N(R^{71})R^{81}$ {wherein each of R^{71} and R^{81} which may be the same or different, is a hydrogen atom, a lower alkyl group which may have substituents or an amino-protecting group, or R^{71} and R^{81} form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8- membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X^1 or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X^1 is a lower alkylene group which may have substituents}, provided that at least one of R^{40} , R^{50} and R^{60} is the group of the formula $-X^1-N(R^{71})R^{81}$ wherein R^{71} , R^{81} and X^1 are as defined above, and Y is a lower alkylene group or a single bond (provided that the substituents of the lower alkyl group, the heterocyclic group and the lower alkylene group, as well as the carbamoyl group and the imino group on the heterocyclic ring, may be protected, as the case requires), to obtain a compound of the formula (IV):

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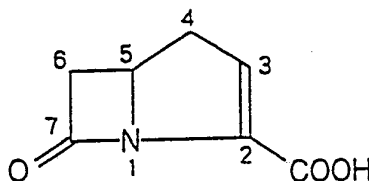
wherein R¹, R⁹, R²⁰, R³⁰, R⁴⁰, R⁵⁰ and R⁶⁰ are as defined above, and if necessary, removing any protecting group of the compound of the formula (IV).

Further, the present invention provides an
 10 antibacterial agent comprising an antibacterially effective amount of the compound of the formula (I) or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable carrier or diluent.

BEST MODE FOR CARRYING OUT THE INVENTION

15 Now, the present invention will be described in detail with reference to the preferred embodiments. Firstly, the symbols and terms used in this specification will be explained.

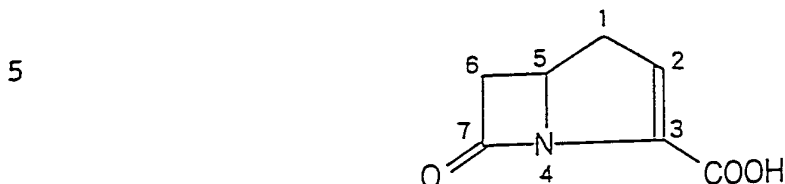
The compound of the present invention has a basic
 20 structure of the formula:



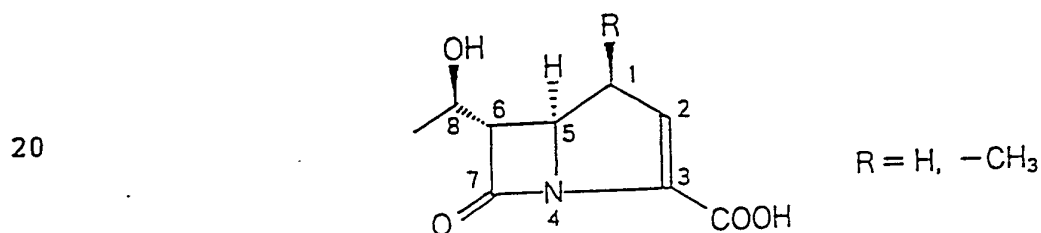
25 which is systematically referred to as a 7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylic acid. For the convenience sake, in this specification, this basic

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structure will be referred to as a 1-carbapen-2-em-3-carboxylic acid by putting the numbers based on a commonly widely used carbapenem of the formula:



The present invention includes optical isomers based on the asymmetrical carbon atoms at the 1-position, 5-
 10 position, 6-position and 8-position of the carbapenem structure and stereoisomers. Among these isomers, preferred is a compound of a (5R,6S,8R) configuration i.e. a compound having a steric configuration of (5R,6S) (5,6-trans) like thienamycin and in which the carbon atom
 15 at the 8-position takes a R-configuration, or a compound of a (1R,5S,6S,8R) configuration in a case where a methyl group is present at the 1-position.



Also with respect to the 2-substituted pyrrolidin-4-ylthio group in the side chain at the 2-position, the
 25 present invention includes isomers based on the asymmetrical carbon atoms at the 2-position and 4-position of the pyrrolidine structure and in the side

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chain at the 2-position. Among these isomers, preferred are compounds of (2'S,4'S) configuration and (2'R,4'R) configuration.

Further, with respect to the side chain at the 2-
5 position of the pyrrolidine structure, there exist isomers based on asymmetrical carbons, and the present invention includes such isomers as well.

The lower alkyl group means a linear or branched alkyl group having from 1 to 6 carbon atoms, such as a
10 methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a sec-butyl group, a tert-butyl group, a pentyl group or a hexyl group. Among them, a methyl group, an ethyl group or a tert-butyl group, is preferred.

15 The lower alkyl group which may have substituents means the above-mentioned lower alkyl group which is unsubstituted, or a lower alkyl group having at least one substituent at an optional position substitutable on the above-mentioned lower alkyl group.

20 The substituents of the lower alkyl group may, for example, be a carbamoyl group; a hydroxyl group; an amino group; a trifluoromethyl group; a carbamoyloxy group; a lower alkyl carbamoyl group mono- or di-substituted by the above-mentioned lower alkyl group, such as a methyl
25 carbamoyl group, an ethyl carbamoyl group, a dimethyl carbamoyl group or a diethyl carbamoyl group; a lower alkyl carbamoyloxy group mono- or di-substituted by the

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above-mentioned lower alkyl group, such as a methyl carbamoyloxy group, an ethyl carbamoyloxy group, a dimethyl carbamoyloxy group or a diethyl carbamoyloxy group; a lower alkyl amino group mono- or di-substituted
5 by the above-mentioned lower alkyl group, such as an N-methylamino group, an N-ethylamino group, an N,N-dimethylamino group or an N,N-diethylamino group; and a lower alkanoyl amino group such as an N-formylamino group or an N-acetylamino group.

10 Specific examples of the lower alkyl group which may have substituents, include a carbamoyl lower alkyl group such as a carbamoylmethyl group, a 1-carbamoylethyl group or a 2-carbamoylethyl group; a hydroxy lower alkyl group such as a hydroxymethyl group, a 1-hydroxyethyl group or
15 a 2-hydroxyethyl group; an amino lower alkyl group such as an aminomethyl group, a 1-aminoethyl group or a 2-aminoethyl group; a trihalomethyl group such as a trifluoromethyl group; a carbamoyloxy lower alkyl group such as a carbamoyloxymethyl group, a 1-
20 (carbamoyloxy)ethyl group or a 2-(carbamoyloxy)ethyl group; a (lower alkyl carbamoyl) lower alkyl group having a carbamoyl group mono- or di-substituted by the above-mentioned lower alkyl group, such as a
(methylcarbamoyl)methyl group, an (ethylcarbamoyl)methyl
25 group, a (dimethylcarbamoyl)methyl group or a (diethylcarbamoyl)methyl group; a (lower alkyl carbamoyloxy) lower alkyl group having a carbamoyloxy

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group mono- or di-substituted by the above lower alkyl group, such as a (methylcarbamoyloxy)methyl group, an (ethylcarbamoyloxy)methyl group, a (dimethylcarbamoyloxy)methyl group or a

5 (diethylcarbamoyloxy)methyl group; a trifluoromethyl lower alkyl group such as a trifluoromethylmethyl group, a 1-(trifluoromethyl)ethyl group or a 2-(trifluoromethyl)ethyl group; a (lower alkyl amino) lower alkyl group having an amino group mono- or di-substituted

10 by the above lower alkyl group, such as an N-methylaminomethyl group, an N-ethylaminomethyl group, an N,N-dimethylaminomethyl group or an N,N-diethylamino methyl group; and a (lower alkanoyl amino) lower alkyl group such as an N-formylaminomethyl group or an N-

15 acetylaminomethyl group.

The heterocyclic group may, for example, be a 3- to 8-membered heterocyclic group such as an aziridinyl group, an azetidiny group, a pyrrolidinyl group, a piperidino group, a piperazinyl group, a morpholino

20 group, a thiomorpholino group, a hexahydro-1H-azepinyl group or an octahydroazocinyl group. Further, the above-mentioned lower alkyl group which may have substituents, may be bonded, or either the nitrogen atom adjacent to X or other nitrogen atom on the heterocyclic ring may form

25 an ammonio group. Such a heterocyclic group may, for example, be an N-methylaziridinio group, an N-methylazetidinio group, an N-methylpyrrolidinio group, an

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N-methylpiperidinio group, a 1-methylpiperazinio group, a 4,4-dimethylpiperazinio group, an N-methylmorpholinio group, an N-methylthiomorpholinio group, an N-methylhexahydro-1H-azepinio group, or an N-methyl-
5 octahydroazocinio group. The heterocyclic group may have at least one substituent at an optional position substitutable on the heterocyclic ring.

The substituents of the heterocyclic ring may, for example, be a carbamoyl group; a cyano group; a
10 methanesulfonyl group; an amino group; a lower alkanoyl group such as a formyl group or an acetyl group; a lower alkyl carbamoyl group mono- or di-substituted by the above-mentioned lower alkyl group, such as a methylcarbamoyl group, an ethylcarbamoyl group, a
15 dimethylcarbamoyl group or a diethylcarbamoyl group; an amino group mono- or di-substituted by the above-mentioned lower alkyl group, such as an N-methylamino group, an N-ethylamino group, an N,N-dimethylamino group or an N,N-diethylamino group; a lower alkanoylamino group
20 such as an N-formylamino group or an N-acetylamino group; and a lower alkyl group which may have the above-mentioned substituents.

The lower alkylene group means a linear or branched alkylene group having from 1 to 6 carbon atoms. For
25 examples, a methylene group, an ethylene group, a propylene group, a 1-methylethylene group, a 2-methylethylene group, a methylenemethylene group, a

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dimethylmethylene group, a butylene group, a 1-methylpropylene group, a 2-methylpropylene group, a 3-methylpropylene group, a 1,1-dimethylethylene group or a 2,2-dimethylethylene group, may be mentioned. Among
5 them, a methylene group, an ethylene group or a propylene group is preferred.

The lower alkylene group which may have substituents, means the above-mentioned lower alkylene group which is unsubstituted or a lower alkylene group having at least
10 one substituent at an optional position substitutable on the above-mentioned lower alkylene group.

The substituents of the lower alkylene group may, for example, be a carbamoyl group; a cyano group; a methanesulfonyl group; an amino group; a lower alkyl
15 carbamoyl group mono- or di-substituted by the above-mentioned lower alkyl group, such as a methylcarbamoyl group, an ethylcarbamoyl group, a dimethylcarbamoyl group or a diethylcarbamoyl group; an amino group mono- or di-substituted by the above-mentioned lower alkyl group,
20 such as an N-methylamino group, an N-ethylamino group, an N,N-dimethylamino group or an N,N-diethylamino group; a lower alkanoyl amino group such as an N-formylamino group or an N-acetylamino group; and the above-mentioned lower alkyl group which may have substituents.

25 The carbamoyl group which may have substituents, means an unsubstituted carbamoyl group or a lower alkyl carbamoyl group mono- or di-substituted by the above-

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mentioned lower alkyl group, such as a methylcarbamoyl group, an ethylcarbamoyl group, a dimethylcarbamoyl group or a diethylcarbamoyl group.

The carboxyl-protecting group may, for example, be a
5 lower alkyl group such as a methyl group, an ethyl group, a propyl group, an isopropyl group or a tert-butyl group; a halogenated lower alkyl group such as a 2,2,2-trichloroethyl group or a 2,2,2-trifluoroethyl group; a lower alkanoyloxyalkyl group such as an acetoxymethyl
10 group, a propionyloxymethyl group, a pivaloyloxymethyl group, a 1-acetoxyethyl group or a 1-propionyloxyethyl group; a lower alkoxycarbonyloxyalkyl group such as a 1-(methoxycarbonyloxy)ethyl group, a 1-(ethoxycarbonyloxy)ethyl group or a 1-
15 (isopropoxycarbonyloxy)ethyl group; a lower alkenyl group such as a 2-propenyl group, a 2-chloro-2-propenyl group, a 3-methoxycarbonyl-2-propenyl group, a 2-methyl-2-propenyl group, a 2-butenyl group or a cinnamyl group; an aralkyl group such as a benzyl group, a p-methoxybenzyl
20 group, a 3,4-dimethoxybenzyl group, an o-nitrobenzyl group, a p-nitrobenzyl group, a benzhydryl group or a bis(p-methoxyphenyl)methyl group; a (5-substituted 2-oxo-1,3-dioxol-4-yl)methyl group such as a (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group; a lower alkylsilyl group
25 such as a trimethylsilyl group or a tert-butyltrimethylsilyl group; an indanyl group, a phthalidyl group or a methoxymethyl group. Particularly preferred

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are a 2-propenyl group, a p-nitrobenzyl group, a p-methoxybenzyl group, a benzhydryl group and a tert-butyldimethylsilyl group.

The hydroxyl-protecting group may, for example, be a
5 lower alkylsilyl group such as a trimethylsilyl group or a tert-butyldimethylsilyl group; a lower alkoxyethyl group such as a methoxyethyl group or a 2-methoxyethoxyethyl group; a tetrahydropyranyl group; an aralkyl group such as a benzyl group, a p-methoxybenzyl
10 group, a 2,4-dimethoxybenzyl group, an o-nitrobenzyl group, a p-nitrobenzyl group or a trityl group; an acyl group such as a formyl group or an acetyl group; a lower alkoxy carbonyl group such as a tert-butoxycarbonyl group, a 2-iodoethoxycarbonyl group or a 2,2,2-
15 trichloroethoxycarbonyl group; an alkenyloxycarbonyl group such as a 2-propenyloxycarbonyl group, a 2-chloro-2-propenyloxycarbonyl group, a 3-methoxycarbonyl-2-propenyloxycarbonyl group, a 2-methyl-2-propenyloxycarbonyl group, a 2-butenyloxycarbonyl group
20 or a cinnamyloxycarbonyl group; or an aralkyloxycarbonyl group such as a benzyloxycarbonyl group, a p-methoxybenzyloxycarbonyl group, an o-nitrobenzyloxycarbonyl group or a p-nitrobenzyloxycarbonyl group. Particularly preferred are
25 a 2-propenyloxycarbonyl group, a p-nitrobenzyloxycarbonyl group and a tert-butyldimethylsilyl group.

The amino- or imino-protecting group may, for

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example, be an aralkylidene group such as a benzylidene group, a p-chlorobenzylidene group, a p-nitrobenzylidene group, a salicylidene group, an α -naphthylidene group or a β -naphthylidene group; an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a 3,4-dimethoxybenzyl group, an o-nitrobenzyl group, a p-nitrobenzyl group, a benzhydryl group, a bis(p-methoxyphenyl)methyl group or a trityl group; a lower alkanoyl group such as a formyl group, an acetyl group, a propionyl group, a butyryl group, an oxalyl group, a succinyl group, or a pivaloyl group; a halogenated lower alkanoyl group such as a chloroacetyl group, a dichloroacetyl group, a trichloroacetyl group or a trifluoroacetyl group; an arylalkanoyl group such as a phenylacetyl group or a phenoxyacetyl group; a lower alkoxy carbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group or a tert-butoxycarbonyl group; a halogenated lower alkoxy carbonyl group such as a 2-iodoethoxycarbonyl group or a 2,2,2-trichloroethoxycarbonyl group; an alkenyloxycarbonyl group such as a 2-propenyloxycarbonyl group, a 2-chloro-2-propenyloxycarbonyl group, a 3-methoxycarbonyl-2-propenyloxycarbonyl group, a 2-methyl-2-propenyloxycarbonyl group, a 2-butenyloxycarbonyl group or a cinnamyloxycarbonyl group; an aralkyloxycarbonyl group such as a benzyloxycarbonyl group, an o-nitrobenzyloxycarbonyl group, a p-nitrobenzyloxycarbonyl

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group or a phenethyloxycarbonyl group; or a lower
alkylsilyl group such as a trimethylsilyl group or a
tert-butyldimethylsilyl group. Particularly preferred
are a 2-propenyloxycarbonyl group, a tert-butoxycarbonyl
5 group and a p-nitrobenzyloxycarbonyl group.

Each of R^4 , R^5 and R^6 which may be the same or
different, is a hydrogen atom, a cyano group, a
methanesulfonyl group, a lower alkyl group which may have
substituents, a carbamoyl group which may have
10 substituents or a group of the formula $-X-N(R^7)R^8$
{wherein each of R^7 and R^8 which may be the same or
different, is a hydrogen atom or a lower alkyl group
which may have substituents, or R^7 and R^8 form, together
with the adjacent nitrogen atom and, if necessary,
15 together with a hetero atom selected from the group
consisting of a nitrogen atom, an oxygen atom and a
sulfur atom in addition to the adjacent nitrogen atom, a
3- to 8-membered heterocyclic group which may be
substituted (provided that either the nitrogen atom
20 adjacent to X or other nitrogen atom on the heterocyclic
ring may form an ammonio group), and X is a lower
alkylene group which may have substituents}, provided
that at least one of R^4 , R^5 and R^6 is the group of the
formula $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined
25 above, the rest being a hydrogen atom, a cyano group, a
methanesulfonyl group, a lower alkyl group which may have
substituents or a carbamoyl group which may have

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substituents. Namely, the compound of the present invention is characterized in that at least one of R^4 , R^5 and R^6 has a primary, secondary or tertiary amino group, or an ammonio group. Among them, a compound is preferred wherein R^5 or R^6 is a group of the formula $-(CH_2)_n-N(R^{70})R^{80}$ wherein each of R^{70} and R^{80} which may be the same or different, is a hydrogen atom or a lower alkyl group, or R^{70} and R^{80} form, together with the adjacent nitrogen atom, a 3- to 8-membered heterocyclic group, and n is an integer of from 1 to 4. Further, a compound wherein R^5 or R^6 is a group of the formula $-CH_2-N(R^{77})R^{88}$ wherein each of R^{77} and R^{88} which may be the same or different, is a hydrogen atom or a lower alkyl group, or R^{77} and R^{88} form, together with the adjacent nitrogen atom, a 4- to 6-membered heterocyclic group, or a compound wherein each of R^5 and R^6 is a hydrogen atom, is more preferred. Particularly preferred is a compound wherein R^5 or R^6 is a group of the formula $-CH_2-NH_2$, $-CH_2-NHCH_3$ or $-CH_2-N(CH_3)_2$. The present invention also covers a case where in addition to R^7 and R^8 , the above-mentioned lower alkyl group which may have substituents, is bonded to the nitrogen atom adjacent to X so that the nitrogen atom forms an ammonio group.

R^2 is a hydrogen atom or a negative charge. When the side chain at the 2-position of the pyrrolidine ring forms an ammonio group, R^2 represents a negative charge forming a pair with the ammonium ion, whereby the

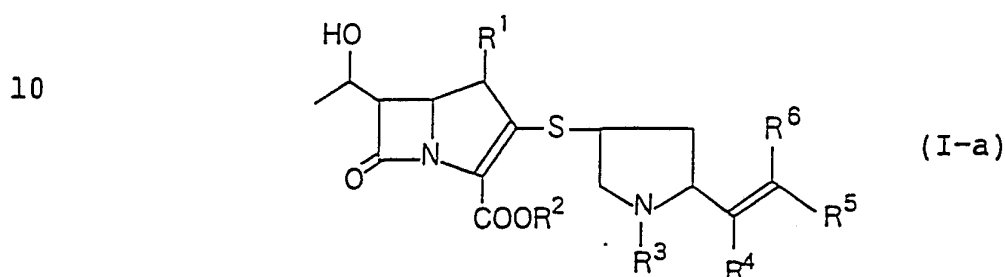
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compound of the formula (I) forms an intramolecular salt.

Y is a lower alkylene group or a single bond,
preferably a methylene group or a single bond.
Particularly preferred is a single bond.

5 Now, the compound of the formula (I) will be
described more specifically.

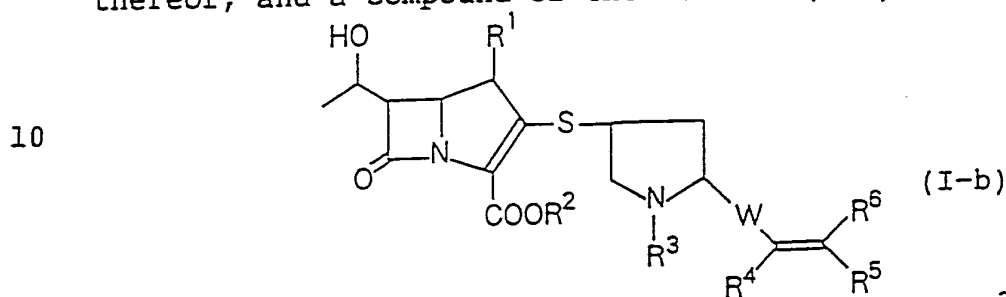
The compound of the formula (I) includes a compound
of the formula (I-a):



wherein R^1 is a hydrogen atom or a methyl group, R^2 is a
15 hydrogen atom or a negative charge, R^3 is a hydrogen atom
or a lower alkyl group, each of R^4 , R^5 and R^6 is a
hydrogen atom, a cyano group, a methanesulfonyl group, a
lower alkyl group which may have substituents, a
carbamoyl group which may have substituents or a group of
20 the formula $-X-N(R^7)R^8$ {wherein each of R^7 and R^8 which
may be the same or different, is a hydrogen atom or a
lower alkyl group which may have substituents, or R^7 and
 R^8 form, together with the adjacent nitrogen atom and, if
necessary, together with a hetero atom selected from the
25 group consisting of a nitrogen atom, an oxygen atom and a
sulfur atom in addition to the adjacent nitrogen atom, a
3- to 8- membered heterocyclic group which may be

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substituted (provided that either the nitrogen atom adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents}, provided
 5 that at least one of R^4 , R^5 and R^6 is the group of the formula $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined above; or a pharmaceutically acceptable salt or ester thereof, and a compound of the formula (I-b):



wherein R^1 is a hydrogen atom or a methyl group, R^2 is a hydrogen atom or a negative charge, R^3 is a hydrogen atom
 15 or a lower alkyl group, each of R^4 , R^5 and R^6 is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula $-X-N(R^7)R^8$ {wherein each of R^7 and R^8 which
 20 may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R^7 and R^8 form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a
 25 sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8- membered heterocyclic group which may be substituted (provided that either the nitrogen atom

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adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents, provided that at least one of R^4 , R^5 and R^6 is the group of the formula
5 $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined above, and W is a lower alkylene group; or a pharmaceutically acceptable salt or ester thereof.

The salt of the compound of the formula (I) is a common pharmaceutically acceptable salt and may, for
10 example, be a salt at the carboxyl group at the 3-position of the carbapenem structure, or at the pyrrolidine base at the 2-position of the carbapenem structure or the base on the side chain substituted on the pyrrolidine ring.

15 The basic addition salt at said carboxyl group includes, for example, an alkali metal salt such as a sodium salt or a potassium salt; an alkaline earth metal salt such as a calcium salt or a magnesium salt; an ammonium salt; an aliphatic amine salt such as a
20 trimethylamine salt, a triethylamine salt, a dicyclohexylamine salt, an ethanolamine salt, a diethanolamine salt, a triethanolamine salt or a procaine salt; an aralkylamine salt such as an N,N'-dibenzylethylenediamine salt; an aromatic heterocyclic
25 amine salt such as a pyridine salt, a picoline salt, a quinoline salt or an isoquinoline salt; a quaternary ammonium salt such as a tetramethylammonium salt, a

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tetraethylammonium salt, a benzyltrimethylammonium salt, a benzyltriethylammonium salt, a benzyltributylammonium salt, a methyltrioctylammonium salt or a tetrabutylammonium salt; and a basic amino acid salt such as an arginine salt or a lysine salt.

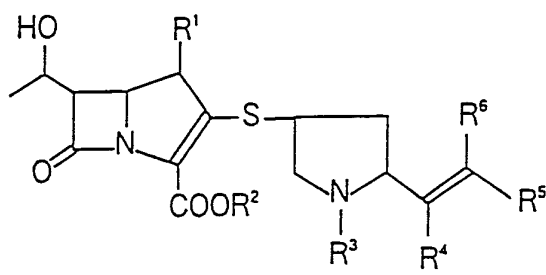
The acid addition salt at the pyrrolidine base or at the base on the side chain substituted on the pyrrolidine ring includes, for example, an inorganic salt such as a hydrochloride, a sulfate, a nitrate, a phosphate, a carbonate, a hydrogencarbonate or a perchlorate; an organic salt such as an acetate, a propionate, a lactate, a maleate, a fumarate, a tartrate, a malate, a succinate or an ascorbate; a sulfonate such as a methanesulfonate, an isethionate, a benzenesulfonate or a p-toluenesulfonate; and an acidic amino acid salt such as an aspartate or a glutamate.

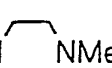
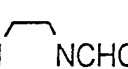
The non-toxic ester of the compound of the formula (I) means a common pharmaceutically acceptable ester at the carboxyl group at the 3-position of the carbapenem structure. For example, it includes an ester with an alkanoyloxymethyl group such as an acetoxymethyl group or a pivaloyloxymethyl group, an ester with an alkoxycarbonyloxyalkyl group such as a 1-(ethoxycarbonyloxy)ethyl group, an ester with a phthalidyl group and an ester with a (5-substituted-2-oxo-1,3-dioxol-4-yl)methyl group such as a (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group.

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Specific examples of the compound of the formula (I) include the following compounds. In the following compounds, the abbreviations have the following meanings:

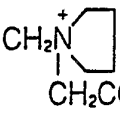
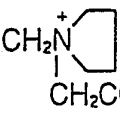
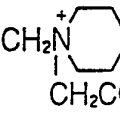
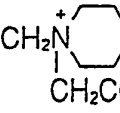
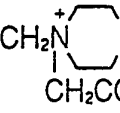
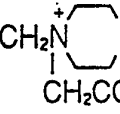
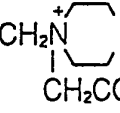
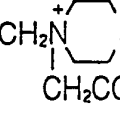
- Ac: acetyl group
- 5 Et: ethyl group
- iPr: isopropyl group
- Me: methyl group
- Pr: propyl group

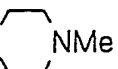
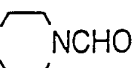
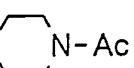
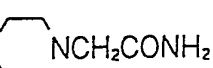
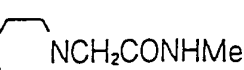


No.	R¹	R²	R³	R⁴	R⁵	R⁶
1	Me	H	H	CH₂NH₂	H	H
2	Me	H	H	CH₂NHMe	H	H
3	Me	H	H	CH₂NHEt	H	H
4	Me	H	H	CH₂NH <i>i</i> Pr	H	H
5	Me	H	H	CH₂NMe₂	H	H
6	Me	H	H	CH₂NEt₂	H	H
7	Me	H	H	CH₂N 	H	H
8	Me	H	H	CH₂N 	H	H
9	Me	H	H	CH₂N 	H	H
10	Me	H	H	CH₂N 	H	H
11	Me	H	H	CH₂N  NH	H	H
12	Me	H	H	CH₂N  NMe	H	H
13	Me	H	H	CH₂N  NCHO	H	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
14	Me	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{N-Ac}$	H	H
15	Me	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{NCH}_2\text{CONH}_2$	H	H
16	Me	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{NCH}_2\text{CONHMe}$	H	H
17	Me	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{NCH}_2\text{CONMe}_2$	H	H
18	Me	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{O}$	H	H
19	Me	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{S}$	H	H
20	Me	Nega- tive charge	H	$\text{CH}_2\text{N}^+\text{Me}_3$	H	H
21	Me	Nega- tive charge	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{Me}$	H	H
22	Me	Nega- tive charge	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{Me}$	H	H
23	Me	Nega- tive charge	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{NH}$	H	H
24	Me	Nega- tive charge	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{NCHO}$	H	H
25	Me	Nega- tive charge	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{N-Ac}$	H	H

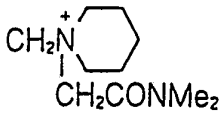
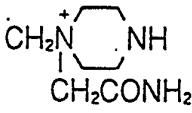
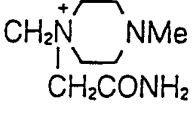
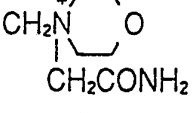
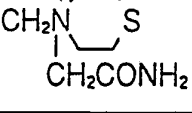
No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
26	Me	Negative charge	H		H	H
27	Me	Negative charge	H		H	H
28	Me	Negative charge	H		H	H
29	Me	Negative charge	H		H	H
30	Me	Negative charge	H		H	H
31	Me	Negative charge	H		H	H
32	Me	Negative charge	H		H	H
33	Me	Negative charge	H		H	H
34	Me	Negative charge	H		H	H
35	Me	Negative charge	H		H	H
36	Me	Negative charge	H		H	H
37	Me	Negative charge	H		H	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
38	Me	Negative charge	H		H	H
39	Me	Negative charge	H		H	H
40	Me	Negative charge	H		H	H
41	Me	Negative charge	H		H	H
42	Me	Negative charge	H		H	H
43	Me	Negative charge	H		H	H
44	Me	Negative charge	H		H	H
45	Me	Negative charge	H		H	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
46	Me	H	H	H	CH ₂ NH ₂	H
47	Me	H	H	H	CH ₂ NHMe	H
48	Me	H	H	H	CH ₂ NHEt	H
49	Me	H	H	H	CH ₂ NH <i>i</i> Pr	H
50	Me	H	H	H	CH ₂ NMe ₂	H
51	Me	H	H	H	CH ₂ NEt ₂	H
52	Me	H	H	H	CH ₂ N 	H
53	Me	H	H	H	CH ₂ N 	H
54	Me	H	H	H	CH ₂ N 	H
55	Me	H	H	H	CH ₂ N 	H
56	Me	H	H	H	CH ₂ N  NH	H
57	Me	H	H	H	CH ₂ N  NMe	H
58	Me	H	H	H	CH ₂ N  NCHO	H
59	Me	H	H	H	CH ₂ N  N-Ac	H
60	Me	H	H	H	CH ₂ N  NCH ₂ CONH ₂	H
61	Me	H	H	H	CH ₂ N  NCH ₂ CONHMe	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
62	Me	H	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONMe}_2$	H
63	Me	H	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{O}$	H
64	Me	H	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{S}$	H
65	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+\text{Me}_3$	H
66	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{Me}$	H
67	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{Me}$	H
68	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NH}$	H
69	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCHO}$	H
70	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{N-Ac}$	H
71	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONH}_2$	H
72	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONHMe}$	H
73	Me	Negative charge	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONMe}_2$	H

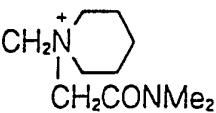
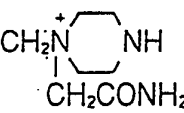
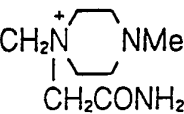
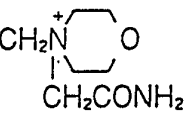
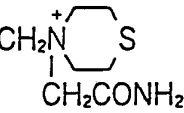
No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
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75	Me	Negative charge	H	H		H
76	Me	Negative charge	H	H		H
77	Me	Negative charge	H	H		H
78	Me	Negative charge	H	H		H
79	Me	Negative charge	H	H		H
80	Me	Negative charge	H	H		H
81	Me	Negative charge	H	H		H
82	Me	Negative charge	H	H		H
83	Me	Negative charge	H	H		H
84	Me	Negative charge	H	H		H
85	Me	Negative charge	H	H		H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
86	Me	Negative charge	H	H		H
87	Me	Negative charge	H	H		H
88	Me	Negative charge	H	H		H
89	Me	Negative charge	H	H		H
90	Me	Negative charge	H	H		H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
91	Me	H	H	H	H	CH ₂ NH ₂
92	Me	H	H	H	H	CH ₂ NHMe
93	Me	H	H	H	H	CH ₂ NHEt
94	Me	H	H	H	H	CH ₂ NH <i>i</i> Pr
95	Me	H	H	H	H	CH ₂ NMe ₂
96	Me	H	H	H	H	CH ₂ NEt ₂
97	Me	H	H	H	H	CH ₂ N 
98	Me	H	H	H	H	CH ₂ N 
99	Me	H	H	H	H	CH ₂ N 
100	Me	H	H	H	H	CH ₂ N 
101	Me	H	H	H	H	CH ₂ N  NH
102	Me	H	H	H	H	CH ₂ N  NMe
103	Me	H	H	H	H	CH ₂ N  NCHO
104	Me	H	H	H	H	CH ₂ N  N-Ac
105	Me	H	H	H	H	CH ₂ N  NCH ₂ CONH ₂
106	Me	H	H	H	H	CH ₂ N  NCH ₂ CONHMe

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
107	Me	H	H	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONMe}_2$
108	Me	H	H	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{O}$
109	Me	H	H	H	H	$\text{CH}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{S}$
110	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+\text{Me}_3$
111	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{Me}$
112	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{Me}$
113	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NH}$ Me
114	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCHO}$ Me
115	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{N-Ac}$ Me
116	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONH}_2$ Me
117	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONHMe}$ Me
118	Me	Nega- tive charge	H	H	H	$\text{CH}_2\text{N}^+ \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} \text{NCH}_2\text{CONMe}_2$ Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
119	Me	Nega- tive charge	H	H	H	
120	Me	Nega- tive charge	H	H	H	
121	Me	Nega- tive charge	H	H	H	
122	Me	Nega- tive charge	H	H	H	
123	Me	Nega- tive charge	H	H	H	
124	Me	Nega- tive charge	H	H	H	
125	Me	Nega- tive charge	H	H	H	
126	Me	Nega- tive charge	H	H	H	
127	Me	Nega- tive charge	H	H	H	
128	Me	Nega- tive charge	H	H	H	
129	Me	Nega- tive charge	H	H	H	
130	Me	Nega- tive charge	H	H	H	

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
131	Me	Negative charge	H	H	H	$\begin{array}{c} \text{CH}_2\text{N}^+ \\ \\ \text{CH}_2\text{CONMe}_2 \end{array}$ 
132	Me	Negative charge	H	H	H	$\begin{array}{c} \text{CH}_2\text{N}^+ \\ \quad \text{NH} \\ \text{CH}_2\text{CONH}_2 \end{array}$ 
133	Me	Negative charge	H	H	H	$\begin{array}{c} \text{CH}_2\text{N}^+ \\ \quad \text{NMe} \\ \text{CH}_2\text{CONH}_2 \end{array}$ 
134	Me	Negative charge	H	H	H	$\begin{array}{c} \text{CH}_2\text{N}^+ \\ \quad \text{O} \\ \text{CH}_2\text{CONH}_2 \end{array}$ 
135	Me	Negative charge	H	H	H	$\begin{array}{c} \text{CH}_2\text{N}^+ \\ \quad \text{S} \\ \text{CH}_2\text{CONH}_2 \end{array}$ 

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
136	Me	H	H	CH ₂ NH ₂	CONH ₂	H
137	Me	H	H	CH ₂ NHMe	CONH ₂	H
138	Me	H	H	CH ₂ NMe ₂	CONH ₂	H
139	Me	H	H	CH ₂ N 	CONH ₂	H
140	Me	H	H	CH ₂ N 	CONH ₂	H
141	Me	Negative charge	H	CH ₂ N ⁺ Me ₃	CONH ₂	H
142	Me		H	CH ₂ N ⁺  Me	CONH ₂	H
143	Me		H	CH ₂ N ⁺  Me	CONH ₂	H
144	Me	H	H	CH ₂ NH ₂	H	CONH ₂
145	Me	H	H	CH ₂ NHMe	H	CONH ₂
146	Me	H	H	CH ₂ NMe ₂	H	CONH ₂
147	Me	H	H	CH ₂ N 	H	CONH ₂
148	Me	H	H	CH ₂ N 	H	CONH ₂
149	Me	Negative charge	H	CH ₂ N ⁺ Me ₃	H	CONH ₂
150	Me		H	CH ₂ N ⁺  Me	H	CONH ₂
151	Me		H	CH ₂ N ⁺  Me	H	CONH ₂

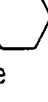
No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
152	Me	H	H	CH ₂ NH ₂	Me	H
153	Me	H	H	CH ₂ NHMe	Me	H
154	Me	H	H	CH ₂ NMe ₂	Me	H
155	Me	H	H	CH ₂ N 	Me	H
156	Me	H	H	CH ₂ N 	Me	H
157	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	Me	H
158	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	Me	H
159	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	Me	H
160	Me	H	H	CH ₂ NH ₂	H	Me
161	Me	H	H	CH ₂ NHMe	H	Me
162	Me	H	H	CH ₂ NMe ₂	H	Me
163	Me	H	H	CH ₂ N 	H	Me
164	Me	H	H	CH ₂ N 	H	Me
165	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	H	Me
166	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	H	Me
167	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	H	Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
168	Me	H	H	CH ₂ NH ₂	CF ₃	H
169	Me	H	H	CH ₂ NHMe	CF ₃	H
170	Me	H	H	CH ₂ NMe ₂	CF ₃	H
171	Me	H	H	CH ₂ N 	CF ₃	H
172	Me	H	H	CH ₂ N 	CF ₃	H
173	Me	Negative charge	H	CH ₂ N ⁺ Me ₃	CF ₃	H
174	Me		H	CH ₂ N ⁺  Me	CF ₃	H
175	Me		H	CH ₂ N ⁺  Me	CF ₃	H
176	Me		H	CH ₂ NH ₂	CN	H
177	Me	H	H	CH ₂ NHMe	CN	H
178	Me	H	H	CH ₂ NMe ₂	CN	H
179	Me	H	H	CH ₂ N 	CN	H
180	Me	H	H	CH ₂ N 	CN	H
181	Me	Negative charge	H	CH ₂ N ⁺ Me ₃	CN	H
182	Me		H	CH ₂ N ⁺  Me	CN	H
183	Me		H	CH ₂ N ⁺  Me	CN	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
184	Me	H	H	CH ₂ NH ₂	H	CN
185	Me	H	H	CH ₂ NHMe	H	CN
186	Me	H	H	CH ₂ NMe ₂	H	CN
187	Me	H	H	CH ₂ N 	H	CN
188	Me	H	H	CH ₂ N 	H	CN
189	Me	Negative charge	H	CH ₂ N ⁺ Me ₃	H	CN
190	Me		H	CH ₂ N ⁺  Me	H	CN
191	Me		H	CH ₂ N ⁺  Me	H	CN
192	Me		H	CH ₂ NH ₂	SO ₂ Me	H
193	Me	H	H	CH ₂ NHMe	SO ₂ Me	H
194	Me	H	H	CH ₂ NMe ₂	SO ₂ Me	H
195	Me	H	H	CH ₂ N 	SO ₂ Me	H
196	Me	H	H	CH ₂ N 	SO ₂ Me	H
197	Me	Negative charge	H	CH ₂ N ⁺ Me ₃	SO ₂ Me	H
198	Me		H	CH ₂ N ⁺  Me	SO ₂ Me	H
199	Me		H	CH ₂ N ⁺  Me	SO ₂ Me	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
200	Me	H	H	CH ₂ NH ₂	H	SO ₂ Me
201	Me	H	H	CH ₂ NHMe	H	SO ₂ Me
202	Me	H	H	CH ₂ NMe ₂	H	SO ₂ Me
203	Me	H	H	CH ₂ N 	H	SO ₂ Me
204	Me	H	H	CH ₂ N 	H	SO ₂ Me
205	Me	Negative charge	H	CH ₂ N ⁺ Me ₃	H	SO ₂ Me
206	Me		H	CH ₂ N ⁺  Me	H	SO ₂ Me
207	Me		H	CH ₂ N ⁺  Me	H	SO ₂ Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
208	Me	H	H	H	CH ₂ NH ₂	CONH ₂
209	Me	H	H	H	CH ₂ NHMe	CONH ₂
210	Me	H	H	H	CH ₂ NMe ₂	CONH ₂
211	Me	H	H	H	CH ₂ N 	CONH ₂
212	Me	H	H	H	CH ₂ N 	CONH ₂
213	Me	Negative charge	H	H	CH ₂ N ⁺ Me ₃	CONH ₂
214	Me		H	H	CH ₂ N ⁺  Me	CONH ₂
215	Me		H	H	CH ₂ N ⁺  Me	CONH ₂
216	Me		H	CONH ₂	CH ₂ NH ₂	H
217	Me	H	H	CONH ₂	CH ₂ NHMe	H
218	Me	H	H	CONH ₂	CH ₂ NMe ₂	H
219	Me	H	H	CONH ₂	CH ₂ N 	H
220	Me	H	H	CONH ₂	CH ₂ N 	H
221	Me	Negative charge	H	CONH ₂	CH ₂ N ⁺ Me ₃	H
222	Me		H	CONH ₂	CH ₂ N ⁺  Me	H
223	Me		H	CONH ₂	CH ₂ N ⁺  Me	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
224	Me	H	H	H	CH ₂ NH ₂	Me
225	Me	H	H	H	CH ₂ NHMe	Me
226	Me	H	H	H	CH ₂ NMe ₂	Me
227	Me	H	H	H	CH ₂ N 	Me
228	Me	H	H	H	CH ₂ N 	Me
229	Me	Negative charge	H	H	CH ₂ N ⁺ Me ₃	Me
230	Me		H	H	CH ₂ N ⁺ 	Me
231	Me		H	H	CH ₂ N ⁺ 	Me
232	Me		H	Me	CH ₂ NH ₂	H
233	Me	H	H	Me	CH ₂ NHMe	H
234	Me	H	H	Me	CH ₂ NMe ₂	H
235	Me	H	H	Me	CH ₂ N 	H
236	Me	H	H	Me	CH ₂ N 	H
237	Me	Negative charge	H	Me	CH ₂ N ⁺ Me ₃	H
238	Me		H	Me	CH ₂ N ⁺ 	H
239	Me		H	Me	CH ₂ N ⁺ 	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
240	Me	H	H	H	CH ₂ NH ₂	CF ₃
241	Me	H	H	H	CH ₂ NHMe	CF ₃
242	Me	H	H	H	CH ₂ NMe ₂	CF ₃
243	Me	H	H	H	CH ₂ N 	CF ₃
244	Me	H	H	H	CH ₂ N 	CF ₃
245	Me	Negative charge	H	H	CH ₂ N ⁺ Me ₃	CF ₃
246	Me		H	H	CH ₂ N ⁺  Me	CF ₃
247	Me		H	H	CH ₂ N ⁺  Me	CF ₃
248	Me	H	H	H	CH ₂ NH ₂	CN
249	Me	H	H	H	CH ₂ NHMe	CN
250	Me	H	H	H	CH ₂ NMe ₂	CN
251	Me	H	H	H	CH ₂ N 	CN
252	Me	H	H	H	CH ₂ N 	CN
253	Me	Negative charge	H	H	CH ₂ N ⁺ Me ₃	CN
254	Me		H	H	CH ₂ N ⁺  Me	CN
255	Me		H	H	CH ₂ N ⁺  Me	CN

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
256	Me	H	H	CN	CH ₂ NH ₂	H
257	Me	H	H	CN	CH ₂ NHMe	H
258	Me	H	H	CN	CH ₂ NMe ₂	H
259	Me	H	H	CN	CH ₂ N 	H
260	Me	H	H	CN	CH ₂ N 	H
261	Me	Negative charge	H	CN	CH ₂ N ⁺ Me ₃	H
262	Me		H	CN	CH ₂ N ⁺  Me	H
263	Me		H	CN	CH ₂ N ⁺  Me	H
264	Me		H	H	CH ₂ NH ₂	SO ₂ Me
265	Me	H	H	H	CH ₂ NHMe	SO ₂ Me
266	Me	H	H	H	CH ₂ NMe ₂	SO ₂ Me
267	Me	H	H	H	CH ₂ N 	SO ₂ Me
268	Me	H	H	H	CH ₂ N 	SO ₂ Me
269	Me	Negative charge	H	H	CH ₂ N ⁺ Me ₃	SO ₂ Me
270	Me		H	H	CH ₂ N ⁺  Me	SO ₂ Me
271	Me		H	H	CH ₂ N ⁺  Me	SO ₂ Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
272	Me	H	H	SO ₂ Me	CH ₂ NH ₂	H
273	Me	H	H	SO ₂ Me	CH ₂ NHMe	H
274	Me	H	H	SO ₂ Me	CH ₂ NMe ₂	H
275	Me	H	H	SO ₂ Me	CH ₂ N 	H
276	Me	H	H	SO ₂ Me	CH ₂ N 	H
277	Me	Negative charge	H	SO ₂ Me	CH ₂ N ⁺ Me ₃	H
278	Me		H	SO ₂ Me	CH ₂ N ⁺  Me	H
279	Me		H	SO ₂ Me	CH ₂ N ⁺  Me	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
280	Me	H	H	CONH ₂	H	CH ₂ NH ₂
281	Me	H	H	CONH ₂	H	CH ₂ NHMe
282	Me	H	H	CONH ₂	H	CH ₂ NMe ₂
283	Me	H	H	CONH ₂	H	CH ₂ N 
284	Me	H	H	CONH ₂	H	CH ₂ N 
285	Me	Negative charge	H	CONH ₂	H	CH ₂ N ⁺ Me ₃
286	Me		H	CONH ₂	H	CH ₂ N ⁺  Me
287	Me		H	CONH ₂	H	CH ₂ N ⁺  Me
288	Me	H	H	H	CONH ₂	CH ₂ NH ₂
289	Me	H	H	H	CONH ₂	CH ₂ NHMe
290	Me	H	H	H	CONH ₂	CH ₂ NMe ₂
291	Me	H	H	H	CONH ₂	CH ₂ N 
292	Me	H	H	H	CONH ₂	CH ₂ N 
293	Me	Negative charge	H	H	CONH ₂	CH ₂ N ⁺ Me ₃
294	Me		H	H	CONH ₂	CH ₂ N ⁺  Me
295	Me		H	H	CONH ₂	CH ₂ N ⁺  Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
296	Me	H	H	Me	H	CH ₂ NH ₂
297	Me	H	H	Me	H	CH ₂ NHMe
298	Me	H	H	Me	H	CH ₂ NMe ₂
299	Me	H	H	Me	H	CH ₂ N 
300	Me	H	H	Me	H	CH ₂ N 
301	Me	Negative charge	H	Me	H	CH ₂ N ⁺ Me ₃
302	Me		H	Me	H	CH ₂ N ⁺  Me
303	Me		H	Me	H	CH ₂ N ⁺  Me
304	Me	H	H	H	Me	CH ₂ NH ₂
305	Me	H	H	H	Me	CH ₂ NHMe
306	Me	H	H	H	Me	CH ₂ NMe ₂
307	Me	H	H	H	Me	CH ₂ N 
308	Me	H	H	H	Me	CH ₂ N 
309	Me	Negative charge	H	H	Me	CH ₂ N ⁺ Me ₃
310	Me		H	H	Me	CH ₂ N ⁺  Me
311	Me		H	H	Me	CH ₂ N ⁺  Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
312	Me	H	H	CF ₃	H	CH ₂ NH ₂
313	Me	H	H	CF ₃	H	CH ₂ NHMe
314	Me	H	H	CF ₃	H	CH ₂ NMe ₂
315	Me	H	H	CF ₃	H	CH ₂ N 
316	Me	H	H	CF ₃	H	CH ₂ N 
317	Me	Nega- tive charge	H	CF ₃	H	CH ₂ N ⁺ Me ₃
318	Me	Nega- tive charge	H	CF ₃	H	CH ₂ N ⁺  Me
319	Me	Nega- tive charge	H	CF ₃	H	CH ₂ N ⁺  Me
320	Me	H	H	CN	H	CH ₂ NH ₂
321	Me	H	H	CN	H	CH ₂ NHMe
322	Me	H	H	CN	H	CH ₂ NMe ₂
323	Me	H	H	CN	H	CH ₂ N 
324	Me	H	H	CN	H	CH ₂ N 
325	Me	Nega- tive charge	H	CN	H	CH ₂ N ⁺ Me ₃
326	Me	Nega- tive charge	H	CN	H	CH ₂ N ⁺  Me
327	Me	Nega- tive charge	H	CN	H	CH ₂ N ⁺  Me

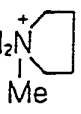
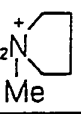
No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
328	Me	H	H	H	CN	CH ₂ NH ₂
329	Me	H	H	H	CN	CH ₂ NHMe
330	Me	H	H	H	CN	CH ₂ NMe ₂
331	Me	H	H	H	CN	CH ₂ N 
332	Me	H	H	H	CN	CH ₂ N 
333	Me	Negative charge	H	H	CN	CH ₂ N ⁺ Me ₃
334	Me		H	H	CN	CH ₂ N ⁺  Me
335	Me		H	H	CN	CH ₂ N ⁺  Me
336	Me	H	H	SO ₂ Me	H	CH ₂ NH ₂
337	Me	H	H	SO ₂ Me	H	CH ₂ NHMe
338	Me	H	H	SO ₂ Me	H	CH ₂ NMe ₂
339	Me	H	H	SO ₂ Me	H	CH ₂ N 
340	Me	H	H	SO ₂ Me	H	CH ₂ N 
341	Me	Negative charge	H	SO ₂ Me	H	CH ₂ N ⁺ Me ₃
342	Me		H	SO ₂ Me	H	CH ₂ N ⁺  Me
343	Me		H	SO ₂ Me	H	CH ₂ N ⁺  Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
344	Me	H	H	H	SO ₂ Me	CH ₂ NH ₂
345	Me	H	H	H	SO ₂ Me	CH ₂ NHMe
346	Me	H	H	H	SO ₂ Me	CH ₂ NMe ₂
347	Me	H	H	H	SO ₂ Me	CH ₂ N 
348	Me	H	H	H	SO ₂ Me	CH ₂ N 
349	Me	Negative charge Negative charge Negative charge	H	H	SO ₂ Me	CH ₂ N ⁺ Me ₃
350	Me		H	H	SO ₂ Me	CH ₂ N ⁺  Me
351	Me		H	H	SO ₂ Me	CH ₂ N ⁺  Me
352	H	H	H	H	CH ₂ NH ₂	H
353	H	H	H	H	H	CH ₂ NH ₂

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
354	Me	H	H	CH ₂ NH ₂	Et	H
355	Me	H	H	CH ₂ NHMe	Et	H
356	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	Et	H
357	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	Et	H
358	Me	H	H	CH ₂ NH ₂	Pr	H
359	Me	H	H	CH ₂ NHMe	Pr	H
360	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	Pr	H
361	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	Pr	H
362	Me	H	H	CH ₂ NH ₂	iPr	H
363	Me	H	H	CH ₂ NHMe	iPr	H
364	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	iPr	H
365	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	iPr	H
366	Me	H	H	CH ₂ NH ₂	H	Et
367	Me	H	H	CH ₂ NHMe	H	Et
368	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	H	Et
369	Me	Nega- tive charge	H	CH ₂ N ⁺  Me	H	Et

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
370	Me	H	H	CH ₂ NH ₂	H	Pr
371	Me	H	H	CH ₂ NHMe	H	Pr
372	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	H	Pr
373	Me	Nega- tive charge	H	CH ₂ N ⁺ Me	H	Pr
374	Me	H	H	CH ₂ NH ₂	H	iPr
375	Me	H	H	CH ₂ NHMe	H	iPr
376	Me	Nega- tive charge	H	CH ₂ N ⁺ Me ₃	H	iPr
377	Me	Nega- tive charge	H	CH ₂ N ⁺ Me	H	iPr

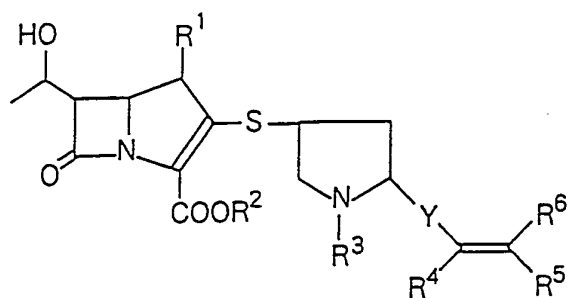
No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
378	Me	H	H	H	CH ₂ NH ₂	Et
379	Me	H	H	H	CH ₂ NHMe	Et
380	Me	Nega- tive charge	H	H	CH ₂ N ⁺ Me ₃	Et
381	Me	Nega- tive charge	H	H	CH ₂ N ⁺ 	Et
382	Me	H	H	H	CH ₂ NH ₂	Pr
383	Me	H	H	H	CH ₂ NHMe	Pr
384	Me	Nega- tive charge	H	H	CH ₂ N ⁺ Me ₃	Pr
385	Me	Nega- tive charge	H	H	CH ₂ N ⁺ 	Pr
386	Me	H	H	H	CH ₂ NH ₂	iPr
387	Me	H	H	H	CH ₂ NHMe	iPr
388	Me	Nega- tive charge	H	H	CH ₂ N ⁺ Me ₃	iPr
389	Me	Nega- tive charge	H	H	CH ₂ N ⁺ 	iPr
390	Me	H	H	Et	CH ₂ NH ₂	H
391	Me	H	H	Et	CH ₂ NHMe	H
392	Me	Nega- tive charge	H	Et	CH ₂ N ⁺ Me ₃	H
393	Me	Nega- tive charge	H	Et	CH ₂ N ⁺ 	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
394	Me	H	H	Pr	CH ₂ NH ₂	H
395	Me	H	H	Pr	CH ₂ NHMe	H
396	Me	Nega- tive charge	H	Pr	CH ₂ N ⁺ Me ₃	H
397	Me	Nega- tive charge	H	Pr	CH ₂ N ⁺ Me 	H
398	Me	H	H	iPr	CH ₂ NH ₂	H
399	Me	H	H	iPr	CH ₂ NHMe	H
400	Me	Nega- tive charge	H	iPr	CH ₂ N ⁺ Me ₃	H
401	Me	Nega- tive charge	H	iPr	CH ₂ N ⁺ Me 	H

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
402	Me	H	H	Et	H	CH ₂ NH ₂
403	Me	H	H	Et	H	CH ₂ NHMe
404	Me	Nega- tive charge	H	Et	H	CH ₂ N ⁺ Me ₃
405	Me	Nega- tive charge	H	Et	H	CH ₂ N ⁺  Me
406	Me	H	H	Pr	H	CH ₂ NH ₂
407	Me	H	H	Pr	H	CH ₂ NHMe
408	Me	Nega- tive charge	H	Pr	H	CH ₂ N ⁺ Me ₃
409	Me	Nega- tive charge	H	Pr	H	CH ₂ N ⁺  Me
410	Me	H	H	iPr	H	CH ₂ NH ₂
411	Me	H	H	iPr	H	CH ₂ NHMe
412	Me	Nega- tive charge	H	iPr	H	CH ₂ N ⁺ Me ₃
413	Me	Nega- tive charge	H	iPr	H	CH ₂ N ⁺  Me
414	Me	H	H	H	Et	CH ₂ NH ₂
415	Me	H	H	H	Et	CH ₂ NHMe
416	Me	Nega- tive charge	H	H	Et	CH ₂ N ⁺ Me ₃
417	Me	Nega- tive charge	H	H	Et	CH ₂ N ⁺  Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
418	Me	H	H	H	Pr	CH ₂ NH ₂
419	Me	H	H	H	Pr	CH ₂ NHMe
420	Me	Nega- tive charge	H	H	Pr	CH ₂ N ⁺ Me ₃
421	Me	Nega- tive charge	H	H	Pr	CH ₂ N ⁺ Me
422	Me	H	H	H	iPr	CH ₂ NH ₂
423	Me	H	H	H	iPr	CH ₂ NHMe
424	Me	Nega- tive charge	H	H	iPr	CH ₂ N ⁺ Me ₃
425	Me	Nega- tive charge	H	H	iPr	CH ₂ N ⁺ Me

No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
426	H	H	H	CH ₂ NH ₂	H	H
427	H	H	H	H	CH ₂ NHMe	H
428	H	H	H	H	H	CH ₂ NHMe
429	H	H	H	H	H	CH ₂ NMe ₂
430	H	H	H	H	H	CH ₂ N 
431	H	H	H	H	CH ₂ NH ₂	Me
432	H	H	H	H	CH ₂ NHMe	Me
433	H	H	H	H	Me	CH ₂ NH ₂
434	H	H	H	H	Me	CH ₂ NHMe



No.	R ¹	R ²	R ³	Y	R ⁴	R ⁵	R ⁶
435	Me	H	H	CH ₂	CH ₂ NH ₂	H	H
436	Me	H	H	CH ₂	CH ₂ NHMe	H	H
437	Me	H	H	CH ₂	H	CH ₂ NH ₂	H
438	Me	H	H	CH ₂	H	CH ₂ NHMe	H
439	Me	H	H	CH ₂	H	H	CH ₂ NH ₂
440	Me	H	H	CH ₂	H	H	CH ₂ NHMe

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Among the above compounds, preferred are compounds identified by compound Nos. 1, 2, 5, 9, 12, 15, 21, 26, 35, 38, 46, 47, 50, 54, 57, 60, 66, 71, 80, 83, 91, 92, 95, 99, 102, 105, 111, 116, 125, 128, 136, 137, 138, 139, 142, 144, 145, 147, 150, 152, 153, 154, 155, 158, 160, 161, 162, 163, 166, 168, 169, 170, 171, 174, 176, 177, 178, 179, 182, 184, 185, 186, 187, 190, 192, 193, 194, 195, 198, 200, 201, 202, 203, 206, 208, 209, 210, 211, 214, 216, 217, 218, 219, 222, 224, 225, 226, 227, 230, 232, 233, 234, 235, 238, 240, 241, 242, 243, 246, 248, 249, 250, 251, 254, 256, 257, 258, 259, 262, 264, 265, 266, 267, 270, 272, 273, 274, 275, 278, 280, 281, 282, 283, 286, 288, 289, 290, 291, 294, 296, 297, 298, 299, 302, 304, 305, 306, 307, 310, 312, 313, 314, 315, 318, 320, 321, 322, 323, 326, 328, 329, 330, 331, 334, 336, 337, 338, 339, 342, 344, 345, 346, 347, 350, 352, 353, 426, 427, 428, 429, 430, 431, 432, 433 and 434.

Among them, particularly preferred are as follows:

- 1 (1R,5S,6S)-2-[(2S,4S)-2-[[1-(aminomethyl)vinyl]pyrrolidin-4-ylthio]]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
- 2 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[1-(N-methylaminomethyl)vinyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 5 (1R,5S,6S)-2-[(2S,4S)-2-[1-(N,N-dimethylaminomethyl)vinyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

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- 9 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[1-(1-pyrrolidinylmethyl)vinyl]pyrrolidin-4-
ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 12 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
5 [(2S,4S)-2-[1-(4-methyl-1-piperazinylmethyl)vinyl]-
pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 15 (1R,5S,6S)-2-[(2S,4S)-2-[1-(4-carbamoylmethyl-1-
piperazinylmethyl)vinyl]pyrrolidin-4-ylthio]-6-[(R)-1-
hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
- 10 21 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[1-(N-methylpyrrolidinomethyl)vinyl]-
pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate,
- 26 (1R,5S,6S)-2-[(2S,4S)-2-[1-(4-carbamoylmethyl-1-
methylpiperazinomethyl)vinyl]pyrrolidin-4-ylthio]-6-
15 [(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-
carboxylate,
- 38 (1R,5S,6S)-2-[(2S,4S)-2-[1-(N-carbamoylmethyl-1-
pyrrolidinomethyl)vinyl]pyrrolidin-4-ylthio]-6-[(R)-1-
hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate,
- 20 46 (1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-amino-1-
propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-
methyl-1-carbapen-2-em-3-carboxylic acid,
- 47 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(E)-3-(N-methylamino)-1-propenyl]pyrrolidin-
25 4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 50 (1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-(N,N-
dimethylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-

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hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

54 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(E)-3-(1-pyrrolidinyl)-1-propenyl]pyrrolidin-
4-ylthio]-1-carbapen-2-em-3-carboxylic acid,

5 57 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(E)-3-(4-methyl-1-piperazinyl)-1-
propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-
carboxylic acid,

60 (1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-(4-
10 carbamoylmethyl-1-piperazinyl)-1-propenyl]pyrrolidin-4-
ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-
3-carboxylic acid,

66 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(E)-3-(N-methylpyrrolidinio)-1-
15 propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-
carboxylate,

71 (1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-(4-
carbonylmethyl-1-methylpiperazinio)-1-
propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-
20 methyl-1-carbapen-2-em-3-carboxylate,

83 (1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-(N-
carbamoylmethyl-1-pyrrolidinio)-1-propenyl]pyrrolidin-4-
ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-
3-carboxylate,

25 91 (1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-1-
propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-
methyl-1-carbapen-2-em-3-carboxylic acid,

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- 92 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(Z)-3-(N-methylamino)-1-propenyl]pyrrolidin-
4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 95 (1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-(N,N-
5 dimethylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-
hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
- 99 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(Z)-3-(1-pyrrolidinyl)-1-propenyl]pyrrolidin-
4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 10 102 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(Z)-3-(4-methyl-1-piperazinyl)-1-
propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-
carboxylic acid,
- 105 (1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-(4-
15 carbamoylmethyl-1-piperazinyl)-1-propenyl]pyrrolidin-4-
ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-
3-carboxylic acid,
- 111 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-
[(2S,4S)-2-[(Z)-3-(N-methylpyrrolidinio)-1-
20 propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-
carboxylate,
- 116 (1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-(4-
carbamoylmethyl-1-methylpiperazinio)-1-
propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-
25 methyl-1-carbapen-2-em-3-carboxylate,
- 128 (1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-(N-
carbamoylmethyl-1-pyrrolidinio)-1-propenyl]pyrrolidin-4-

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ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate,

224 (1R,5S,6S)-2-(2S,4S)-2-[(E)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

225 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

304 (1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

305 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

352 (5R,6S)-2-[(2S,4S)-2-[(E)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,

353 (5R,6S)-2-[(2S,4S)-2-[(Z)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,

426 (5R,6S)-2-[(2S,4S)-2-[[1-(aminomethyl)vinyl]pyrrolidin-4-ylthio]]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,

427 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,

428 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-

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[(Z)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,

429 (5R,6S)-2-[(2S,4S)-2-[(Z)-3-(N,N-dimethylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,

430 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(1-pyrrolidinyl)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,

431 (5R,6S)-2-[(2S,4S)-2-[(E)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,

432 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,

433 (5R,6S)-2-[(2S,4S)-2-[(Z)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid and

434 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid.

Especially preferred are compounds No. 91 i.e.

(1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid, No. 304 i.e.

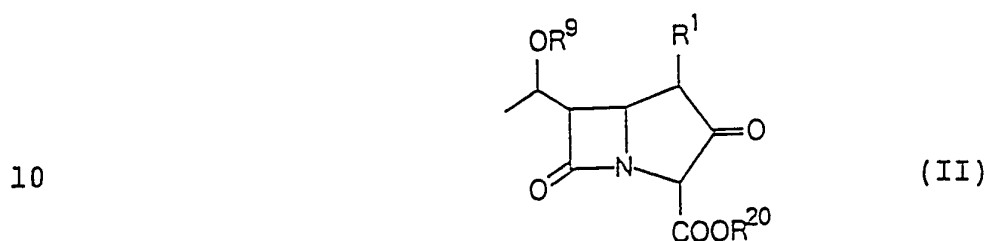
(1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid and No. 305 i.e.

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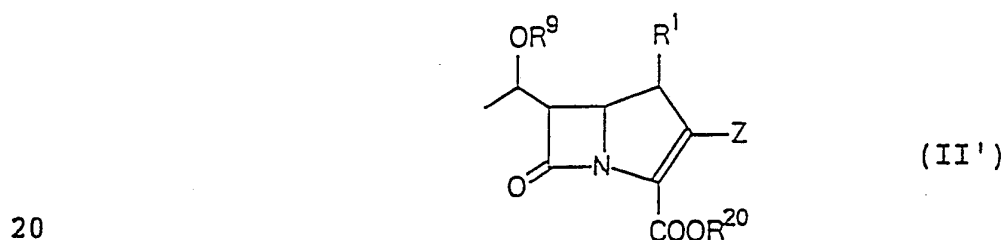
(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid.

Now, the process for producing the compound of the
 5 present invention will be described.

An activating reagent is reacted to a compound of the formula:



wherein R^1 is a hydrogen atom or a methyl group, R^9 is a hydrogen atom or a hydroxyl-protecting group, and R^{20} is a hydrogen atom or a carboxyl-protecting group, in an
 15 inert organic solvent in the presence of a base to form a reactive derivative of the formula (II'):



wherein R^1 , R^9 and R^{20} are as defined above, and Z is a leaving group.

The inert organic solvent to be used for the reaction may, for example, be diethyl ether, tetrahydrofuran,
 25 dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene, acetone, ethyl

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acetate, acetonitrile, N,N-dimethylformamide, hexamethylphosphoric triamide or a mixture of such solvents. Particularly preferred are acetonitrile and benzene.

5 The base to be used for the reaction may, for example, be a tertiary aliphatic amine such as trimethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-
10 diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); or an aromatic amine such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or isoquinoline. Particularly preferred are N,N-diisopropylethylamine and
15 triethylamine.

 The activating reagent to be used for the reaction may, for example, be an acid anhydride such as trifluoroacetic anhydride, methanesulfonic anhydride, trifluoromethanesulfonic anhydride or p-toluenesulfonic
20 anhydride; or an acid chloride such as methanesulfonyl chloride, p-toluenesulfonyl chloride or diphenyl chlorophosphate. Particularly preferred is diphenyl chlorophosphate.

 In the formula (II'), Z is a leaving group such as a
25 trifluoroacetoxy group, a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group, a p-toluenesulfonyloxy group or a diphenoxyphosphoryloxy group. Particularly

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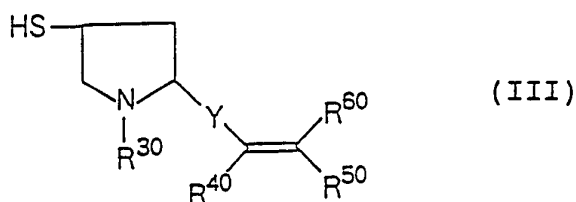
preferred is a diphenoxyphosphoryloxy group.

For the reaction, from 1 to 3 mols, preferably from 1 to 1.5 mols, of the base and from 1 to 1.2 mols of the activating reagent are used per mol of the compound of the formula (II).

The reaction is conducted usually within a temperature range of from -40 to 50°C, preferably from -20 to 20°C, and usually completed quantitatively in from 0.5 to 3 hours.

After completion of the reaction, the reaction product is treated in accordance with a usual method to obtain the reactive derivative (II') of the compound of the formula (II) quantitatively.

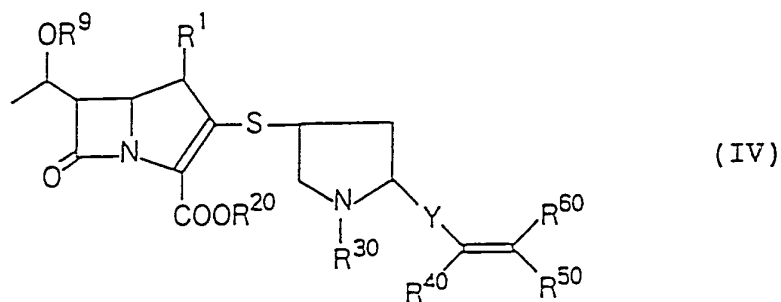
The reaction of the reactive derivative of the formula (II') with a compound of the formula:



wherein R^{30} is a hydrogen atom, a lower alkyl group or an imino-protecting group, each of R^{40} , R^{50} and R^{60} is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula $-X^1-N(R^{71})R^{81}$ {wherein each of R^{71} and R^{81} which may be the same or different, is a hydrogen atom, a

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lower alkyl group which may have substituents or an amino-protecting group, or R^{71} and R^{81} form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8- membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X^1 or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X^1 is a lower alkylene group which may have substituents}, provided that at least one of R^{40} , R^{50} and R^{60} is the group of the formula $-X^1-N(R^{71})R^{81}$ wherein R^{71} , R^{81} and X^1 are as defined above, and Y is a lower alkylene group or a single bond (provided that the substituents of the lower alkyl group, the heterocyclic group and the lower alkylene group, as well as the carbamoyl group and the imino group on the heterocyclic ring, may be protected, as the case requires), is conducted using the above mentioned inert organic solvent and base to form a compound of the formula:



wherein R^1 , R^9 , R^{20} , R^{30} , R^{40} , R^{50} , R^{60} and Y are as

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defined above.

The reaction is conducted using from 1 to 2 mols, preferably from 1 to 1.5 mols, of the base and from 1 to 1.2 mols of the compound of the formula (III), per mol of
5 the reactive derivative of the formula (II'). The reaction is conducted usually within a temperature range of from -40 to 50°C, preferably from -20 to 20°C, and the reaction is completed usually in from 0.5 to 3 hours.

Further, the compound of the formula (IV) can be
10 prepared in one step from the compound of the formula (II). Namely, without isolating the reactive derivative of the formula (II') prepared from the compound of the formula (II), the compound of the formula (III) is reacted thereto in the same reaction system to prepare
15 the compound of the formula (IV) efficiently. To conduct the production in one step, from 2 to 4 mols, preferably from 2.5 to 3.5 mols, of the base is employed per mol of the compound of the formula (II).

After completion of the reaction, usual treatment is
20 conducted to obtain a crude product of the formula (IV), which may be subjected to a reaction for removing a protecting group without purification. However, it is preferred to purify the crude product (IV) by crystallization or by column chromatography by means of
25 e.g. silica gel.

From the compound of the formula (IV) thus obtained, a compound of the formula (I) can be obtained, if

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necessary, by conducting a reaction for removing a protecting group for a hydroxyl group, an amino or imino group and a carboxyl group.

For the removal of the protecting groups, the method
5 varies depending upon the type of the protecting groups. However, the removal can be conducted in accordance with conventional methods, for example, by solvolysis, by chemical reduction or by hydrogenation.

For example, when in the above formula (IV), the
10 protecting group for the hydroxyl group and/or for the amino or imino group is an aralkyloxycarbonyl group such as a benzyloxycarbonyl group or a p-nitrobenzyloxycarbonyl group, and the protecting group for the carboxyl group is an aralkyl group such as a
15 benzyl group, a p-nitrobenzyl group or a benzhydryl group, such protecting groups can be removed by catalytic hydrogenation by means of a platinum catalyst such as platinum oxide, platinum wire or platinum black, or a palladium catalyst such as palladium black, palladium
20 oxide, palladium-carbon or palladium hydroxide-carbon.

As a solvent to be used for such a catalytic hydrogenation reaction, methanol, ethanol, tetrahydrofuran, dioxane, acetic acid or a solvent mixture of such an organic solvent with water or with a
25 buffer solution of e.g. a phosphate, may be used.

The reaction can be completed in from 0.5 to 4 hours at a temperature within a range of from 0 to 50°C under

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hydrogen gas stream of from 1 to 4 atm.

When in the above formula (IV), the protecting group for the hydroxyl group and/or the amino or imino group is an allyloxycarbonyl group, and the protecting group for
5 the carboxyl group is an allyl group, such protecting groups can be removed by reacting an organo-soluble palladium complex catalyst in an inert organic solvent containing an allyl group-capturing agent (method by W. McCombie et al., J. Org. Chem., vol. 47, p. 587-590
10 (1982) and method by F. Guibé, the same literature, vol. 52, p. 4,984-4,993 (1987)).

The solvent useful for the reaction includes, for example, water, acetone, diethyl ether, tetrahydrofuran, dioxane, ethyl acetate, acetonitrile, methylene chloride,
15 chloroform and a solvent mixture thereof.

The palladium compound complex useful for this reaction includes, for example, palladium-carbon, palladium hydroxide-carbon, palladium(II) chloride, palladium(II) acetate,
20 tetrakis(triphenylphosphine)palladium (0),
tetrakis(triphenoxyphosphine)palladium (0),
tetrakis(triethoxyphosphine)palladium (0),
bis[ethylenebis(diphenylphosphine)]palladium (0),
tetrakis[tri(2-furyl)phosphine]palladium (0),
25 bis(triphenylphosphine)palladium(II) chloride and
bis(triphenylphosphine)palladium(II) acetate.

The allyl group-capturing agent may, for example, be

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dimedone, formic acid, acetic acid, ammonium formate, sodium formate, sodium 2-ethylhexanoate, potassium 2-ethylhexanoate, pyrrolidine, piperidine and tributyltin hydride.

5 The reaction is conducted usually within a temperature range of from -10 to 50°C, preferably from 0 to 30°C using from 0.01 to 0.5 mol of the catalyst and from 1 to 6 mols of the nucleophilic agent relative to 1 mol of the compound of the formula (IV), and the reaction
10 is completed usually in from 0.5 to 3 hours.

Further, when in the above formula (IV), the protecting group for the hydroxyl group and/or the amino or imino group is an o-nitrobenzyloxycarbonyl group, and the protecting group for the carboxyl group is an o-
15 nitrobenzyl group, such protecting groups can be removed by a photo reaction (method by Amit et al., J. Org. Chem., vol. 39, p. 192-196 (1974)).

After completion of the reactions for removing the protecting groups, the compound of the formula (I) can be
20 isolated by usual treatment such as column chromatography using silica gel or adsorptive resin, freeze-drying or crystallization.

Further, when the protecting group for the carboxyl group at the 3-position of the compound of the formula
25 (IV) is a lower alkanoyloxyalkyl group such as an acetoxymethyl group or a pivaloyloxymethyl group, a methoxymethyl group, an indanyl group or a phthalidyl

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group, such an ester will be physiologically hydrolyzed in vivo. Therefore, such a compound can directly be administered to a human being or to an animal without preliminarily removing the protecting group.

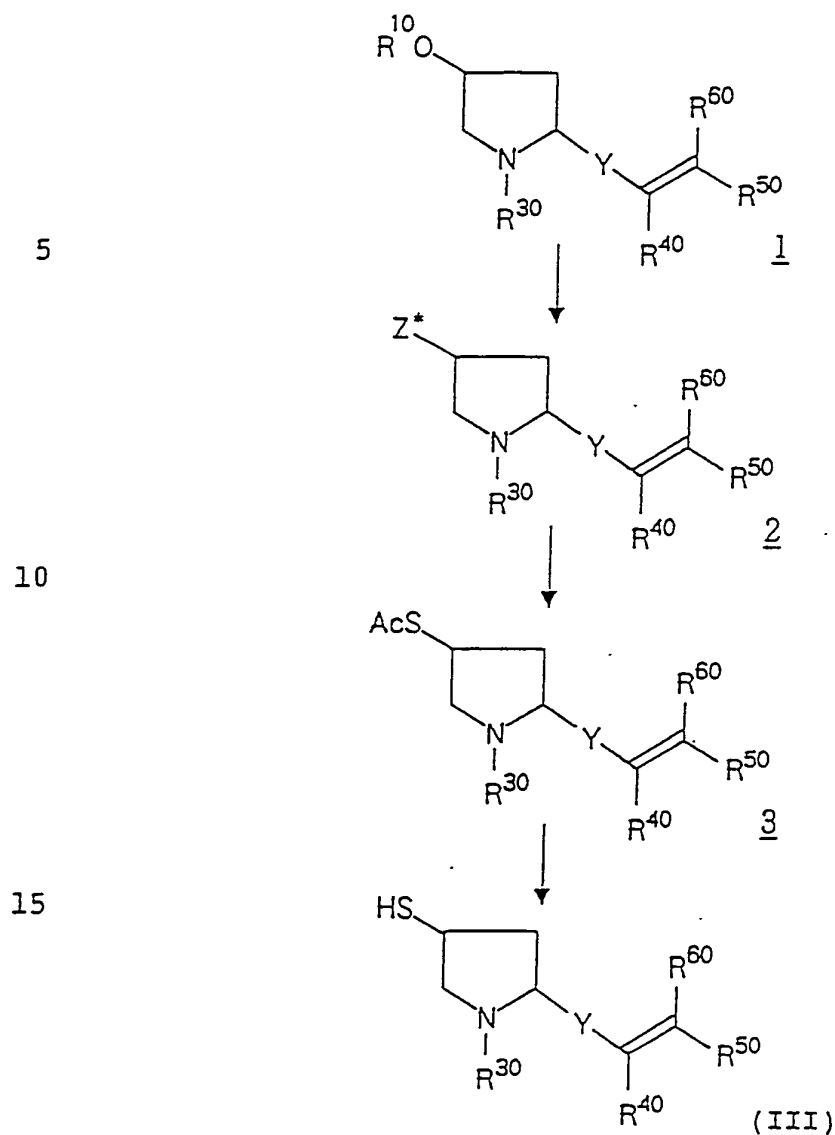
- 5 The compound of the formula (I) can be converted to a pharmaceutically acceptable salt or ester by a conventional method.

 The starting material of the formula (II) can be prepared, for example, by a method by Salzmann et al.
10 when R¹ is a hydrogen atom (J. Am. Chem. Soc., vol. 102, p.6161-6163 (1981)) or by a method by Shih et al. when R¹ is a methyl group (Heterocycles, vol. 21, p.29-40 (1984)).

 The starting material of the formula (III) can be
15 synthesized by the following method.

 The hydroxyl group of the compound 1 is activated by a usual method, and a thioacetate such as potassium thioacetate is reacted thereto to convert it to an acetylthio derivative 3, followed by alkali or acid
20 hydrolysis to obtain a thiol derivative of the formula (III).

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In the above formulas, R^{10} is a hydrogen atom or a hydroxyl-protecting group, Z^* is a leaving group selected from the group consisting of a chlorine atom, a bromine atom, an iodine atom, a trifluoroacetoxy group, a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group and a p-toluenesulfonyloxy group, Ac is an acetyl group, and R^{30} , R^{40} , R^{50} , R^{60} and Y are as defined above.

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A group of compounds having the formula 1 can be prepared in accordance with the methods described in the Reference Examples.

The compounds of the present invention exhibit strong
5 antibacterial activities against various gram positive bacteria and gram negative bacteria.

To demonstrate the usefulness of the compounds of the present invention, the in vitro antibacterial activities against bacteria were measured by the following agar
10 plate dilution method (standard method by Japan Chemotherapy Society, Chemotherapy, vol. 29, p. 76-79 (1981)). One platinum loopful of each test microorganism incubated overnight in Mueller Hinton broth, was inoculated to Mueller Hinton agar (inoculum size: 10^6
15 CFU/ml). Such culture media contained antibacterial agents in various concentrations. After incubation at 37°C for 16 hours, the minimum inhibitory concentrations (MIC: $\mu\text{g/ml}$) were measured.

The results of the antibacterial activities of the
20 compounds of the present invention are shown in Table 1.

Table 1
Minimum Inhibitory Concentration(MIC: $\mu\text{g}/\text{ml}$)

Test microorganism	Example 2	Example 7	Example 9	BO-2171	Imipenem
<u>S. aureus</u> 209P NIHJ JCl	<0.006	<0.006	<0.006	0.025	<0.006
<u>S. aureus</u> MB 4970	0.012	<0.006	<0.006	0.025	0.012
<u>S. aureus</u> BB 5939*	1.56	1.56	1.56	6.25	6.25
<u>P. aeruginosa</u> MB 5002	0.78	0.78	0.78	6.25	1.56
<u>P. aeruginosa</u> MB 5178	1.56	1.56	3.13	12.5	25

* β -lactamase producing microorganism

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The antibacterial activities of the compounds of the present invention described in the Examples, as representative examples of the compound of the present invention, were measured by a disc diffusion test by the method of Bauer et al. (Amer. J. Clin. Pathol., vol. 45, p. 493 (1966)). Thienamycin or imipenem was used as the internal standard.

MIC of each test compound was calculated from the diameter of the inhibition ring formed by the disc containing the test compound by using the calculation formula reported by Humphrey and Lightbown (J. Gen. Microbiol., vol. 7, p. 129 (1952)). For each microorganism, a geometrical average of MIC was obtained, and the activity ratio to thienamycin was calculated.

The antibacterial activities are represented by the ratio to thienamycin (= 1.0), whereby the larger the numerical value, the higher the activities.

The DHP-I susceptibility was quantitatively analyzed by the method by Kropp et al., Antimicrob. Agents Chemother., vol. 22, p. 62-70 (1982), whereby the smaller the numerical value representing the ratio to imipenem (=1.0), the higher the stability. The antibacterial potency and the DHP-I susceptibility of the compounds of the present invention were compared with imipenem and BO-2171. The results are shown in Table 2.

Table 2
Relative antibacterial potency to thienamycin and DHP-I susceptibility

Test microorganism	Example 2	Example 7	Example 9	BO-2171	Imipenem
Meth-R <u>S. aureus</u>	12.9	13.5	19.7	7.68	2.57
THM-R <u>P.aeruginosa</u>	15.2	31.3	13.4	3.28	2.0
DHP-I susceptibility	<0.05	<0.05	0.10	0.3	1.0

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The compounds of the present invention are characterized in that at least one of R⁴, R⁵ and R⁶ has a primary, secondary or tertiary amino group or an ammonio group, and they have excellent antibacterial activities
5 against various gram positive bacteria and gram negative bacteria and are useful as antibacterial agents for the treatment and prevention of the human infectious diseases caused by such bacteria. Typical pathogens sensitive to the antibacterial agents of the present invention
10 include, for example, species of genus Staphylococcus, genus Enterococcus, genus Escherichia, genus Enterobacter, genus Klebsiella, genus Serratia, genus Proteus and genus Pseudomonas. The compounds of the present invention exhibit excellent antibacterial
15 activities particularly against Methicillin resistant Staphylococcus aureus and against thienamycin resistant Pseudomonas aeruginosa.

The compounds of the present invention are very stable against DHP-I although the stability varies
20 depending upon the individual compounds, and they are excellent also in the physicochemical stability and in the solubility in water.

The compounds of the present invention may be used in the form of drug formulations suitable for non-oral
25 administration, oral administration or external administration, by mixing them with carriers of solid or liquid excipients known in this field. The main

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administration route is non-oral (intravenous or intramuscular injection) administration by injection or local administration. Drug formulations include liquid formulations such as injection solutions, syrups or
5 emulsions, solid formulations such as tablets, capsules or granules, and external application formulations such as ointments or suppositories. These formulations may contain additives such as a base, an assisting agent, a stabilizer, a wetting agent, an emulsifier, an
10 absorption-promoting agent, a surfactant, etc. which are commonly employed, as the case requires.

The additives include, for example, distilled water for injection, Ringer's solution, glucose, sucrose syrup, gelatin, edible oil, cacao butter, ethylene glycol,
15 sucrose, corn starch, magnesium stearate and talc.

The dose varies depending upon the condition of the patient, the weight, the age, the sex, the type of formulation, the number of administration times, etc. Usually, however, a preferred daily dose of the active
20 ingredient to an adult is from about 5 to 50 mg/kg, and a preferred daily dose to a child is within a range of from about 5 to 25 mg/kg, which is preferably administered once a day or in a few times a day.

The compound of the present invention may be
25 administered in combination with a DHP-I inhibiting agent such as cilastatin [sodium (Z)-7-(L-amino-2-carboxyethylthio)-2-(2,2-

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dimethylcyclopropanecarboxamide)-2-heptenoate] (Japanese Unexamined Patent Publication No. 81518/1981; European Patent No. 28,778; J. Med. Chem., vol. 30, p. 1074 (1987)).

5 Now, the present invention will be described in further detail with reference to Examples and Reference Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

10 In the thin layer chromatography in the Examples and Reference Examples, silica gel 60F₂₄₅ (Merck) was used as the plate, and an ultraviolet detector was used as a detecting device. As the silica gel for the column, WakogelTM C-300 (Wako Junyaku) was used, and as the
15 silica gel for reversed phase column, LC-SORBTM SP-B-ODS (Chemco) or YMC-GELTM ODS-AQ 120-S50 (Yamamura Chemical Laboratories) was used. As the high pressure liquid chromatograph, JASCO 800 series (Nippon Bunko) was used. When the NMR spectrum was measured using a dimethyl
20 sulfoxide-d₆ or chloroform-d solution, tetramethylsilane (TMS) was used as the internal standard, and when measured using a deuterium oxide solution, 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as the internal
standard, and the measurement was conducted by means of
25 XL-200 (200 MHz; Varian) model spectrometer. All δ values are shown by ppm.

The meanings of the abbreviations used for the NMR

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measurement are as follows:

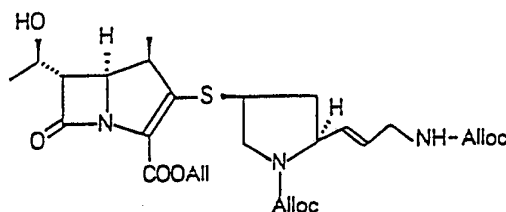
- s: singlet
- d: doublet
- t: triplet
- 5 q: quartet
- ABq: AB-type quartet
- dd: double doublet
- m: multiplet
- br: broad
- 10 J: coupling constant
- Hz: hertz
- CDCl₃: chloroform-d
- D₂O: deuterium oxide
- The meanings of the abbreviations used in the
- 15 reaction formulas are as follows:
- Ac: acetyl group
- All: allyl group
- Alloc: allyloxycarbonyl group
- Boc: tert-butoxycarbonyl group
- 20 Ms: methanesulfonyl group
- TBS: tert-butyldimethylsilyl group
- Tr: trityl group

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EXAMPLE 1

(1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5 1)



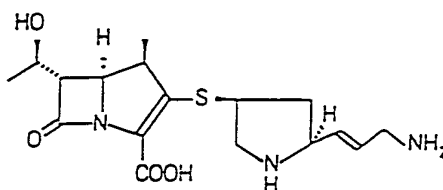
10 Allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (516 mg, 1.03 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-1-propenyl]-4-mercaptopyrrolidine (360 mg, 1.05 mmol, compound of Reference Example 1) were
 15 dissolved in acetonitrile (20 ml). Under a nitrogen stream, N,N-diisopropylethylamine (0.19 ml, 1.09 mmol) was dropwise added thereto at -10°C, and then the mixture was stirred overnight at 5°C. The reaction solution was concentrated under reduced pressure, and the residue was
 20 subjected to silica gel column chromatography (Wakogel™ C-300, ethyl acetate) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-
 25 carboxylate (296 mg, yield: 49.8%).
 IR(KBr)cm⁻¹: 1770, 1700, 1540, 1400

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NMR(CDCl₃) δ :

1.25(3H,d,J=8Hz), 1.34(3H,d,J=7Hz), 1.80(1H,m),
2.35-2.68(3H,m), 3.13-3.45(4H,m), 5.15-5.55(6H,m),
5.64(2H,m), 5.80-6.10(3H,m)

5 2)



10 To a methylene chloride solution (11 ml) of the
compound (295 mg, 0.51 mmol) obtained by the above
reaction, water (46 μ l),
bis(triphenylphosphine)palladium(II) chloride (18 mg,
0.025 mmol) and tributyltin hydride (0.54 ml, 2.0 mmol)
15 were added in a nitrogen stream under cooling with ice.
This solution was stirred at the same temperature for 20
minutes and at room temperature for 20 minutes. The
reaction mixture was extracted with water (70 ml). The
aqueous layer was washed twice with chloroform, and then
20 insoluble matters were filtered off. The filtrate was
concentrated to a volume of about 15 ml under reduced
pressure and then subjected to reversed phase column
chromatography (YMC-GELTM ODS-AQ 120-S50, 50 ml, a 20%
methanol aqueous solution). The fraction containing the
25 desired product was concentrated and freeze-dried to
obtain the above-identified compound (58 mg, yield:
30.8%).

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IR(KBr)cm⁻¹: 1750, 1580, 1390NMR(D₂O) δ :

1.20(3H,d,J=7Hz), 1.29(3H,d,J=6Hz), 1.47(1H,m),
 2.54(1H,m), 3.02(1H,dd,J=12,3Hz), 3.20-3.47(3H,m),
 5 3.59(2H,d,J=6Hz), 3.78(2H,m), 4.22(2H,m),
 5.81(1H,dt,J=16,6Hz), 5.98(1H,dd,J=16,7Hz)

HPLC:

Column: YMCTM-Pack ODS-AQ, 5 μ , 4.6 ϕ x 150 mm

Eluent: 0.01 M Phosphate buffer (pH 6.5)-Methanol

10 (80:20)

Flow rate: 1.0 ml/min

Temperature: 40°C

Detector: 290 nm

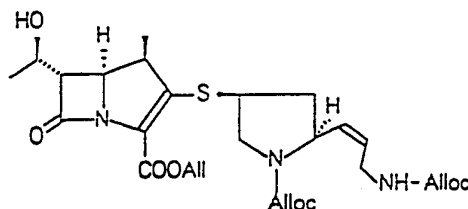
Retention time: 3.14 min

15 EXAMPLE 2

(1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-1-
propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-
methyl-1-carbapen-2-em-3-carboxylic acid

1)

20



The same procedure as in Example 1-1 was carried out
 25 by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-
 [(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-
 carboxylate (850 mg, 1.70 mmol) and (2S,4S)-N-

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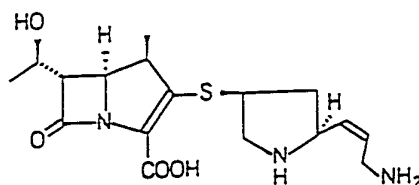
allyloxycarbonyl-2-[(Z)-3-allyloxycarbonylamino-1-propenyl]-4-mercaptopyrrolidine (460 mg, 1.42 mmol, compound of Reference Example 2) to obtain allyl
 (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-allyloxycarbonylamino-1-propenyl]pyrrolidin-4-ylthio]-6-
 5 [(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (399 mg, yield: 40.7%).

IR(KBr) cm^{-1} : 1780, 1700, 1410

NMR(CDCl_3) δ :

10 1.28(3H,d,J=8Hz), 1.38(3H,d,J=7Hz), 2.62(1H,m),
 3.22-3.45(3H,m), 4.26(2H,m), 5.82-6.10(3H,m)
 2)

15



20 (78 mg, yield: 32.0%).

IR(KBr) cm^{-1} : 1750, 1580, 1390

NMR(D_2O) δ :

1.21(3H,d,J=8Hz), 1.29(3H,d,J=7Hz), 1.44(1H,m),
 2.76(1H,m), 3.04(1H,dd,J=12,4Hz), 3.20-3.48(3H,m),
 25 3.70(2H,d,J=8Hz), 4.23(2H,m), 5.68(1H,dt,J=10,8Hz),
 5.87(1H,dd,J=10,9Hz)

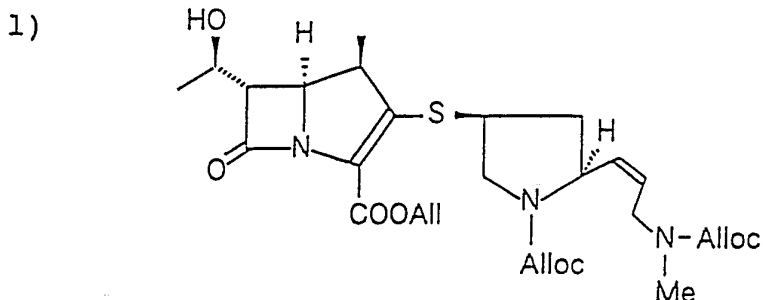
HPLC (the same condition as in Example 1)

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Retention time: 2.92 min

EXAMPLE 3

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-
 [(Z)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-
 5 carbapen-2-em-3-carboxylic acid



10

The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (760 mg, 1.52 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]-4-mercaptopyrrolidine (416 mg, 1.26 mmol, compound of Reference Example 3) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (502 mg, yield: 56.9%).

20

IR(KBr)cm⁻¹: 1780, 1700, 1400, 1210

NMR(CDCl₃) δ:

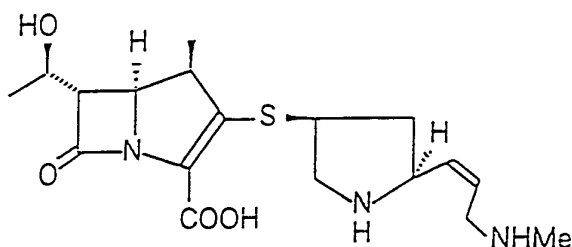
1.28(3H,d,J=8Hz), 1.37(3H,d,J=7Hz), 1.70(1H,m),

25

4.52-4.92(6H,m), 5.16-5.66(8H,m), 5.80-6.10(3H,m)

- 90 -

2)



5

The same procedure as in Example 1-2 was carried out by using the compound (500 mg, 0.85 mol) obtained by the above reaction, to obtain the above-identified compound (84 mg, yield: 30.0%).

10 IR(KBr)cm⁻¹: 1750, 1590, 1390

NMR(D₂O) δ:

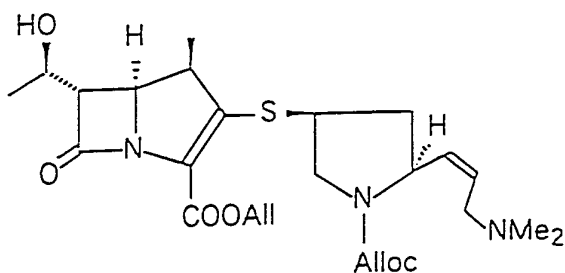
1.18(3H,d,J=8Hz), 1.26(3H,d,J=7Hz), 1.44(1H,m),
 2.55(1H,m), 2.67(3H,s), 3.04(1H,dd,J=12,4Hz),
 3.22-3.46(3H,m), 3.73(2H,d,J=8Hz), 3.82(1H,m),
 15 4.05(1H,q,J=8Hz), 4.20(2H,m), 5.67(1H,m),
 5.94(1H,t,J=10Hz)

EXAMPLE 4

(1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-(N,N-dimethylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

20

1)



25

The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-

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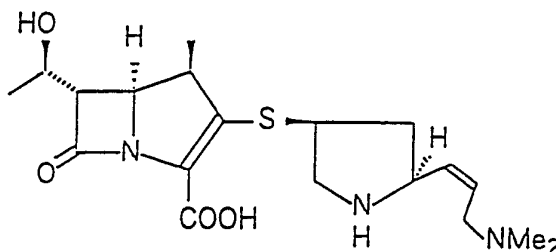
[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1.0 g, 20 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N,N-dimethylamino)-1-propenyl]-4-mercaptopyrrolidine trifluoroacetate (640 mg, 1.68 mmol, compound of Reference example 4) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N,N-dimethylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (150 mg, yield: 14.5 %).

IR(KBr) cm^{-1} : 1770, 1700, 1400, 1200

NMR(CDCl_3) δ :

1.24 (3H,d,J=8Hz), 1.33 (3H,d,J=7Hz), 1.68 (1H,m),
2.07-2.66 (7H,m), 4.46-4.90 (5H,m), 5.12-5.52 (4H,m),
5.62 (2H,m), 5.94 (2H,m)

2)



The same procedure as in Example 1-2 was carried out by using the compound (150 mg, 0.29 mmol) obtained by the above reaction, to obtain the above-identified compound (38 mg, yield: 33.1%).

IR(KBr) cm^{-1} : 1760, 1600, 1390

NMR(D_2O) δ :

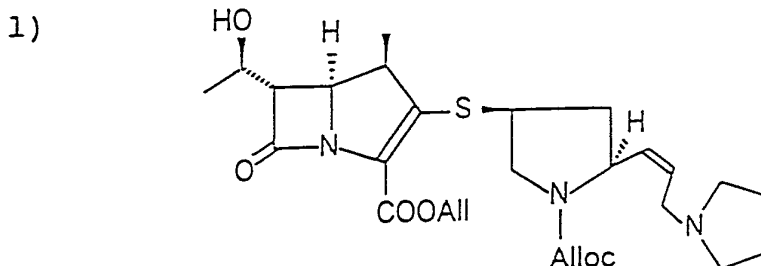
1.20 (3H,d,J=8Hz), 1.28 (3H,d,J=7Hz), 1.53 (1H,m),
2.60 (1H,m), 2.79 (6H,s), 3.10 (1H,dd,J=12,4Hz),

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3.28-3.48(3H,m), 3.75(2H,d,J=8Hz), 3.87(1H,m),
4.21(3H,m)

EXAMPLE 5

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-
5 [(Z)-3-(1-pyrrolidinyl)-1-propenyl]pyrrolidin-4-ylthio]-
1-carbapen-2-em-3-carboxylic acid



The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (900 mg, 1.8 mmol) and (2S,4S)-N-allyloxycarbonyl-4-mercapto-2-[(Z)-3-(1-pyrrolidinyl)-1-propenyl]pyrrolidine trifluoroacetate (513 mg, 1.26 mmol, compound of Reference Example 5) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[3-(1-pyrrolidinyl)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (253 mg, yield: 25.8%).

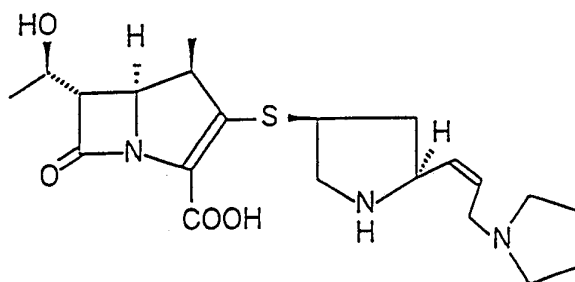
IR(KBr)cm⁻¹: 1770, 1700, 1400, 1200

NMR(CDCl₃) δ:

1.24(3H,d,J=8Hz), 1.32(3H,d,J=7Hz), 1.66-2.00(5H,m),
25 4.44-4.90(5H,m), 5.10-5.55(4H,m), 5.65(2H,m), 5.94(2H,m)

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2)



5

The same procedure as in Example 1-2 was carried out by using the compound (253 mg, 0.466 mmol) obtained by the above reaction, to obtain the above-identified compound (50 mg, yield: 25.5%).

10 IR(KBr)cm⁻¹: 1760, 1600, 1390

NMR(D₂O) δ:

1.18(3H,d,J=8Hz), 1.26(3H,d,J=7Hz), 1.42(1H,m),

2.02(4H,m), 2.54(1H,m), 3.00(1H,dd,J=12,4Hz),

3.14-3.48(7H,m), 3.82(3H,m), 4.00(1H,q,J=8Hz),

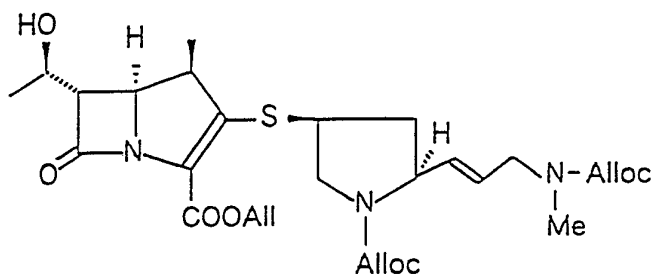
15 4.18(2H,m), 5.68(1H,m), 5.94(1H,t,J=10Hz)

EXAMPLE 6

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid hydrochloride

20

1)



25

The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-

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carboxylate (1.5 g, 3.0 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]-4-mercaptopyrrolidine (850 mg, 2.51 mmol), compound of Reference Example 6) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (627 mg, yield: 35.4%).

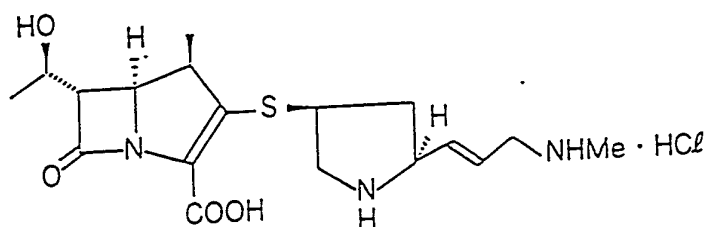
IR(KBr)cm⁻¹: 1770, 1700, 1400, 1200

10 NMR(CDCl₃) δ:

1.26(3H,d,J=8Hz), 1.36(3H,d,J=7Hz), 1.76(1H,m),
2.60(1H,m), 2.86(3H,s), 4.50-4.95(6H,m),
5.15-5.55(6H,m), 5.60(2H,m), 5.95(2H,m)

2)

15



To a methylene chloride solution (22.5 ml) of the compound (592 mg, 1.0 mmol) obtained by the above reaction, water (91 μl), bis(triphenylphosphine) palladium(II) chloride (35.2 mg, 0.05 mmol) and tributyltin hydride (1.03 ml, 3.83 mmol) were added in a nitrogen stream under cooling with ice. This solution was stirred at the same temperature for 20 minutes and at room temperature for 20 minutes. The reaction mixture was extracted with water (150 ml). The aqueous layer was

- 95 -

washed twice with chloroform, and insoluble matters were filtered off. The filtrate was concentrated under reduced pressure to a volume of 30 ml and then subjected to reversed phase column chromatography (YMC-GEL™ ODS-AQ 120-S50, 50 ml, a 20% methanol aqueous solution). The fraction containing the desired product was collected and adjusted to pH 6.5 with 1N hydrochloric acid, and then it was concentrated and freeze-dried to obtain the above-

IR(KBr)cm⁻¹: 1750, 1700, 1390

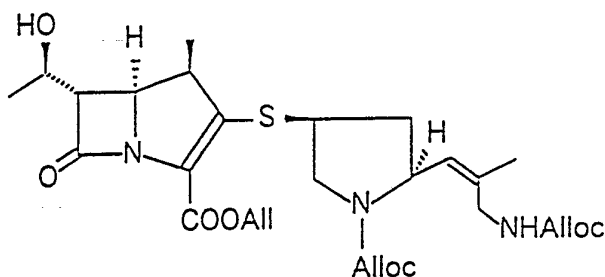
NMR(D₂O) δ:

1.22(3H,d,J=8Hz), 1.30(3H,d,J=7Hz), 1.89(1H,m),
2.74(3H,s), 2.82(1H,m), 3.28-3.52(3H,m),
3.64-3.80(3H,m), 4.08(1H,m), 4.18-4.44(3H,m),
6.04(1H,dt,J=15,6Hz), 6.19(1H,dd,J=15,8Hz)

EXAMPLE 7

(1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride

20 1)



25 The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-

- 96 -

carboxylate (600 mg, 1.20 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-allyloxycarbonylamino-2-methyl-1-propenyl]-4-mercaptopyrrolidine (326 mg, 0.96 mmol, compound of Reference Example 7) to obtain allyl

5 (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-allyloxycarbonylamino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (260 mg, yield: 36%).

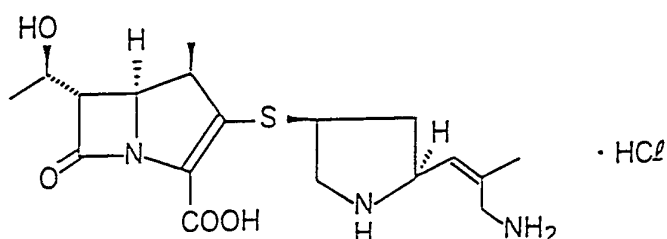
IR(KBr)cm⁻¹: 1770, 1700, 1410

10 NMR(CDCl₃) δ:

1.27(3H,d,J=8Hz), 1.35(3H,d,J=7Hz), 1.56-1.82(4H,m),
2.60(1H,m), 3.16-3.47(3H,m), 3.60(1H,m),
4.44-4.90(7H,m), 5.10-5.54(7H,m), 5.88-6.10(3H,m)

2)

15



The same procedure as in Example 6-2 was carried out

20 by using the compound (255 mg, 0.42 mmol) obtained by the above reaction, to obtain the above-identified compound (60 mg, yield: 33.8%).

IR(KBr)cm⁻¹: 1760, 1700, 1390

NMR(D₂O) δ:

25 1.22(3H,d,J=8Hz), 1.29(3H,d,J=7Hz), 1.80(1H,m),
1.92(3H,s), 2.78(1H,m), 3.27-3.52(3H,m),
3.58-3.86(3H,m), 4.05(1H,m), 4.25(2H,m), 4.56(1H,m),

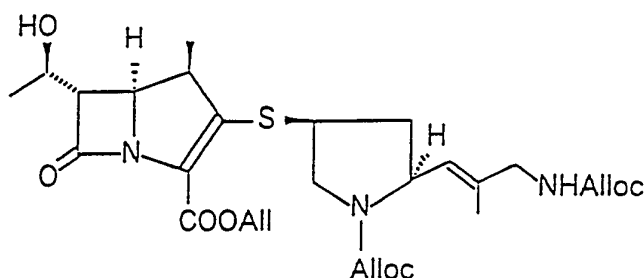
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5.76(1H,d,J=8Hz)

EXAMPLE 8

(1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride

1)



10

The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (890 mg, 1.78 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-2-methyl-1-propenyl]-4-mercaptopyrrolidine (463 mg, 1.32 mmol, compound of Reference Example 8) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (366 mg, yield: 34.1%).

20

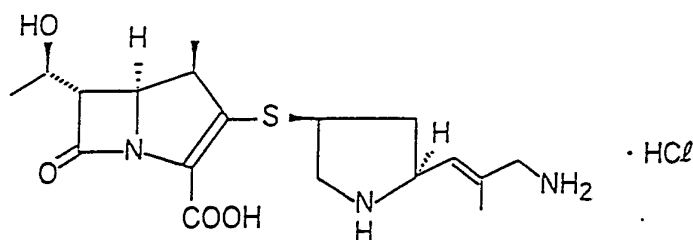
IR(KBr)cm⁻¹: 1770, 1710, 1540, 1410NMR(CDCl₃) δ:

1.27(3H,d,J=8Hz), 1.35(3H,d,J=7Hz), 1.52-1.82(4H,m),
2.58(1H,m), 3.20-3.45(3H,m), 3.62(1H,m), 3.74(2H,m),
4.45-4.98(7H,m), 5.12-5.55(7H,m), 5.78-6.10(3H,m)

25

- 98 -

2)



5

The same procedure as in Example 6-2 was carried out by using the compound (360 mg, 0.60 mmol) obtained by the above reaction, to obtain the above-identified compound (73 mg, yield: 29.2%).

10 IR(KBr) cm^{-1} : 1750, 1600, 1390

NMR(D_2O) δ :

1.24(3H, d, $J=8\text{Hz}$), 1.30(3H, d, $J=7\text{Hz}$), 1.70-1.93(4H, m),

2.82(1H, m), 3.30-3.54(3H, m), 3.58-3.80(3H, m),

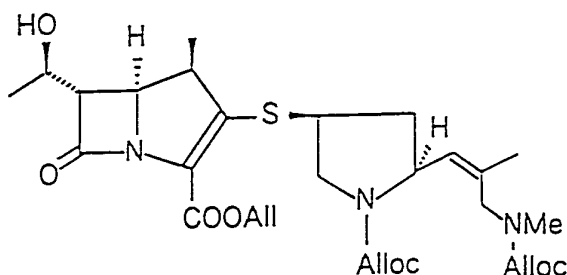
4.06(1H, m), 4.27(2H, m), 5.70(1H, d, $J=8\text{Hz}$)

15 EXMAPLE 9

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride

1)

20



The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (550 mg, 1.10 mmol) and (2S,4S)-N-

- 99 -

allyloxycarbonyl-2-[(Z)-3-(N-allyloxycarbonyl-N-methylamino)-2-methyl-1-propenyl]-4-mercaptopyrrolidine (308 mg, 0.87 mmol, compound of Reference Example 9) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-
 5 [(Z)-3-(N-allyloxycarbonyl-N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (194 mg, yield: 29.3%).

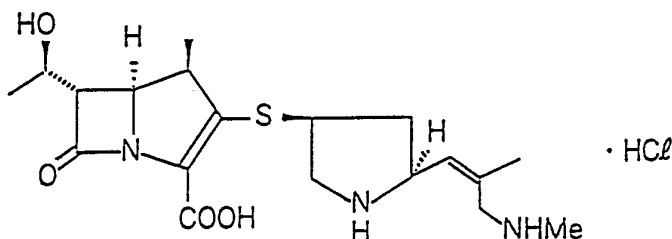
IR(KBr)cm⁻¹: 1780, 1700, 1400, 1280, 1140

10 NMR(CDCl₃) δ:

1.25(3H,d,J=8Hz), 1.34(3H,d,J=7Hz), 1.52-1.80(4H,m),
 2.56(1H,m), 2.84(3H,s), 3.14-3.46(3H,m), 3.58(1H,m),
 4.40-4.90(7H,m), 5.10-5.53(7H,m), 5.72-6.12(3H,m)

2)

15



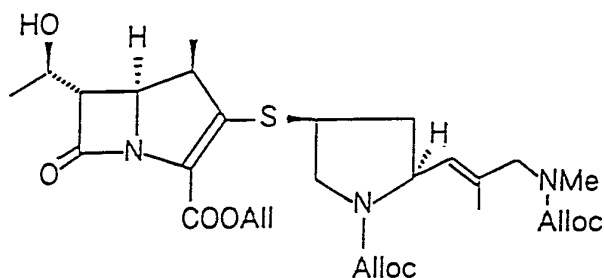
The same procedure as in Example 6-2 was carried out
 20 by using the compound (192 mg, 0.32 mmol) obtained by the above reaction, to obtain the above-identified compound (55 mg, yield: 39.9%).

EXMAPLE 10

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(E)-3-(N-
 25 methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-
methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride

- 100 -

1)



5

The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (500 mg, 1.0 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(N-allyloxycarbonyl-N-methylamino)-2-methyl-1-propenyl]-4-mercaptopyrrolidine (290 mg, 0.84 mmol, compound of Reference Example 10) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(N-allyloxycarbonyl-N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (304 mg, yield: 50.5%).

15

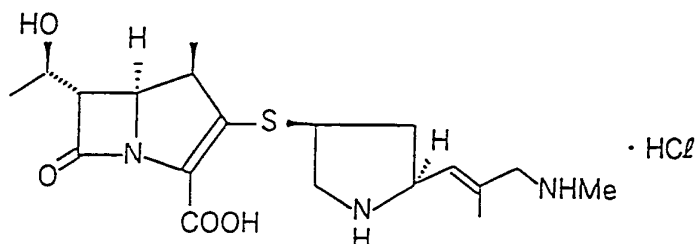
IR(KBr) cm^{-1} : 1780, 1700, 1400

NMR(CDCl_3) δ :

20

1.26 (3H, d, $J=8\text{Hz}$), 1.34 (3H, d, $J=7\text{Hz}$), 1.53-1.80 (4H, m),
2.60 (1H, m), 2.80 (3H, s), 3.18-3.46 (3H, m), 3.60 (1H, m),
3.85 (2H, m), 4.44-4.90 (7H, m), 5.08-5.53 (7H, m),
5.72-6.10 (3H, m)

2)



25

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The same procedure as in Example 6-2 was carried out by using the compound (302 mg, 0.50 mmol) obtained by the above reaction, to obtain the above-identified compound (78 mg, yield: 36.0%).

5 IR(KBr) cm^{-1} : 1750, 1690, 1390

NMR(CDCl_3) δ :

1.25(3H,d,J=8Hz), 1.32(3H,d,J=7Hz), 1.74-1.96(4H,m),

2.86(1H,m), 3.34-3.46(3H,m), 3.64-3.82(3H,m),

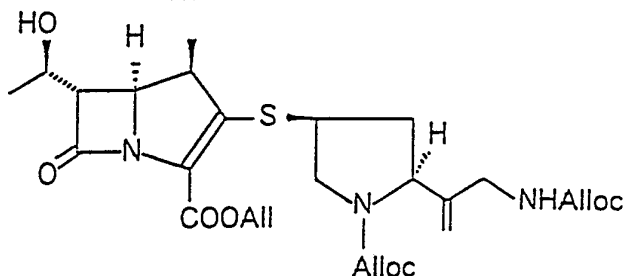
4.10(1H,m), 4.29(2H,m), 4.64(1H,m), 5.83(1H,d,J=8Hz)

10 EXAMPLE 11

(1R,5S,6S)-2-[(2S,4S)-2-[[1-(aminomethyl)vinyl]pyrrolidin-4-ylthio]]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

1)

15



The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1.10 g, 2.2 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-4-mercaptopyrrolidine (530 mg, 1.62 mmol, compound of Reference Example 11) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]pyrrolidin-4-

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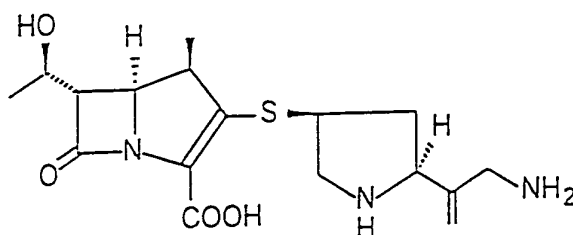
ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (643 mg, yield: 68%).

NMR(CDCl₃) δ :

1.26(3H,d,J=8Hz), 1.35(3H,d,J=7Hz), 4.49-4.93(6H,m),

5 4.97-5.53(8H,m), 5.75-6.11(3H,m)

2)



10

The same procedure as in Example 6-2 was carried out by using the compound (332 mg, 0.58 mmol) obtained by the above reaction, to obtain the above-identified compound (17 mg, yield: 8%).

15 IR(KBr)cm⁻¹: 1750

NMR(D₂O) δ :

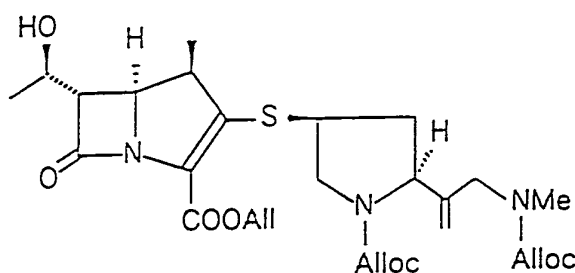
1.21(3H,d,J=8Hz), 1.26(3H,d,J=7Hz), 5.50(1H,br s),

5.63(1H,br s)

EXAMPLE 12

20 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[1-[(N-methylamino)methyl]vinyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid hydrochloride

1)



25

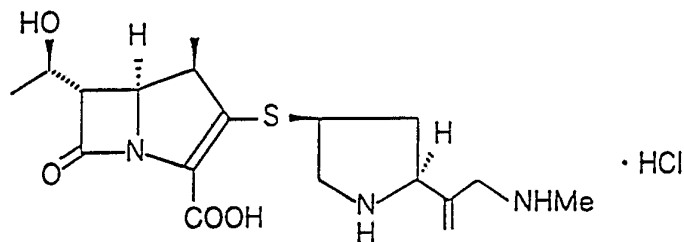
- 103 -

The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (4.3 g, 8.6 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonyl-N-methylamino)methyl]vinyl]-4-mercaptopyrrolidine (2.87 g, 8.4 mmol, compound of Reference Example 12) to obtain allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonyl-N-methylamino)methyl]vinyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (3.53 g, yield: 69%).

NMR(CDCl₃) δ :

1.24(3H,d,J=7.3Hz), 1.35(3H,d,J=6.3Hz), 1.73(3H,m),
2.12(1H,m), 2.47(1H,m), 2.86(3H,br s), 3.20-3.40(3H,m),
4.50-4.98(6H,m), 5.12-5.48(4H,m), 5.80-6.01(2H,m)

2)



20

The same procedure as in Example 6-2 was carried out by using the compound (1.39 g, 2.36 mmol) obtained by the above reaction, to obtain the above-identified compound (267 mg, yield: 27%).

IR(KBr)cm⁻¹: 1750

NMR(D₂O) δ :

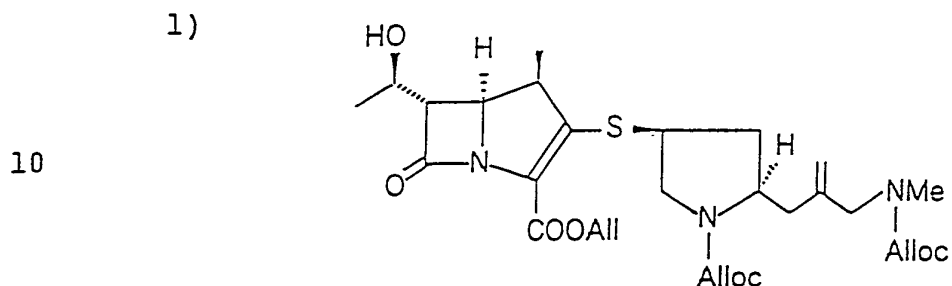
1.06(3H,d,J=7.3Hz), 1.13(3H,d,J=6.3Hz), 1.63(1H,m),

- 104 -

2.61(3H,s), 3.09-3.48(4H,m), 3.50-3.75(2H,m),
 3.82(1H,m), 3.94(1H,m), 4.09(2H,m), 5.32(1H,s),
 5.47(1H,s)

EXAMPLE 13

5 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-
[2-[(N-methylamino)methyl]allyl]pyrrolidin-4-ylthio]-1-
carbapen-2-em-3-carboxylic acid hydrochloride



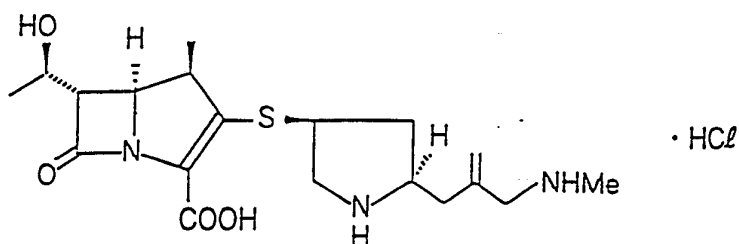
The same procedure as in Example 1-1 was carried out by using allyl (1R,5S,6S)-2-diphenoxyphosphoryloxy-6-
 15 [(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1.71 g, 3.43 mmol) and (2S,4S)-N-allyloxycarbonyl-2-[[2-(N-allyloxycarbonyl-N-methylamino)methyl]allyl]-4-mercaptopyrrolidine (1.22 g, 3.43 mmol, compound of Reference Example 13) to obtain
 20 allyl (1R,5S,6S)-2-[(2S,4S)-N-allyloxycarbonyl-2-[2-(N-allyloxycarbonyl-N-methylamino)methyl]allylpyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (1.36 g, yield: 65%).

NMR(CDCl₃) δ:

25 1.24(3H,d,J=7.3Hz), 1.35(3H,d,J=6.3Hz), 1.73(3H,m),
 2.86(3H,br s), 3.20-3.41(3H,m), 4.50-4.98(6H,m),
 5.12-5.50(4H,m), 5.80-6.01(2H,m)

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2)



5

The same procedure as in Example 6-2 was carried out by using the compound (1.36 g, 2.25 mmol) obtained by the above reaction, to obtain the above-identified compound (213 mg, yield: 21%).

10 IR(KBr)cm⁻¹: 1750

NMR(D₂O) δ:

1.17(3H,d,J=7.3Hz), 1.24(3H,d,J=8.4Hz), 1.70(1H,m),

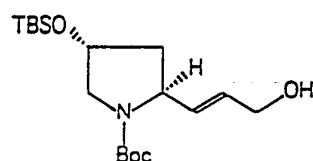
2.63(2H,m), 2.70(3H,s), 3.25-3.60(3H,m),

3.60-3.80(4H,m), 4.20(2H,m), 5.32(1H,s), 5.36(1H,s)

15 REFERENCE EXAMPLE 1

(2S,4S)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-1-propenyl]-4-mercaptopyrrolidine

1)



20

To a methylene chloride solution (70 ml) of ethyl 3-[(2S,4R)-N-tert-butoxycarbonyl-4-tert-butyltrimethylsilyloxypyrrolidin-2-yl]acrylate (3.55 g, 8.9 mmol, compound of Reference Example 1-4 of Japanese Patent Application No. 87628/1991), a toluene solution

25

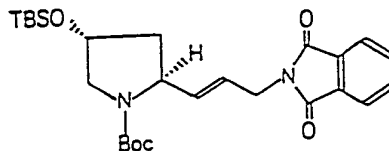
- 106 -

(19.2 ml) of 1.0 M diisobutylaluminum hydride was dropwise added in a nitrogen stream at -78°C , and the mixture was stirred at the same temperature for two hours. To the reaction solution, acetic acid (2.55 ml, 44.5 mmol) was added. Then, the mixture was extracted with methylene chloride (100 ml). The organic layer was washed sequentially with a 1N aqueous sodium hydroxide solution, water and a saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [WakogelTM C-300, hexane-ethyl acetate (3:1)] to obtain (2S,4R)-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[(E)-3-hydroxy-1-propenyl]pyrrolidine (918 mg, yield: 28.9%).

15 NMR(CDCl_3) δ :

0.04(6H,s), 0.86(9H,s), 1.42(9H,s), 1.78(1H,m),
2.01(1H,m), 3.40(2H,m), 4.12(2H,d, $J=5\text{Hz}$),
4.34(2H,m), 5.58(1H,dd, $J=16, 6\text{Hz}$), 5.74(1H,dt, $J=16, 5\text{Hz}$)
2)

20



To a tetrahydrofuran solution (40 ml) of the compound (918 mg, 2.57 mmol) obtained by the above reaction, triphenylphosphine (1.01 g, 3.85 mmol) and phthalimide (662 mg, 4.50 mmol) were added. Then, diethyl

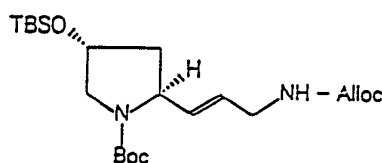
- 107 -

azodicarboxylate (0.607 ml, 3.85 mmol) was dropwise added thereto in a nitrogen stream under cooling with ice, and the mixture was stirred at the same temperature for 2.5 hours. The reaction solution was extracted with ethyl acetate (70 ml). The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, hexane-ethyl acetate (10:1)] to obtain (2S,4R)-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[(E)-3-phthalimido-1-propenyl]pyrrolidine (961 mg, yield: 76.9%).

NMR(CDCl₃) δ:

0.03(6H,s), 0.85(9H,s), 1.37(9H,br s), 1.78(1H,m),
1.98(1H,m), 3.42(2H,m), 4.29(4H,m), 5.64(2H,m),
7.74(2H,m), 7.88(2H,m)

3)



20

To an ethanol solution (15 ml) of the compound (960 mg, 1.98 mmol) obtained by the above reaction, hydrazine monohydrate (0.288 ml, 5.94 mmol) was added at room temperature, and the mixture was stirred overnight at the same temperature. Insoluble matters were filtered off from the reaction mixture. Then, the filtrate was

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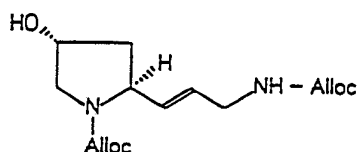
concentrated under reduced pressure, and the residue was extracted with ethyl acetate (70 ml). The organic layer was washed sequentially with 3N aqueous ammonia, water and a saturated sodium chloride aqueous solution, then
5 dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (15 ml), and triethylamine (0.35 ml, 2.52 mmol) and allyl chloroformate (0.24 ml, 2.26 mmol) were added thereto under cooling with ice, and the mixture was
10 stirred at the same temperature for one hour. The reaction mixture was extracted with ethyl acetate (50 ml). The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then concentrated under
15 reduced pressure. The residue was subjected to silica gel column chromatography [WakogelTM C-300, hexane-ethyl acetate (5:1)] to obtain (2S,4R)-2-[(E)-3-allyloxycarbonylamino-1-propenyl]-N-allyloxycarbonyl-4-tert-butyl dimethylsiloxypyrrolidine (680 mg, yield:
20 75.5%).

NMR(CDCl₃) δ :

0.06(6H,s), 0.87(9H,s), 1.44(9H,s), 1.77(1H,m),
2.02(1H,m), 3.42(2H,m), 3.82(2H,m), 4.33(2H,m),
4.58(2H,m), 5.17-5.39(2H,m), 5.57(2H,m), 5.95(1H,m)

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4)



5

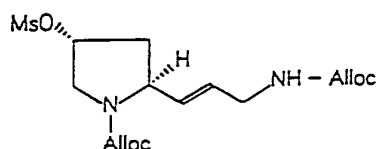
A methanol solution (10 ml) of 7.5N hydrogen chloride was added to the compound (680 mg, 1.49 mmol) obtained by the above reaction, and the mixture was stirred overnight at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was dissolved in a mixed solution of dioxane (10 ml) and water (5 ml). While adjusting the pH to 9 with a 1N sodium hydroxide aqueous solution under cooling with ice, allyl chloroformate (0.24 ml, 2.26 mmol) was dropwise added thereto. The reaction solution was stirred at the same temperature for further 30 minutes and then concentrated under reduced pressure. The residue was extracted with ethyl acetate (70 ml). The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (WakogelTM C-300, 1.5% methanol-chloroform) to obtain (2S,4R)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-1-propenyl]-4-hydroxypyrrolidine (440 mg, yield: 90.5%).

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NMR(CDCl₃) δ :

1.84(1H,m), 2.17(1H,m), 3.55(2H,m), 3.79(2H,m),
 4.32-4.64(6H,m), 5.12-5.38(4H,m), 5.57(2H,m),
 5.90-6.04(2H,m)

5 5)



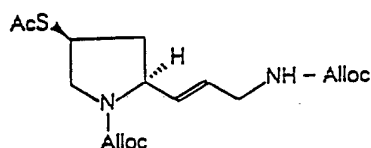
10 To a tetrahydrofuran solution (10 ml) of the compound
 (440 mg, 1.35 mmol) obtained by the above reaction,
 triethylamine (0.207 ml, 1.49 mmol) and methanesulfonyl
 chloride (0.112 ml, 1.45 mmol) were dropwise added in a
 nitrogen stream under cooling with ice. The reaction
 15 mixture was stirred at the same temperature for one hour
 and then extracted with ethyl acetate (70 ml). The
 organic layer was washed with water and a saturated
 sodium chloride aqueous solution, dried over anhydrous
 sodium sulfate and concentrated under reduced pressure to
 20 obtain (2S,4R)-N-allyloxycarbonyl-2-[(E)-3-
 allyloxycarbonylamino-1-propenyl]-4-
 methanesulfonyloxypyrrolidine (550 mg, yield: 100%).

NMR(CDCl₃) δ :

25 2.05(1H,m), 2.48(1H,m), 3.07(3H,s), 3.66(1H,dd,
 $J=12,4\text{Hz}$), 3.82(2H,m), 3.96(1H,br d, $J=12\text{Hz}$),
 4.44-4.72(5H,m), 4.98(1H,m), 5.16-5.42(4H,m),
 5.62(2H,m), 5.84-6.06(2H,m)

- 111 -

6)



5

To an N,N-dimethylformamide solution (20 ml) of the compound (550mg, 1.36 mmol) obtained by the above reaction, potassium thioacetate (315 mg, 2.76 mmol) and sodium iodide (228 mg, 1.52 mmol) were added. The mixture was stirred overnight in a nitrogen stream at a temperature of from 60 to 70°C. The reaction mixture was extracted with ethyl acetate (70 ml). The organic layer was washed three times with water and once with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, hexane-ethyl acetate (3:1)] to obtain (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-1-propenyl]-4-acetylthiopyrrolidine (397 mg, yield: 74.8%).

20 acetylthiopyrrolidine (397 mg, yield: 74.8%).

NMR(CDCl₃) δ:

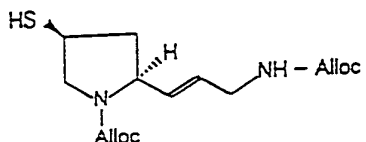
1.76(1H,m), 2.35(3H,s), 2.48(1H,m), 3.26(1H,m),

3.82(2H,m), 3.88-4.14(2H,m), 4.42(1H,m),

4.66(4H,m), 5.16-5.40(4H,m), 5.63(2H,m), 5.80-6.04(2H,m)

- 112 -

7)



5

To a methanol solution (12 ml) of the compound (397 mg, 1.03 mmol) obtained by the above reaction, a 1N sodium hydroxide aqueous solution (1.09 ml) was dropwise added in a nitrogen stream under cooling with ice, and the mixture was stirred at the same temperature for 15 minutes. To the reaction solution, 1N hydrochloric acid (1.1 ml) was added, and the mixture was concentrated under reduced pressure. The residue was extracted with ethyl acetate (70 ml). The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain the above-identified compound (360 mg, yield: 100%).

NMR(CDCl₃) δ :

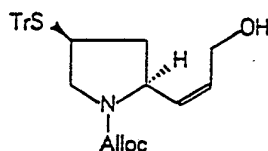
1.56-1.78(2H,m), 2.58(1H,m), 3.23(2H,m), 3.82(2H,m),
4.06(1H,m), 4.35(1H,m), 4.60(4H,m), 5.17-5.42(4H,m),
5.66(2H,m), 5.82-6.06(2H,m)

REFERENCE EXAMPLE 2

(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(allyloxycarbonylamino)-1-propenyl]-4-mercaptopyrrolidine

- 113 -

1)



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To a toluene solution (80 ml) of methyl (Z)-3-[(2S,4S)-N-allyloxycarbonyl-4-tritylthiopyrrolidin-2-yl]acrylate (4.0 g, 7.83 mmol, compound of Reference Example 3-2 of Japanese Patent Application No. 205984/1990), a toluene solution (19.6 ml) of diisobutylaluminum hydride was dropwise added in a nitrogen stream at -78°C , and the mixture was stirred at the same temperature for one hour. Then, temperature was raised to -10°C over a period of 1.5 hours. To the reaction solution, acetic acid (3.5 ml, 61.1 mmol) was dropwise added. Then, the mixture was extracted with ethyl acetate (150 ml). The organic layer was washed sequentially with a 1N sodium hydroxide aqueous solution, water and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [WakogelTM C-300, hexane-ethyl acetate (3:1)] to obtain (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-hydroxy-1-propenyl]-4-tritylthiopyrrolidine (1.90 g, yield: 50.1%).

25

NMR(CDCl_3) δ :

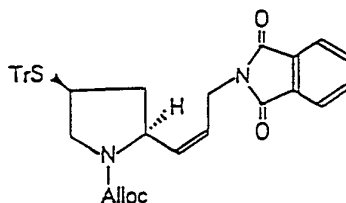
1.53(1H,m), 2.17(1H,m), 2.64-3.00(3H,m),

- 114 -

3.68-3.98(2H,m), 4.24-4.67(4H,m), 5.11-5.40(3H,m),
5.73-5.97(2H,m), 7.16-7.54(15H,m)

2)

5



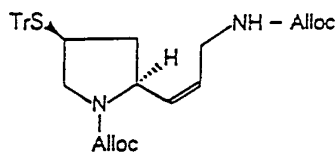
The same procedure as in Reference Example 1-2 was
carried out by using the compound (1.90 g, 3.93 mmol)
10 obtained by the above reaction, to obtain (2S,4S)-N-
allyloxycarbonyl-2-[(Z)-3-phthalimido-1-propenyl]-4-
tritylthiopyrrolidine (2.39 g, yield: 99.4%).

NMR(CDCl₃) δ:

1.53(1H,m), 2.26(1H,m), 2.87(2H,m), 5.00-5.66(4H,m),
15 5.84(1H,m), 7.16-7.56(15H,m), 7.75(2H,m), 7.87(2H,m)

3)

20



The same procedure as in Reference Example 1-3 was
carried out by using the compound (2.39 g, 3.90 mmol)
obtained by the above reaction, to obtain (2S,4S)-N-
allyloxycarbonyl-2-[(Z)-3-(allyloxycarbonylamino)-1-
25 propenyl]-4-tritylthiopyrrolidine (1.93 g, yield: 87.3%).

NMR(CDCl₃) δ:

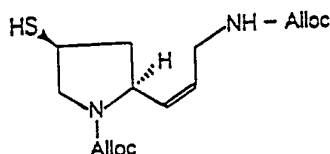
1.54(1H,m), 2.14(1H,m), 2.64-3.02(3H,m),

- 115 -

3.64-4.02(3H,m), 4.22-4.63(5H,m), 5.10-6.02(8H,m),
7.16-7.56(15H,m)

4)

5



To a methylene chloride solution (2.5 ml) of the compound (902 mg, 1.59 mmol) obtained by the above
10 reaction, trifluoroacetic acid (2.5 ml) and triethylsilane (0.268 ml, 1.68 mmol) were added in a nitrogen stream under cooling with ice, and the mixture was stirred at the same temperature for one hour. The reaction solution was concentrated under reduced
15 pressure, and the residue was extracted with ethyl acetate (70 ml). The organic layer was washed twice with 1M phosphate buffer (pH 5.5) and once with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then concentrated under reduced
20 pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, hexane-ethyl acetate (4:1)] to obtain the above-identified compound (460 mg, yield: 89%).

NMR(CDCl₃) δ :

25 1.50-1.78(2H,m), 2.62(1H,m), 3.10-3.42(2H,m),
3.74-4.20(4H,m), 4.58(4H,m), 5.16-6.08(8H,m)

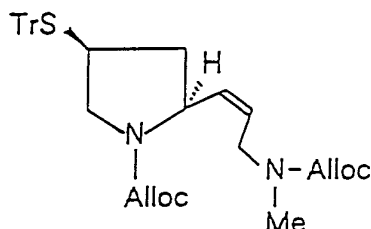
- 116 -

REFERENCE EXAMPLE 3

(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]-4-mercaptopyrrolidine

1)

5



To an N,N-dimethylformamide solution (15 ml) of
 10 (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(allyloxycarbonylamino)-1-propenyl]-4-tritylthiopyrrolidine (1.02 g, 1.8 mmol), 60% sodium hydride (110 mg, 2.75 mmol) was added in a nitrogen stream under cooling with ice, and the mixture was
 15 stirred at the same temperature for 40 minutes. Then, methyl iodide (0.45 ml, 7.2 mmol) was dropwise added thereto, and the mixture was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate (70 ml). The organic layer was washed
 20 three times with water and once with a saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, hexane-ethyl acetate
 25 (3:1)] to obtain (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]-4-tritylthiopyrrolidine (791 mg, yield: 75.4%).

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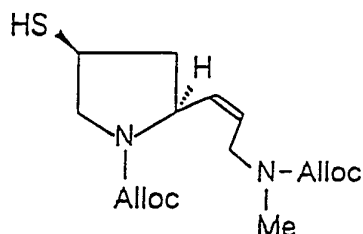
NMR(CDCl₃) δ :

1.50(1H,m), 2.64-3.04(6H,m), 3.66-4.64(8H,m),

5.10-5.50(6H,m), 5.90(2H,m), 7.16-7.60(15H,m)

2)

5



The same procedure as in Reference Example 2-4 was
 10 carried out by using the compound (791 mg, 1.36 mmol)
 obtained by the above reaction, to obtain the above-
 identified compound (416 mg, yield: 90.0%).

NMR(CDCl₃) δ :

1.62(1H,m), 2.60(1H,m), 2.93(3H,s), 3.13-3.38(2H,m),

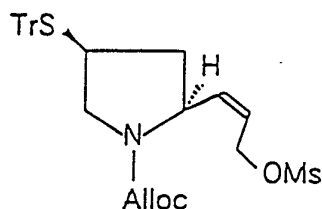
15 3.73-4.40(4H,m), 4.54-4.76(4H,m), 5.14-5.42(4H,m),

5.56(2H,m), 5.92(2H,m)

REFERENCE EXAMPLE 4

(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N,N-dimethylamino)-
1-propenyl]-4-mercaptopyrrolidine trifluoroacetate

20 1)



25 The same procedure as in Reference Example 1-5 was
 carried out by using (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-
 hydroxy-1-propenyl]-4-tritylthiopyrrolidine (3.6 g, 7.45

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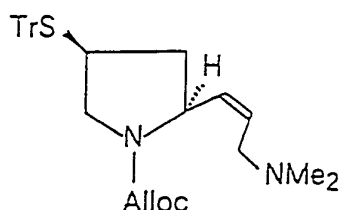
mmol) to obtain (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-methanesulfonyloxy-1-propenyl]-4-tritylthiopyrrolidine (4.07 g, yield: 97.3%).

NMR(CDCl₃) δ :

5 1.48(1H,m), 2.68-3.06(6H,m), 4.20-4.58(4H,m),
4.62-4.98(2H,m), 5.12-5.22(2H,m), 5.60(2H,m),
5.92(1H,m), 7.16-7.54(15H,m)

2)

10



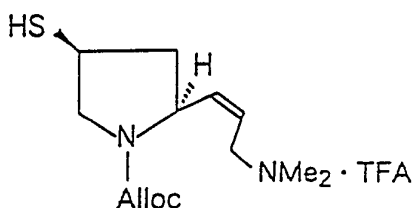
To an N,N-dimethylformamide solution (15 ml) of the compound (2.03 g, 3.62 mmol) obtained by the above
15 reaction, dimethylamine hydrochloride (890 mg, 10.9 mmol) and sodium hydrogencarbonate (1.06 g, 12.6 mmol) were added, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with
20 ethyl acetate (70 ml). The organic layer was washed sequentially with water and a saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography
25 [WakogelTM C-300, 3% methanol-chloroform] to obtain (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N,N-dimethylamino)-1-propenyl]-4-tritylthiopyrrolidine (1.24 g, yield:

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67.2%).

NMR(CDCl₃) δ :

1.48(1H,m), 1.80-2.40(6H,m), 2.64-3.15(4H,m),
4.22-4.62(4H,m), 5.06-5.32(2H,m), 5.35-5.66(2H,m),
5.86(1H,m), 7.18-7.57(15H,m)
3)



10

To a methylene chloride solution (3.5 ml) of the compound (1.23 g, 2.41 mmol) obtained by the above reaction, trifluoroacetic acid (3.5 ml) and triethylsilane (0.41 ml, 2.57 mmol) were added in a nitrogen stream under cooling with ice, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography [WakogelTM C-300, 3% methanol-chloroform] to obtain the above-identified compound (640 mg, yield: 69.5%).

15

20

NMR(CDCl₃) δ :

1.62(1H,m), 2.62(1H,m), 2.84(6H,m), 3.12-3.42(3H,m),
3.74-4.22(3H,m), 4.42-4.66(2H,m), 5.16-5.40(2H,m),
5.55-6.10(3H,m)

25

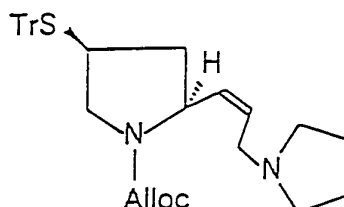
- 120 -

REFERENCE EXAMPLE 5

(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(1-pyrrolidinyl)-1-propenyl]-4-mercaptopyrrolidine trifluoroacetate

1)

5



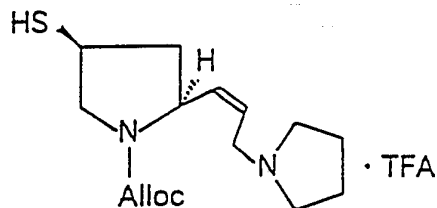
Pyrrolidine (0.91 ml, 10.9 mmol) was added to an N,N-dimethylformamide solution (15 ml) of (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-methanesulfonyloxy-1-propenyl]-4-tritylthiopyrrolidine (2.03 g, 3.62 mmol), and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (70 ml). The organic layer was washed sequentially with water and a saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, 3% methanol-chloroform] to obtain (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(1-pyrrolidinyl)-1-propenyl]-4-tritylthiopyrrolidine (1.34 g, yield: 69.1%).

NMR(CDCl₃) δ:

1.46(1H,m), 1.56-2.10(5H,m), 2.18-2.60(4H,m),
2.65-3.40(5H,m), 4.20-4.60(3H,m), 5.06-5.42(3H,m),
5.58(1H,m), 5.84(1H,m), 7.16-7.60(15H,m)

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2)



5

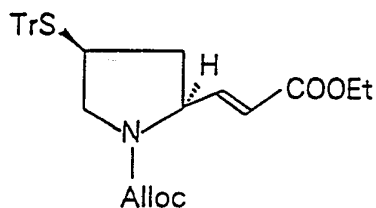
The same procedure as in Reference Example 4-3 was carried out by using the compound (1.34 g, 2.5 mmol) obtained by the above reaction, to obtain the above-identified compound (513 mg, yield: 50.3%).

10 REFERENCE EXAMPLE 6

(2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]-4-mercaptopyrrolidine

1)

15



To a methylene chloride solution (150 ml) of oxalyl chloride (7.05 ml, 80.8 mmol), a methylene chloride solution (25 ml) of dimethyl sulfoxide (8.8 ml, 124 mmol) was dropwise added in a nitrogen stream at -78°C , and the reaction solution was stirred at the same temperature for 30 minutes. To this mixture, a methylene chloride solution (130 ml) of (2S,4S)-N-allyloxycarbonyl-2-hydroxymethyl-4-tritylthiopyrrolidine (27.1 g, 59.0 mmol, compound of Reference Example 3-1 of Japanese Patent Application No. 205984/1990) was dropwise added. This

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reaction mixture was stirred at the same temperature for 30 minutes, and then triethylamine (27.1 ml, 195 mmol) was added thereto. The mixture was further stirred for 30 minutes. This reaction mixture was poured into
5 methylene chloride (200 ml). The organic layer was washed sequentially with dilute hydrochloric acid, water and a saturated sodium chloride aqueous solution, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain an oily residue of
10 (2S,4S)-N-allyloxycarbonyl-2-formyl-4-tritylthiopyrrolidine.

Ethyl diethylphosphonoacetate (14.2 g, 63.3 ml) was added to a tetrahydrofuran suspension (260 ml) of 60% sodium hydride in a nitrogen stream under cooling with
15 ice, and the mixture was stirred at the same temperature for 30 minutes. To this reaction solution, the tetrahydrofuran solution (100 ml) of the (2S,4S)-N-allyloxycarbonyl-2-formyl-4-tritylthiopyrrolidine obtained by the above reaction, was dropwise added, and
20 the mixture was stirred at the same temperature for 30 minutes. The reaction solution was extracted with ethyl acetate (350 ml). The organic layer was washed sequentially with water and a saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate
25 and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [WakogelTM C-300, hexane-ethyl acetate (4:1)] to obtain

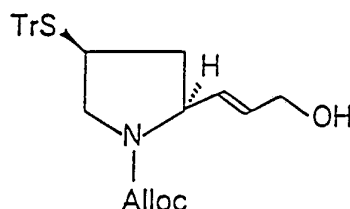
- 123 -

ethyl 3-[(2S,4S)-N-allyloxycarbonyl-4-tritylthiopyrrolidin-2-yl]acrylate (28.31 g, yield: 96.1%).

NMR(CDCl₃) δ :

- 5 1.26 (3H,t,J=8Hz), 1.80-2.20 (1H,m), 2.66-3.50 (3H,m),
 4.18 (3H,m), 4.48 (2H,m), 5.05-5.34 (2H,m),
 5.64-6.00 (2H,m), 6.76 (1H,dd,J=15,7Hz), 7.14-7.58 (15H,m)
 2)

10



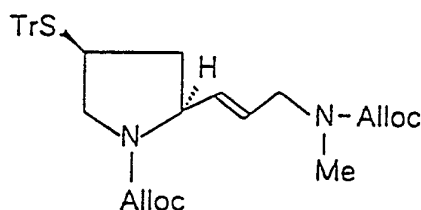
- 15 The same procedure as in Reference Example 2-1 was
 carried out by using the compound (28.31 g, 55.4 mmol)
 obtained by the above reaction, to obtain (2S,4S)-N-
 allyloxycarbonyl-2-[(E)-3-hydroxy-1-propenyl]-4-
 tritylthiopyrrolidine (3.4 g, yield: 12.7%).

NMR(CDCl₃) δ :

- 20 1.56 (1H,m), 2.10 (1H,m), 2.58-3.10 (3H,m),
 3.96-4.16 (2H,m), 4.34-4.60 (2H,m), 5.08-5.32 (2H,m),
 5.48-5.98 (3H,m), 7.14-7.56 (15H,m)

3)

25



To a tetrahydrofuran solution (40 ml) of the compound

- 124 -

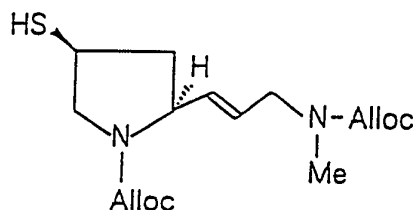
(3.0 g, 6.2 mmol) obtained by the above reaction, methane-sulfonyl chloride (0.514 ml, 6.64 mmol) and triethylamine (0.95 ml, 0.683 mmol) were added in a nitrogen stream under cooling with ice, and the mixture
5 was stirred at the same temperature for 30 minutes. Then, a 40% methylamine solution in methanol (2.5 g) was added thereto, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure and then extracted
10 with ethyl acetate (100 ml). The organic layer was washed sequentially with water and a saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was dissolved in a tetrahydrofuran solution
15 (60 ml), and triethylamine (0.95 ml, 6.83 mmol) and allyl chloroformate (0.66 ml, 6.22 mmol) were added under cooling with ice. The mixture was stirred at the same temperature for one hour. The reaction mixture was extracted with ethyl acetate (100 ml). The organic layer
20 was washed sequentially with water and a saturated sodium chloride aqueous solution and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [WakogelTM C-300, hexane-ethyl acetate (3:1)] to obtain (2S,4S)-N-allyloxycarbonyl-2-
25 [(E)-3-(N-allyloxycarbonyl-N-methylamino)-1-propenyl]-4-tritylthiopyrrolidine (1.73 g, yield: 47.9%).

- 125 -

NMR(CDCl₃) δ :

1.55(1H,m), 2.08(1H,m), 2.58-3.44(6H,m), 3.84(2H,m),
 4.08(1H,m), 4.35-4.62(4H,m), 5.06-5.38(4H,m),
 5.48(2H,m), 5.88(2H,m), 7.15-7.58(15H,m)

5 4)



10 The same procedure as in Reference Example 2-4 was
 carried out by using the compound (1.73 g, 2.97 mmol)
 obtained by the above reaction, to obtain the above-
 identified compound (850 mg, yield: 84.6%).

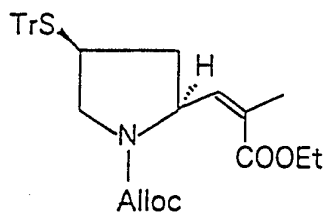
NMR(CDCl₃) δ :

15 1.70(1H,m), 2.58(1H,m), 2.86(3H,s), 3.10-3.38(2H,m),
 3.88(2H,m), 4.06(1H,m), 4.34(1H,m), 4.45-4.66(4H,m),
 5.10-5.40(4H,m), 5.60(2H,m), 5.95(2H,m)

REFERENCE EXAMPLE 7

(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-
 20 (allyloxycarbonylamino)-2-methyl-1-propenyl]-4-
mercaptopyrrolidine

1)



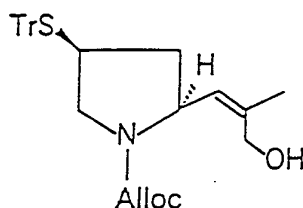
25

The same procedure as in Reference Example 6-1 was

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carried out by using (2S,4S)-N-allyloxycarbonyl-2-hydroxymethyl-4-tritylthiopyrrolidine (8.19 g, 17.8 mmol) and ethyl 2-diethylphosphonopropionate (4.76 g, 20.0 mmol) to obtain ethyl 3-[(2S,4S)-N-allyloxycarbonyl-4-tritylthiopyrrolidin-2-yl]-2-methylacrylate (8.58 g, yield: 91.6%).

2)



10

The same procedure as in Reference Example 2-1 was carried out by using the compound (8.58 g, 15.9 mmol) obtained by the above reaction, to obtain (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-hydroxy-2-methyl-1-propenyl]-4-tritylthiopyrrolidine (1.90 g, yield: 24%, less polar compound) and E-isomer (2.26 g, yield: 28.6%, polar compound).

Z-isomer (less polar compound)

20 NMR(CDCl₃) δ :

1.50(1H,m), 1.80(3H,s), 2.17(1H,m), 2.62-3.02(3H,m),
3.62(1H,m), 4.08(1H,m), 4.32-4.62(4H,m),
5.02(1H,d,J=10Hz), 5.12-5.34(2H,m), 5.88(1H,m),
7.15-7.60(15H,m)

25 E-isomer (polar compound)

NMR(CDCl₃) δ :

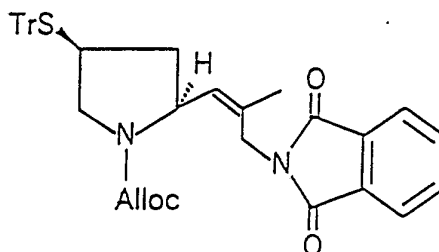
1.45(1H,m), 1.65(3H,br s), 2.02(1H,m), 2.60-3.34(3H,m),

- 127 -

3.97(2H,br s), 4.15-4.58(3H,m), 5.05-5.32(3H,m),
5.83(1H,m), 7.14-7.54(15H,m)

3)

5



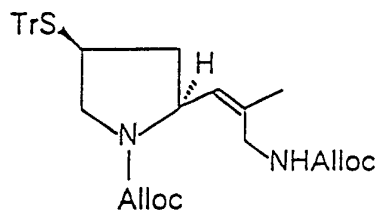
The same procedure as in Reference Example 2-2 was
carried out by using the Z-isomer (1.88 g, 3.78 mmol)
10 obtained by the above reaction, to obtain (2S,4S)-N-
allyloxycarbonyl-2-[(Z)-2-methyl-3-phthalimido-1-
propenyl]-4-tritylthiopyrrolidine (2.089 g, yield:
88.2%).

NMR(CDCl₃) δ :

15 1.40-1.76(4H,m), 2.70-4.30(3H,m), 4.04-4.86(5H,m),
5.10-5.36(3H,m), 5.87(1H,m), 7.18-7.60(15H,m),
7.76(2H,m), 7.90(2H,m)

4)

20



The same procedure as in Reference Example 2-3 was
carried out by using the compound (2.08 g, 3.32 mmol)
25 obtained by the above reaction, to obtain (2S,4S)-N-
allyloxycarbonyl-2-[(Z)-3-allyloxycarbonylamino-2-methyl-
1-propenyl]-4-tritylthiopyrrolidine (1.26 g, yield:

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65.3%).

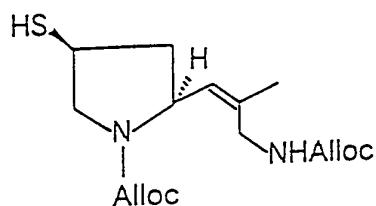
NMR(CDCl₃) δ :

1.50(1H,m), 1.72(3H,s), 2.10(1H,m), 2.60-3.06(3H,m),

3.80(2H,m), 4.20-4.68(7H,m), 4.96-5.40(6H,m),

5 5.92(2H,m), 7.15-7.58(15H,m)

5)



10

The same procedure as in Reference Example 2-4 was carried out by using the compound (640 mg, 1.1 mmol) obtained by the above reaction, to obtain the above-identified compound (326 mg, yield: 85.9%).

15 NMR(CDCl₃) δ :

1.60(1H,m), 1.78(3H,s), 2.58(1H,m), 3.08-3.36(2H,m),

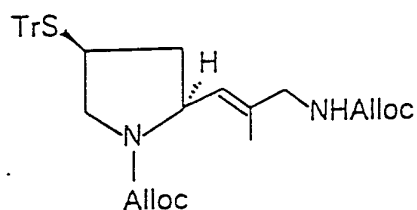
3.88(2H,m), 4.02(1H,m), 4.44-4.82(5H,m),

5.10-5.44(5H,m), 5.80-6.16(3H,m)

REFERENCE EXAMPLE 8

20 (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(allyloxycarbonylamino)-2-methyl-1-propenyl]-4-mercaptopyrrolidine

1)



25

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The same procedures as in Reference Example 2-2 and 2-3 were carried out by using (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-hydroxy-2-methyl-1-propenyl]-4-tritylthiopyrrolidine (2.24 g, 4.5 mmol) to obtain

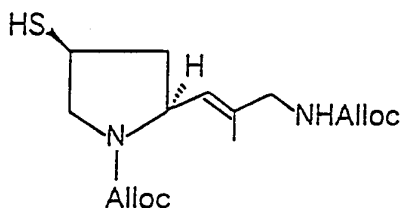
5 (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-allyloxycarbonylamino-2-methyl-1-propenyl]-4-tritylthiopyrrolidine (1.48 g, yield: 56.7%).

NMR(CDCl₃) δ :

1.46(1H,m), 1.64(3H,s), 2.02(1H,m), 2.62-3.40(3H,m),
 10 3.68(2H,m), 4.12-4.72(6H,m), 5.08-5.40(5H,m),
 5.88(2H,m), 7.14-7.52(15H,m)

2)

15



20 The same procedure as in Reference Example 2-4 was carried out by using the compound (860 mg, 1.45 mmol) obtained by the above reaction, to obtain the above-

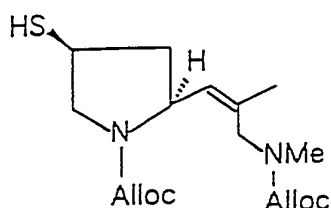
NMR(CDCl₃) δ :

1.47-1.82(4H,m), 2.57(1H,m), 3.10-3.36(2H,m),
 3.72(2H,m), 4.02(1H,m), 4.40-4.66(5H,m),
 5.12-5.40(5H,m), 5.78-6.04(2H,m)

25 REFERENCE EXAMPLE 9

(2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(N-allyloxycarbonyl-N-methylamino)-2-methyl-1-propenyl]-4-mercaptopyrrolidine

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5

The same procedures as in Reference Example 3-1 and 3-2 were carried out by using (2S,4S)-N-allyloxycarbonyl-2-[(Z)-3-(allyloxycarbonylamino)-2-methyl-1-propenyl]-4-tritylthiopyrrolidine (600 mg, 1.03 mmol) to obtain the above-identified compound (308 mg, yield: 84.6%).

10

NMR(CDCl₃) δ :

1.48-1.75(4H,m), 2.76(1H,m), 2.88(3H,br s),

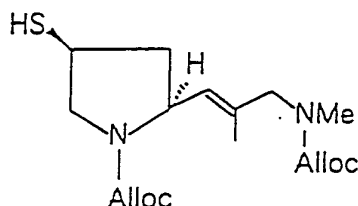
3.22(2H,m), 3.76-4.32(4H,m), 4.44-4.70(4H,m),

5.15-5.42(5H,m), 5.92(2H,m)

15 REFERENCE EXAMPLE 10

(2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(N-allyloxycarbonyl-N-methylamino)-2-methyl-1-propenyl]-4-mercaptopyrrolidine

20



The same procedures as in Reference Example 3-1 and 3-2 were carried out by using (2S,4S)-N-allyloxycarbonyl-2-[(E)-3-(allyloxycarbonylamino)-2-methyl-1-propenyl]-4-tritylthiopyrrolidine (600 mg, 1.03 mmol) to obtain the above-identified compound (295 mg, yield: 81.0%).

25

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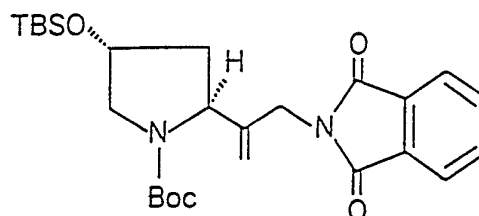
NMR(CDCl₃) δ :

1.46-1.75(4H,m), 2.60(1H,m), 2.82(3H,s), 3.25(2H,m),
 3.86(2H,m), 4.04(1H,m), 4.46-4.68(5H,m),
 5.14-5.42(5H,m), 5.92(2H,m)

5 REFERENCE EXAMPLE 11

(2S,4S)-N-allyloxycarbonyl-2-[1-[(N-
allyloxycarbonylamino)methyl]vinyl]-4-mercaptopyrrolidine
 1)

10



To a tetrahydrofuran solution (25 ml) of (2S,4R)-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[1-
 15 (hydroxymethyl)vinyl]pyrrolidine (2.45 g, 6.9 mmol, compound of Reference Example 5-4 of Japanese Patent Application No. 263270/1991), phthalimide (1.77 g, 12.0 mmol), triphenylphosphine (2.75 g, 10.5 mmol) and diethyl azodicarboxylate (1.65 ml, 10.5 mmol) were added at 0°C,
 20 and the mixture was stirred at the same temperature for two hours. The reaction solution was concentrated under reduced pressure, and the residue was dissolved in a solvent mixture of ethyl acetate (15 ml) and heptane (15 ml) and left to stand overnight. Precipitated solid was
 25 filtered and washed with heptane-ethyl acetate (2:1). The filtrate and the washing solution were put together and distilled under reduced pressure. The residue was

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subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate (4:1)] to obtain (2S,4R)-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[1-(phthalimidomethyl)vinyl]pyrrolidine (2.85 g, yield:

5 84%).

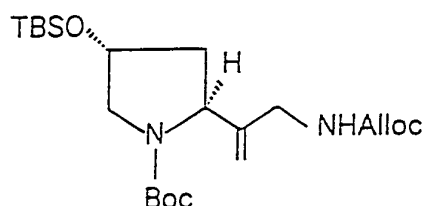
NMR(CDCl₃) δ:

0.05(6H,s), 0.87(9H,s), 1.39(9H,s), 2.07(2H,m),

3.51(2H,br s), 4.10-4.27(2H,m), 4.37(2H,m),

4.83(1H,br s), 4.99(1H,br s), 7.65-7.90(4H,m)

10 2)



15 Hydrazine monohydrate (0.85 ml, 17.6 mmol) was added to an ethanol solution (40 ml) of (2S,4R)-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[1-(phthalimidomethyl)vinyl]pyrrolidine (2.85 g, 5.86 mmol) at room temperature, and the mixture was stirred

20 overnight at the same temperature. The reaction mixture was filtered and washed with ethanol. The filtrate and the washing solution were put together and distilled under reduced pressure. To the residue, ethyl acetate and 8% aqueous ammonia were added and subjected to liquid

25 separation. Then, the organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to obtain 2.11 g of an oily substance. To a dry

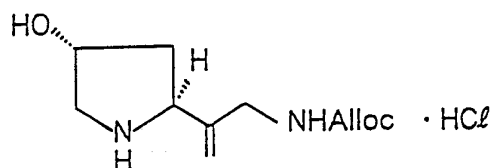
- 133 -

methylene chloride solution (30 ml) of this oily substance, allyl chloroformate (1.92 ml, 18 mmol) and triethylamine (3.34 ml, 24 mmol) were added at 0°C, and the mixture was stirred overnight at the same temperature. The reaction solution was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate (4:1)] to obtain (2S,4R)-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxypyrrolidine (2.15 g, yield: 82%).

NMR(CDCl₃) δ:

0.04(6H,s), 0.86(9H,s), 1.42(9H,s), 1.86(1H,m),
2.06(1H,m), 3.46(2H,m), 3.76(2H,m), 4.32(1H,m),
4.42(1H,m), 4.60(2H,br d), 5.00(2H,br s),
5.12-5.38(3H,m), 5.92(1H,m)
3)

20



A 3N hydrogen chloride solution in methanol was added to (2S,4R)-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxypyrrolidine (2.15 g, 4.88 mmol) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction solution was distilled under

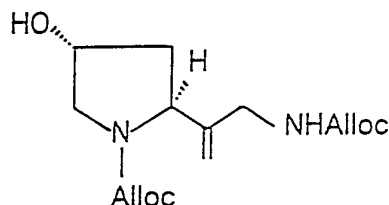
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reduced pressure to obtain crude (2S,4R)-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-4-hydroxypyrrolidine monohydrochloride (1.14 g).

NMR(D₂O) δ :

5 2.03-2.35(2H,m), 3.29(1H,br d), 3.60(1H,m),
 3.83(2H,br s), 4.36(1H,m), 4.55(2H,br d),
 4.69(2H,br s), 5.15-5.23(4H,m), 5.93(1H,m)
 4)

10



(2S,4R)-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-
 4-hydroxypyrrolidine monohydrochloride (1.14 g, 4.4 mmol)
 15 was added to dioxane (15 ml) and water (10 ml). To this
 mixture, allyl chloroformate (0.63 ml, 6 mmol) was
 dropwise added while adjusting the pH to a level of from
 8 to 9 with a 3N sodium hydroxide aqueous solution at
 0°C. After the dropwise addition, the mixture was
 20 stirred at the same temperature for 10 minutes. The
 reaction mixture was distilled under reduced pressure,
 extracted with ethyl acetate (80 ml), washed with a
 saturated sodium hydrogencarbonate solution (40 ml) and a
 saturated sodium chloride aqueous solution (30 ml), dried
 25 over anhydrous sodium sulfate and then distilled off
 under reduced pressure. The residue thereby obtained was
 subjected to silica gel column chromatography [WakogelTM

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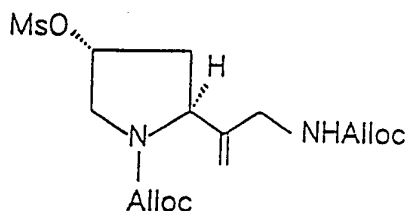
C-300, heptane-ethyl acetate (1:1)-ethyl acetate] to obtain (2S,4R)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-4-hydroxypyrrolidine (1.1 g, yield: 80%).

5 NMR(CDCl₃) δ :

2.00(1H,m), 2.20(1H,m), 3.60-4.00(4H,m),
4.60(4H,d,J=6Hz), 5.00-5.64(4H,m), 5.94(2H,m)

5)

10



To a methylene chloride solution (10 ml) of (2S,4R)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-4-hydroxypyrrolidine (892 mg, 2.87 mmol), methanesulfonyl chloride (0.29 ml, 3.73 mmol) and triethylamine (0.68 ml, 4.88 mmol) were added at 0°C, and the mixture was stirred at the same temperature for 15 minutes. To the reaction solution, 20 chloroform (40 ml) was added, and the mixture was washed with dilute hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then distilled under reduced pressure. The 25 residue thereby obtained, was subjected to silica gel column chromatography (WakogelTM C-300, ethyl acetate) to obtain (2S,4R)-N-allyloxycarbonyl-2-[1-[(N-

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allyloxycarbonylamino)methyl]vinyl]-4-

methanesulfonyloxypyrrolidine (943 mg, yield: 84%).

NMR(CDCl₃) δ :

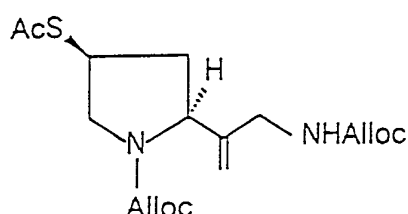
2.14(1H,m), 2.56(1H,m), 3.06(3H,s), 3.62-3.94(3H,m),

5 4.04(1H,m), 4.40(4H,br s), 5.10(2H,br s),

5.16-5.40(5H,m), 5.92(2H,m)

6)

10



To a dimethylformamide solution (15 ml) of (2S,4R)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-4-

15 methanesulfonyloxypyrrolidine (943 mg, 2.43 mmol), potassium thioacetate (560 mg, 4.9 mmol) and potassium iodide (475 mg, 3.16 mmol) were added under a nitrogen stream, and the mixture was stirred at 70°C for 3.5 hours. To the reaction mixture, ethyl acetate (100 ml)

20 was added, and the mixture was washed with water (40 ml) and a saturated sodium chloride aqueous solution (40 ml), dried over anhydrous sodium sulfate and then distilled under reduced pressure. The residue thereby obtained, was subjected to silica gel column chromatography

25 [Wakogel™ C-300, heptane-ethyl acetate (2:1)] to obtain (2S,4S)-4-acetylthio-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]pyrrolidine (831 mg,

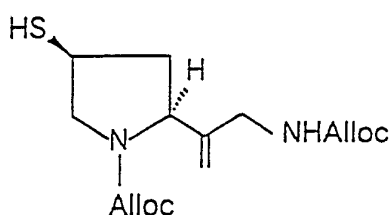
- 137 -

yield: 92%).

NMR(CDCl₃) δ :

1.86(1H,m), 2.14(3H,s), 2.64(1H,m), 3.28(1H,m),
 3.70-4.04(4H,m), 4.20(1H,m), 4.42(1H,t, J=8Hz),
 5 4.58(4H,d, J=7Hz), 5.09(2H,br s), 5.22-5.42(4H,m),
 5.94(2H,m)
 7)

10



A 1N sodium hydroxide aqueous solution (2.0 ml) was added to a methanol solution (6 ml) of (2S,4S)-4-acetylthio-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]pyrrolidine (622 mg, 1.68 mmol) at 0°C, and the mixture was stirred at the same temperature for 15 minutes. To this reaction mixture, 1N hydrochloric acid (2.1 ml) was added, and the pH was adjusted to 4. Then, the mixture was distilled under reduced pressure. To the residue, ethyl acetate (50 ml) and water (20 ml) were added. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and then distilled under reduced pressure to obtain crude (2S,4S)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-4-mercaptopyrrolidine (530 mg, yield: 96%).

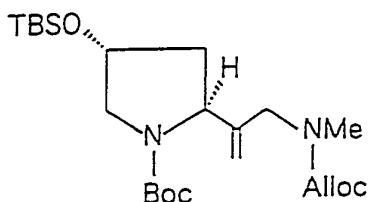
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REFERENCE EXAMPLE 12

(2S,4S)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonyl-N-methylamino)methyl]vinyl]-2-mercaptopyrrolidine

1)

5



60% sodium hydride (980 mg, 25 mmol) was added to a
 10 DMF solution (80 ml) of (2S,4R)-2-[1-[(N-allyloxycarbonylamino)methyl]vinyl]-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxypyrrolidine (5.42 g, 12.3 mmol) at 0°C, and the mixture was stirred at the same temperature for 25 minutes. Then, methyl
 15 iodide (1.56 ml, 25 mmol) was added thereto, and the mixture was stirred overnight at room temperature. To the reaction mixture, water (100 ml) was added, and the mixture was extracted with ethyl acetate (450 ml). The organic layer was washed with water and a saturated
 20 sodium chloride aqueous solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude (2S,4R)-2-[1-[(N-allyloxycarbonyl-N-methylamino)methyl]vinyl]-N-tert-butoxycarbonyl-4-tert-butyldimethylsiloxypyrrolidine (6.0 g).

25 NMR(CDCl₃) δ:

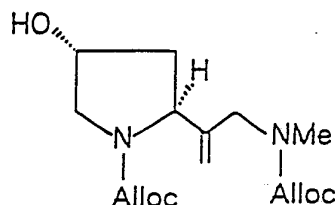
0.04(6H,s), 0.85(9H,s), 1.41(9H,s), 2.88(3H,s),
 4.58(2H,br s), 4.80(1H,br s), 4.96(1H,br s),

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5.10-5.32 (2H,m), 5.90(1H,m)

2)

5



A 4.8N hydrogen chloride solution in methanol (40 ml) was added to the compound (6.0 g) obtained by the above reaction, and the mixture was stirred overnight at room temperature. The reaction solution was concentrated under reduced pressure. To the residue, chloroform (20 ml × 2) was added, and the mixture was concentrated. To the residue, water (30 ml) and dioxane (60 ml) were added, and allyl chlorocarbonate (1.35 ml, 12.9 mmol) was dropwise added thereto, while adjusting the pH to a level of from 9 to 10 with 1N sodium hydroxide under cooling with ice. The mixture was stirred at the same temperature for 20 minutes. The reaction solution was extracted with ethyl acetate (250 ml). The organic layer was washed with water (80 ml × 2) and with a saturated sodium chloride aqueous solution (80 ml × 2), dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate (2:1)→ethyl acetate] to obtain (2S,4R)-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonyl-N-methylamino)methyl]vinyl]-4-hydroxypyrrolidine (3.09 g,

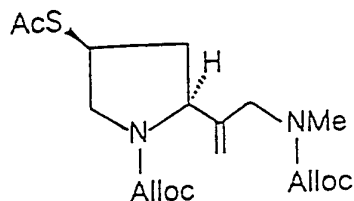
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yield: 80.9%).

NMR(CDCl₃) δ :

1.94(1H,m), 2.21(1H,m), 2.91(3H,br s), 4.43-4.60(6H,m),
4.87(1H,br s), 5.01(1H,s), 5.10-5.40(4H,m), 5.92(2H,m)

5 3)



10 To a methylene chloride solution (40 ml) of the
compound (3.09 g, 9.5 mmol) obtained by the above
reaction, triethylamine (1.86 ml, 13.3 mmol) and
methanesulfonyl chloride (0.88 ml, 11.4 mmol) were added
under cooling with ice, and the mixture was stirred at
15 the same temperature for 15 minutes. To the reaction
solution, chloroform (100 ml) was added, and the mixture
was washed with dilute hydrochloric acid, a saturated
sodium hydrogencarbonate aqueous solution and a saturated
sodium chloride aqueous solution, dried over anhydrous
20 sodium sulfate and concentrated under reduced pressure.
The residue was subjected to silica gel column
chromatography [WakogelTM C-300, heptane-ethyl acetate
(1:2)] to obtain 3.0 g of an oily substance. Potassium
thioacetate (2.53 g, 22.2 mmol) was added to a DMF
25 solution (30 ml) of the obtained oily substance (3.0 g),
and the mixture was stirred under a nitrogen stream at
70°C for 4 hours. To the reaction mixture, ethyl acetate

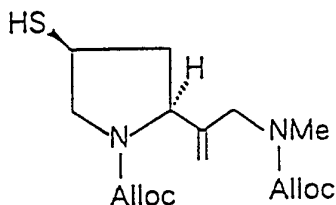
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(250 ml) was added, and the mixture was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure. The residue
 5 thereby obtained, was subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate (2:1+1:1)] to obtain (2S,4S)-4-acetylthio-N-allyloxycarbonyl-2-[1-[(N-allyloxycarbonyl-N-methylamino)methyl]vinyl]pyrrolidine (3.3 g, yield: 90%).

10 NMR(CDCl₃) δ :

1.91(1H,m), 2.31(3H,s), 2.62(1H,m), 2.88(3H,br s),
 3.26(1H,m), 3.63(1H,m), 3.89(1H,m), 4.17(1H,m),
 4.34(1H,m), 4.58(4H,m), 4.93(1H,br s), 5.06(1H,br s),
 5.15-5.36(4H,m), 5.88(2H,m)

15 4)



20 1N sodium hydroxide (8.7 ml) was dropwise added to a methanol solution (30 ml) of the compound (3.3 g, 8.6 mmol) obtained by the above reaction, at 0°C, and the mixture was stirred for 10 minutes. Then, 1N
 hydrochloric acid (9.0 ml) was dropwise added thereto at
 25 the same temperature. The reaction mixture was concentrated and then extracted with ethyl acetate. The organic layer was washed with a saturated sodium chloride

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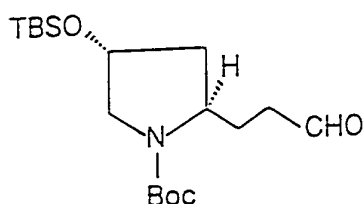
aqueous solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product of the above-identified compound (2.87 g).

REFERENCE EXAMPLE 13

5 (2S,4S)-N-allyloxycarbonyl-2-[2-(N-allyloxycarbonyl-N-methylamino)allyl]-4-mercaptopyrrolidine

1)

10



Oxalyl chloride (1.58 ml, 18.5 mmol) was dropwise added to a methylene chloride solution (40 ml) of dimethyl sulfoxide (2.5 ml, 35 mmol) at -70°C, and the mixture was stirred at the same temperature for 30 minutes. Then, a methylene chloride solution (10 ml) of (2S,4R)-4-tert-butyldimethylsiloxy-N-tert-butoxycarbonyl-2-(2-hydroxyethyl)pyrrolidine (3.7 g, 10.3 mmol) was dropwise added thereto, and the mixture was stirred at the same temperature for 30 minutes. Then, triethylamine (10 ml, 72 mmol) was dropwise added thereto, and the temperature was raised to room temperature. Water was added to the reaction solution, and the organic layer was washed with dilute hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The

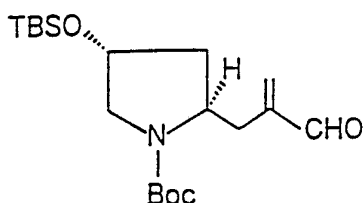
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obtained oily substance was subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate (4:1)] to obtain (2S,4R)-4-tert-butyltrimethylsiloxy-N-tert-butoxycarbonyl-2-(2-formylethyl)pyrrolidine (3.14 g, yield: 85%).

NMR (CDCl₃) δ:

0.04(6H,s), 0.85(9H,s), 1.44(9H,s), 1.66(1H,m),
1.92(1H,m), 2.00(2H,m), 2.42(2H,m), 3.22-3.60(2H,m),
3.95(1H,m), 4.31(1H,m), 9.74(1H,s)

10 2)



15 To a methylene chloride solution (40 ml) of the
compound (3.14 g, 8.8 mmol) obtained by the above
reaction, triethylamine (2.7 ml, 19.4 mmol) and N,N-
dimethylmethyleammonium chloride (1.65 g, 17.6 mmol)
were added, and the mixture was stirred overnight at room
20 temperature. The reaction solution was washed with
water, dilute hydrochloric acid, a saturated sodium
hydrogencarbonate aqueous solution and a saturated sodium
chloride aqueous solution, then dried over anhydrous
sodium sulfate and concentrated under reduced pressure.
25 The residue was subjected to silica gel column
chromatography [WakogelTM C-300, heptane-ethyl acetate
(4:1)] to obtain (2S,4R)-4-tert-butyl dimethylsiloxy-N-

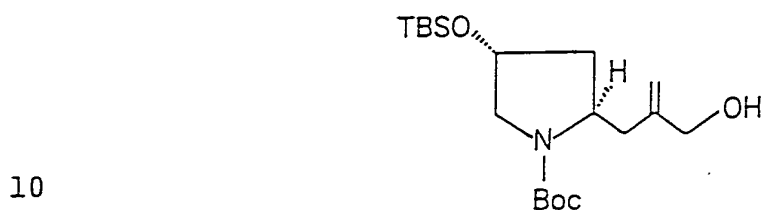
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tert-butoxycarbonyl-2-(2-formylallyl)pyrrolidine (2.33 g, yield: 71%).

NMR(CDCl₃) δ :

0.03(6H,s), 0.84(9H,s), 1.46(9H,s), 2.40(1H,m),
2.68(1H,m), 3.24-3.48(2H,m), 4.03(1H,m), 4.30(1H,m),
6.06(1H,s), 6.32(1H,m), 9.53(1H,m)

3)



A methanol solution (10 ml) of cerium chloride heptahydrate (2.35 g, 6.3 mmol) was added to a methanol solution (25 ml) of the compound (2.33 g, 6.3 mmol) obtained by the above reaction, at 0°C, and sodium borohydride (240 mg, 6.3 mmol) was added thereto at the same temperature, and the mixture was stirred for 10 minutes. To the reaction solution, water (10 ml) was added, and the mixture was concentrated under reduced pressure. The residue was extracted with ethyl acetate. The organic layer was washed with dilute hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [WakogelTM C-300, heptane-ethyl acetate (3:1)] to obtain (2S,4R)-4-

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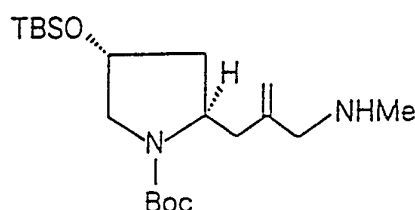
tert-butyldimethylsiloxy-N-tert-butoxycarbonyl-2-[2-(hydroxymethyl)allyl]pyrrolidine (2.24 g, yield: 95%).

NMR(CDCl₃) δ :

0.06(6H,s), 0.87(9H,s), 1.45(9H,s), 3.25-3.44(2H,m),

5 4.11(3H,m), 4.37(1H,m), 4.82(1H,m), 5.01(1H,m)

4)



10

To a methylene chloride solution (30 ml) of the compound (2.24 g, 6.0 mmol) obtained by the above reaction, triethylamine (1.18 ml, 8.44 mmol) and methanesulfonyl chloride (0.56 ml, 7.25 mmol) were

15 dropwise added under cooling with ice, and the mixture was stirred at the same temperature for 15 minutes. The reaction solution was washed with water, dilute hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous

20 solution, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. To a methanol solution (100 ml) of the obtained oily substance, a 40% methylamine solution in methanol (30 ml) was added, and the mixture was stirred overnight at room temperature.

25 The reaction solution was concentrated under reduced pressure, and the residue was extracted with chloroform (70 ml). The organic layer was washed with 1.5N sodium

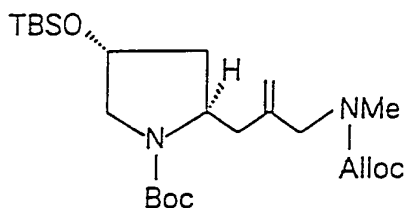
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hydroxide (40 ml) and a saturated sodium chloride aqueous solution (30 ml), then dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain

5 butoxycarbonyl-2-[2-(N-methylaminomethyl)allyl]pyrrolidine (2.24 g).

NMR(CDCl₃) δ :

0.04(6H,s), 0.85(9H,s), 1.45(9H,s), 2.40(3H,s),
3.14(2H,m), 3.20-3.40(2H,m), 3.95-4.15(1H,m),
10 4.83(1H,s), 4.96(1H,s)
5)



15

To a methylene chloride solution (40 ml) of the compound (2.24 g, 5.8 mmol) obtained by the above reaction, triethylamine (1.13 ml, 8.1 mmol) and allyl chlorocarbonate (0.74 ml, 7.0 mmol) were added under
20 cooling with ice, and the mixture was stirred at the same temperature for 30 minutes. The reaction solution was washed with dilute hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution, then dried over anhydrous
25 sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate

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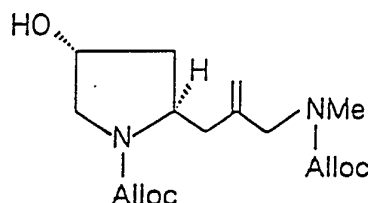
(3:1)] to obtain (2S,4R)-2-[2-(N-allyloxycarbonyl-N-methylaminomethyl)allyl]-4-tert-butyltrimethylsiloxy-N-tert-butoxycarbonylpyrrolidine (2.46 g, yield: 90%).

NMR(CDCl₃) δ :

5 0.04(6H,s), 0.86(9H,s), 1.45(9H,s), 1.71-2.08(3H,m),
 2.50-2.70(1H,m), 2.88(3H,s), 3.37(2H,m),
 3.72-4.20(4H,m), 4.32(1H,m), 4.59(2H,m), 4.88(2H,m),
 5.10-5.38(2H,m), 5.91(1H,m)

6)

10



A 3N hydrogen chloride solution in methanol was added
15 to the compound (2.46 g, 5.2 mmol) obtained by the above
reaction, at room temperature, and the mixture was
stirred overnight. The reaction solution was
concentrated under reduced pressure, and to the residue,
water (20 ml) and dioxane (40 ml) were added. Then,
20 allyl chlorocarbonate (0.67 ml, 6.3 mmol) was dropwise
added thereto while adjusting the pH to a level of from 9
to 10 with an aqueous sodium hydroxide solution under
cooling with ice, and the mixture was stirred at the same
temperature for 10 minutes. The reaction solution was
25 extracted with ethyl acetate (150 ml), and the organic
layer was washed with water and a saturated sodium
chloride aqueous solution, then dried over anhydrous

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sodium sulfate and concentrated under reduced pressure.

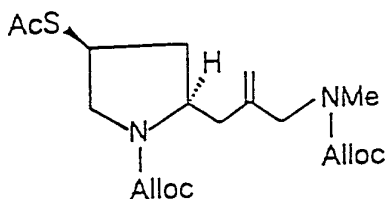
The residue was subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate (2:1)+ethyl acetate] to obtain (2S,4R)-N-

5 allyloxycarbonyl-2-[2-(N-allyloxycarbonyl-N-methylaminomethyl)allyl]-4-hydroxypyrrolidine (1.41 g, yield: 79%).

NMR(CDCl₃) δ :

1.72-2.24(3H,m), 2.55-2.85(1H,m), 2.86(3H,s),
10 3.40-3.72(2H,m), 3.84(2H,m), 4.17(1H,m), 4.40(1H,m),
4.58(4H,m), 4.89(2H,br s), 5.10-5.38(4H,m), 5.90(2H,m)
7)

15



To a methylene chloride solution (30 ml) of the compound (1.41 g, 4.17 mmol) obtained by the above reaction, triethylamine (0.81 ml, 5.0 mmol) and
20 methanesulfonyl chloride (0.39 ml, 5.0 mmol) were added under cooling with ice, and the mixture was stirred at the same temperature for 10 minutes. The reaction solution was washed with dilute hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution and
25 saturated sodium chloride aqueous solution, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Potassium thioacetate (1.42 g, 12.5

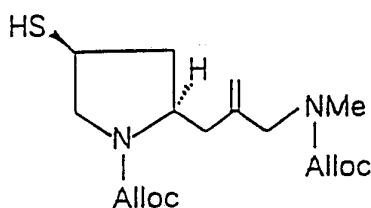
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mmol) was added to a DMF solution (30 ml) of the obtained oily substance, and the mixture was stirred under a nitrogen stream at 70°C for 3 hours. To the reaction mixture, ethyl acetate was added, and the organic layer
5 was washed with water and a saturated sodium chloride aqueous solution, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography [Wakogel™ C-300, heptane-ethyl acetate (2:1→1:1)] to
10 obtain (2S,4S)-4-acetylthio-N-allyloxycarbonyl-2-[2-(N-allyloxycarbonyl-N-methylaminomethyl)allyl]pyrrolidine (1.36 g, yield: 82%).

NMR(CDCl₃) δ:

1.62-1.80(1H,m), 2.02-2.18(1H,m), 2.32(3H,s),
15 2.86(3H,s), 3.21(1H,m), 3.86(3H,m), 4.10(2H,m),
4.58(4H,br s), 4.90(2H,br s), 5.10-5.38(4H,m),
5.90(2H,m)
8)

20



25

1N sodium hydroxide (3.5 ml) was dropwise added to a methanol solution (10 ml) of the compound (1.36 g, 3.43 mmol) obtained by the above reaction under cooling with ice, and the mixture was stirred at the same temperature for 10 minutes. 1N hydrochloric acid (3.7 ml) was added

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to the mixture at 0°C, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, then dried over
5 anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product of the above-identified compound (1.22 g).

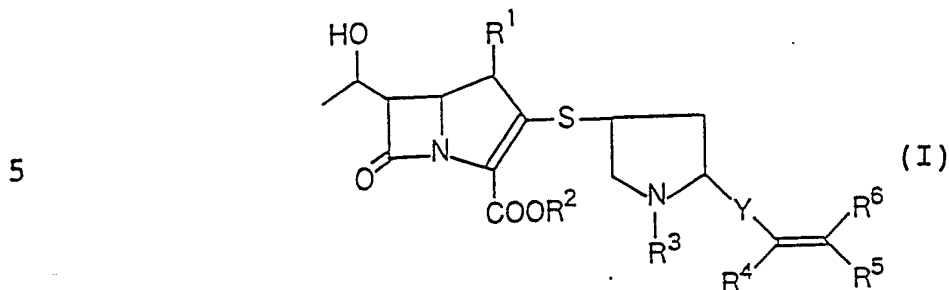
INDUSTRIAL APPLICABILITY

The compounds of the present invention are novel
10 compounds not disclosed any literatures and have strong antibacterial activities against sensitive and resistant gram positive bacteria and gram negative bacteria and excellent stability against β -lactamase and DHP-I. Therefore, they are useful as antibacterial agents.

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CLAIMS

1. A compound of the formula (I):

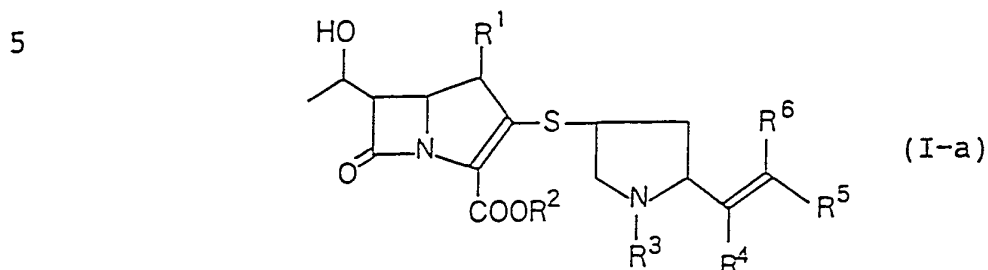


wherein R¹ is a hydrogen atom or a methyl group, R² is a hydrogen atom or a negative charge, R³ is a hydrogen atom or a lower alkyl group, each of R⁴, R⁵ and R⁶ is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula -X-N(R⁷)R⁸ {wherein each of R⁷ and R⁸ which may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R⁷ and R⁸ form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8-membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents}, provided that at least one of R⁴, R⁵ and R⁶ is the group of the formula -X-N(R⁷)R⁸ wherein R⁷, R⁸ and X are as defined

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above, and Y is a lower alkylene group or a single bond;
or a pharmaceutically acceptable salt or ester thereof.

2. The compound according to Claim 1, which is a
compound of the formula (I-a):

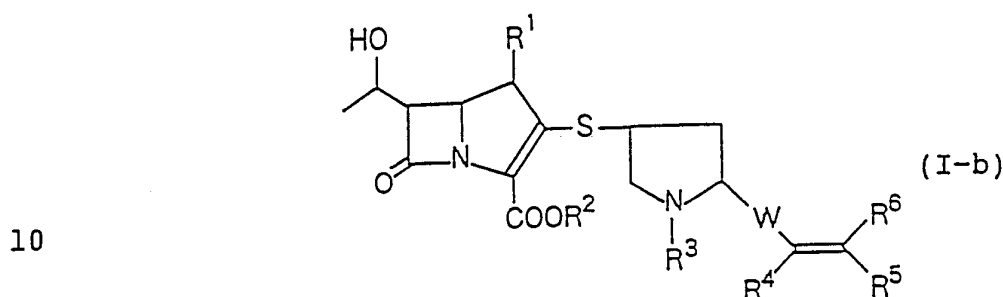


10 wherein R^1 is a hydrogen atom or a methyl group, R^2 is a
hydrogen atom or a negative charge, R^3 is a hydrogen atom
or a lower alkyl group, each of R^4 , R^5 and R^6 is a
hydrogen atom, a cyano group, a methanesulfonyl group, a
lower alkyl group which may have substituents, a
15 carbamoyl group which may have substituents or a group of
the formula $-X-N(R^7)R^8$ {wherein each of R^7 and R^8 which
may be the same or different, is a hydrogen atom or a
lower alkyl group which may have substituents, or R^7 and
 R^8 form, together with the adjacent nitrogen atom and, if
20 necessary, together with a hetero atom selected from the
group consisting of a nitrogen atom, an oxygen atom and a
sulfur atom in addition to the adjacent nitrogen atom, a
3- to 8- membered heterocyclic group which may be
substituted (provided that either the nitrogen atom
25 adjacent to X or other nitrogen atom on the heterocyclic
ring may form an ammonio group), and X is a lower
alkylene group which may have substituents}, provided

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that at least one of R^4 , R^5 and R^6 is the group of the formula $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined above; or a pharmaceutically acceptable salt or ester thereof.

- 5 3. The compound according to Claim 1, which is a compound of the formula (I-b):



- wherein R^1 is a hydrogen atom or a methyl group, R^2 is a hydrogen atom or a negative charge, R^3 is a hydrogen atom or a lower alkyl group, each of R^4 , R^5 and R^6 is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula $-X-N(R^7)R^8$ {wherein each of R^7 and R^8 which may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R^7 and R^8 form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8- membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X or other nitrogen atom on the heterocyclic
- 15
- 20
- 25

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ring may form an ammonio group), and X is a lower alkylene group which may have substituents, provided that at least one of R^4 , R^5 and R^6 is the group of the formula $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined above, and
5 W is a lower alkylene group; or a pharmaceutically acceptable salt or ester thereof.

4. The compound according to Claim 1, wherein R^5 or R^6 is a group of the formula $-(CH_2)_n-N(R^{70})R^{80}$ wherein each of R^{70} and R^{80} which may be the same or different, a
10 hydrogen atom or a lower alkyl group, or R^{70} and R^{80} form, together with the adjacent nitrogen atom, a 3- to 8- heterocyclic group, and n is an integer of from 1 to 4.

5. The compound according to Claim 1, wherein R^5 or R^6 is a group of the formula $-CH_2-N(R^{77})R^{88}$ wherein each of R^{77} and R^{88} which may be the same or different, is a
15 hydrogen atom or a lower alkyl group, or R^{77} and R^{88} form, together with the adjacent nitrogen atom, a 4- to 6- membered heterocyclic group.

20 6. The compound according to Claim 1, wherein each of R^5 and R^6 is a hydrogen atom.

7. The compound according to Claim 1, wherein R^5 or R^6 is a group of the formula $-CH_2-NH_2$, $-CH_2-NHCH_3$ or $-CH_2-N(CH_3)_2$.

25 8. The compound according to Claim 1, which is:

(5R,6S)-2-[(2S,4S)-2-[(E)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-

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- carbapen-2-em-3-carboxylic acid,
(1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
- 5 (5R,6S)-2-[(2S,4S)-2-[(Z)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,
(1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
- 10 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 15 (5R,6S)-2-[(2S,4S)-2-[(Z)-3-(N,N-dimethylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,
(1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-(N,N-dimethylamino)-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
- 20 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(1-pyrrolidinyl)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 25 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(Z)-3-(1-pyrrolidinyl)-1-propenyl]pyrrolidin-

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- 4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
(5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 5 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
(5R,6S)-2-[(2S,4S)-2-[(Z)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,
- 10 (1R,5S,6S)-2-[(2S,4S)-2-[(Z)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
(5R,6S)-2-[(2S,4S)-2-[(E)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,
- 15 (1R,5S,6S)-2-[(2S,4S)-2-[(E)-3-amino-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
(5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,
- 20 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(Z)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid,
(5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-
- 25

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1-carbapen-2-em-3-carboxylic acid,

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-2-methyl-1-propenyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

5 (5R,6S)-2-[(2S,4S)-2-[1-(aminomethyl)vinyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-carbapen-2-em-3-carboxylic acid,

(1R,5S,6S)-2-[(2S,4S)-2-[1-(aminomethyl)vinyl]pyrrolidin-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid,

10 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[1-[(N-methylamino)methyl]vinyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[1-[(N-methylamino)methyl]vinyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid,

(5R,6S)-6-[(R)-1-hydroxyethyl]-2-[(2S,4S)-2-[2-[(N-methylamino)methyl]allyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid or

20 (1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[2-[(N-methylamino)methyl]allyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid.

9. The compound according to Claim 1, which is

(1R,5S,6S)-6-[(R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(E)-3-(N-methylamino)-1-propenyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid.

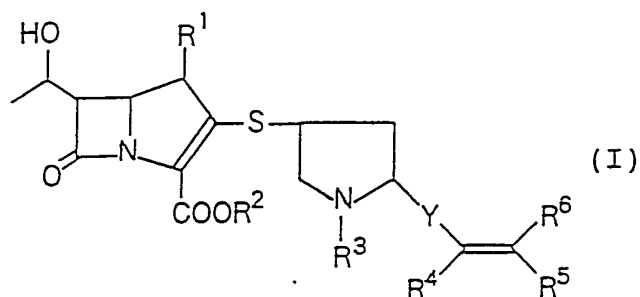
10. The compound according to Claim 1, wherein the steric

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configuration of the compound of the formula (I) is (5R,6S,8R) or (1R,5S,6S,8R).

11. A process for producing a compound of the formula (I):

5



10 wherein R^1 is a hydrogen atom or a methyl group, R^2 is a hydrogen atom or a negative charge, R^3 is a hydrogen atom or a lower alkyl group, each of R^4 , R^5 and R^6 is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a

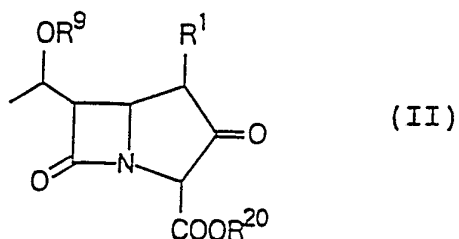
15 carbamoyl group which may have substituents or a group of the formula $-X-N(R^7)R^8$ {wherein each of R^7 and R^8 which may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R^7 and R^8 form, together with the adjacent nitrogen atom and, if

20 necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8-membered heterocyclic group which may be substituted (provided that either the nitrogen atom

25 adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents}, provided

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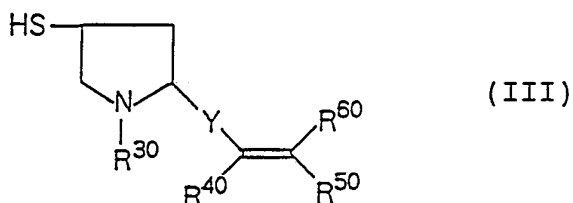
that at least one of R^4 , R^5 and R^6 is the group of the
 formula $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined
 above, and Y is a lower alkylene group or a single bond;
 or a pharmaceutically acceptable salt or ester thereof,
 5 which comprises reacting a compound of the formula (II):



10

wherein R^1 is as defined above, R^9 is a hydrogen atom or
 a hydroxyl-protecting group, and R^{20} is a hydrogen atom
 or a carboxyl-protecting group, or a reactive derivative
 thereof, with a compound of the formula (III):

15

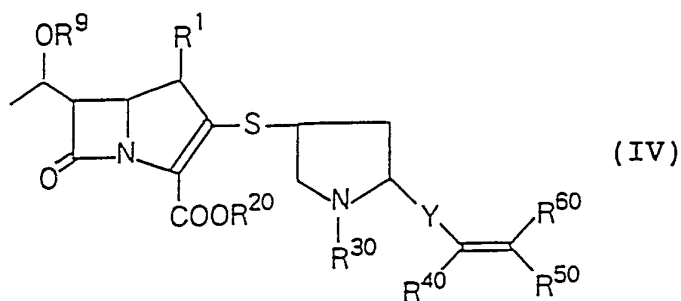


20 wherein R^{30} is a hydrogen atom, a lower alkyl group or an
 imino-protecting group, each of R^{40} , R^{50} and R^{60} is a
 hydrogen atom, a cyano group, a methanesulfonyl group, a
 lower alkyl group which may have substituents, a
 carbamoyl group which may have substituents or a group of
 25 the formula $-X^1-N(R^{71})R^{81}$ {wherein each of R^{71} and R^{81}
 which may be the same or different, is a hydrogen atom, a
 lower alkyl group which may have substituents or an

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amino-protecting group, or R^{71} and R^{81} form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8- membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X^1 or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X^1 is a lower alkylene group which may have substituents}, provided that at least one of R^{40} , R^{50} and R^{60} is the group of the formula $-X^1-N(R^{71})R^{81}$ wherein R^{71} , R^{81} and X^1 are as defined above, and Y is a lower alkylene group or a single bond (provided that the substituents of the lower alkyl group, the heterocyclic group and the lower alkylene group, as well as the carbamoyl group and the imino group on the heterocyclic ring, may be protected, as the case requires), to obtain a compound of the formula (IV):

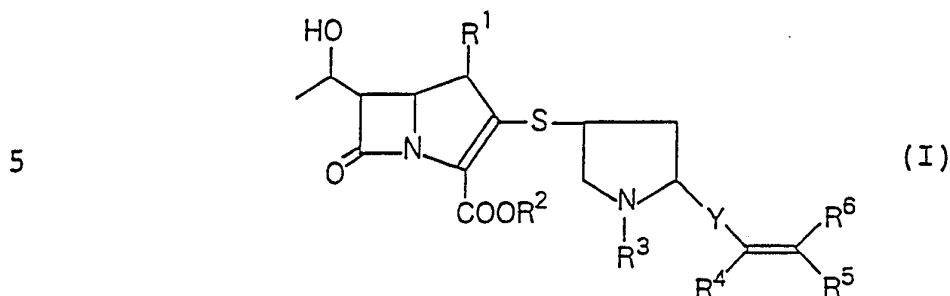
20



25 wherein R^1 , R^9 , R^{20} , R^{30} , R^{40} , R^{50} and R^{60} are as defined above, and if necessary, removing any protecting group of the compound of the formula (IV).

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12. An antibacterial agent comprising an antibacterially effective amount of the compound of the formula (I):



wherein R^1 is a hydrogen atom or a methyl group, R^2 is a hydrogen atom or a negative charge, R^3 is a hydrogen atom or a lower alkyl group, each of R^4 , R^5 and R^6 is a hydrogen atom, a cyano group, a methanesulfonyl group, a lower alkyl group which may have substituents, a carbamoyl group which may have substituents or a group of the formula $-X-N(R^7)R^8$ {wherein each of R^7 and R^8 which may be the same or different, is a hydrogen atom or a lower alkyl group which may have substituents, or R^7 and R^8 form, together with the adjacent nitrogen atom and, if necessary, together with a hetero atom selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to the adjacent nitrogen atom, a 3- to 8-membered heterocyclic group which may be substituted (provided that either the nitrogen atom adjacent to X or other nitrogen atom on the heterocyclic ring may form an ammonio group), and X is a lower alkylene group which may have substituents}, provided that at least one of R^4 , R^5 and R^6 is the group of the formula $-X-N(R^7)R^8$ wherein R^7 , R^8 and X are as defined

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above, and Y is a lower alkylene group or a single bond;
or a pharmaceutically acceptable salt or ester thereof,
and a pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

PCT/JP 92/00864

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC
 Int.Cl. 5 C07D477/00; A61K31/40

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification Systems	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation
 to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP,A,0 182 213 (SUMITOMO PHARMACEUTICALS CO., LTD.) 28 May 1986 see claims	1-12
Y	EP,A,0 411 664 (BANYU PHARMACEUTICAL CO. LTD.) 6 February 1991 cited in the application see claims	1-12

¹⁰ Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

18 SEPTEMBER 1992

Date of Mailing of this International Search Report

02.10.92 02 OCT 1992

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

CHOULY J.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. JP 9200864
SA 61567**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 18/09/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0182213	28-05-86	US-A- 4962103 JP-A- 62155279	09-10-90 10-07-87
EP-A-0411664	06-02-91	AU-A- 6012290 JP-A- 4154782 US-A- 5095013	07-02-91 27-05-92 10-03-92

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82