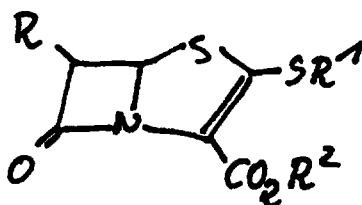


Description

This invention relates to novel β -lactam compounds and a process for producing the same. More particularly, this invention relates to novel β -lactam compounds which are carbapenem or penem derivatives and useful as antimicrobial agents or intermediates therefor and a process for producing the same.

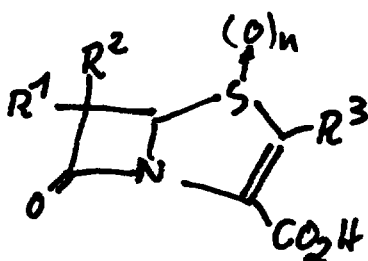
Since the discovery of thienamycin having a potential antimicrobial activity against Gram negative and Gram positive bacteria, studies on synthesis of carbapenem or penem derivatives which are analogous to thienamycin have been widely developed.

JP-A-57,176,988 (C.A. 1983, 143190 w) relates to penem-3-carboxylic acid derivatives of the general formula



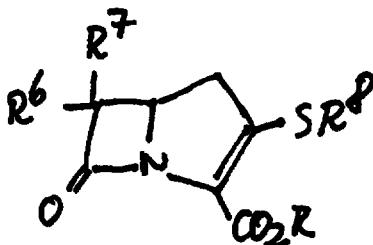
useful as bactericides and methods for preparing them.

In EP-A-0 002 210 6 and 6,6-disubstituted-2-substituted pen-2-em-3-carboxylic acids of the general formula



and their preparation are disclosed. Such compounds are useful as antibiotics.

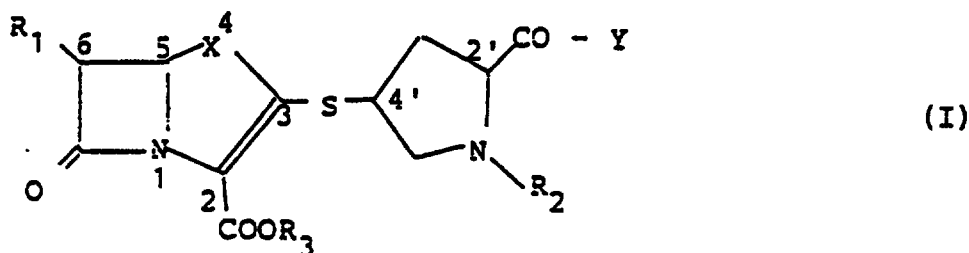
EP-A-0 017 992 relates to the total synthesis of 1-carbapenem antibiotics of the general formula



Therefore, an object of the present invention is to find new carbapenem or penem derivatives which exhibit potential antimicrobial activity.

This object has been solved by carbapenem or penem derivatives having, as their 3-side chain, a substituent easily derived from 4-hydroxy-proline, i.e., a substituted pyrrolidinyl group carrying a carbonyl group substituted with various substituents on its 2-position, which exhibit potential antimicrobial activity and are useful as medicines or are important intermediates for compounds possessing antimicrobial activity.

The present invention relates to novel carboxylic β -lactam compounds represented by the formula (I):



15 wherein R_1 represents a 1-hydroxyethyl group or a 1-hydroxyethyl group in which the hydroxy group is protected with a protecting group; R_2 represents a hydrogen atom or a protecting group for an amino group; R_3 represents a hydrogen atom or a protecting group for a carboxyl group; X represents a substituted or unsubstituted methylene group of the formula (1):



30 wherein R_4 represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, or X represents a sulfur atom; and Y represents a group of the formula (2):



40 wherein R_5 and R_6 , which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a substituted alkyl group having 1 to 5 carbon atoms wherein the substituent is selected from a hydroxy group, a di(C_{1-3})-alkylamino group, a carbamoyl group, a mono- or di(C_{1-3})-alkylaminocarbonyl group and a protected or unprotected carboxyl group or a pyridyl group, or R_5 and R_6 taken together represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1-C_3)-alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond(s) in its ring, wherein the substituent is selected from a (C_{1-3})-alkyl group, a carbamoyl group, a mono- or di(C_{1-3})-alkylaminocarbonyl group and a hydroxy group; or a group of the formula (4):



55 wherein R_8 represents a hydrogen atom, a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms, and pharmacologically acceptable salts thereof; and a process for producing the same.

In the above-described formula (I), the protecting group for a hydroxyl group as represented by R_1 and the protecting group for an amino group as represented by R_2 may be any of those commonly employed. Preferred examples of these protecting groups include a lower alkoxycarbonyl group, e.g., *t*-butoxycarbonyl; a halogenoalkoxycarbonyl group, e.g., 2-iodoethyloxycarbonyl or 2,2,2-trichloroethyloxycarbonyl; an aralkyloxycarbonyl group, e.g., benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl

or p-nitrobenzyloxycarbonyl; and a trialkylsilyl group, e.g., trimethylsilyl or t-butyldimethylsilyl.

The protecting group for a carboxyl group as represented by R_3 may be any of those commonly employed and preferred; examples are straight or branched chain lower alkyl groups, e.g., methyl, ethyl, isopropyl, or t-butyl; halogeno lower alkyl groups, e.g., 2-iodoethyl or 2,2,2-trichloroethyl; lower alkoxy-
 5 methyl groups, e.g., methoxymethyl, ethoxymethyl or isobutoxymethyl; lower aliphatic acyloxymethyl groups, e.g., acetoxymethyl, propionyloxymethyl, butyryloxymethyl, or pivaloyloxymethyl; 1-lower alkoxy-carbonyloxyethyl groups, e.g., 1-methoxycarbonyloxyethyl or 1-ethoxycarbonyloxyethyl; aralkyl groups, e.g., p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, a benzhydryl group and a phthalidyl group.

When X is a (C_1-C_3) alkyl-substituted or unsubstituted methylene group as represented by the formula
 10 (1), the (C_1-C_3) alkyl group includes, for example, methyl, ethyl or n-propyl.

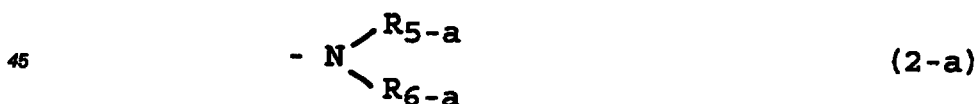
When Y is an amino group represented by the formula (2), R_5 and R_6 may be the same or different from each other. In the definition of R_5 and R_6 , the alkyl group having 1 to 5 carbon atoms includes e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl or t-butyl, the alkenyl group having 3 to 4 carbon atoms includes, for example, propenyl or butenyl. R_5 and R_6 further include a benzyl group, a phenethyl group, a 2-
 15 pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group; in the definition of R_5 and R_6 , the substituted alkyl group having 1 to 5 carbon atoms includes, for example, straight chain or branched chain alkyl groups, e.g., methyl, ethyl, n-propyl, isopropyl or n-butyl, which are substituted with a hydroxyl group, a di- (C_1-C_3) alkylamino group, a carbamoyl group, a mono- or di- (C_1-C_3) alkyl-substituted aminocarbonyl group, a protected or unprotected carboxyl group or a like substituent; and the pyridyl group includes 2-
 20 pyridyl, 3-pyridyl and 4-pyridyl groups.

In cases where R_5 and R_6 jointly represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1-C_3) alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond-
 25 (s) in its ring, the cyclic amino group includes, for example, a saturated cyclic amino group, e.g. an aziridino group, an azetidino group, a pyrrolidino group or a piperidino group; an unsaturated cyclic amino group, e.g., a pyrrolyl group or a 3-pyrrolyl group; and a cyclic amino group having an oxygen atom, a sulfur atom or an alkyl-substituted nitrogen atom in its ring, e.g., a morpholino group, a thiomorpholino group or an N-methylpiperazino group. The substituents for these cyclic amino groups include, for example, an alkyl group having 1 to 3 carbon atoms, a carbamoyl group, a mono- or di- (C_1-C_3) alkyl-substituted
 30 aminocarbonyl group or a hydroxyl group.

In cases where Y is represented by the formula (4), R_8 is a hydrogen atom, a protecting group commonly employed for protection of a hydroxyl group or a lower alkyl group, e.g., methyl, ethyl or n-propyl.

Of the compounds of the above-described formula (I), the carboxylic acid compounds wherein the
 35 group as represented by $-COOR_3$ or $-COY$ is a carboxyl group can be converted into their pharmacologically acceptable salts, if desired. Such salts include those formed with inorganic metals, such as lithium, sodium, potassium, calcium or magnesium and those formed with ammonium, such as ammonium, cyclohexylammonium, diisopropylammonium or triethylammonium, with a sodium salt and a potassium salt being preferred.

40 The preferred compounds of the formula (I) are those wherein R_1 is a 1-hydroxyethyl group; R_2 and R_3 are both hydrogen atoms; and Y is a group represented by the formula (2-a):



wherein R_{5-a} and R_{6-a} each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an
 50 alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, an alkyl group having 1 to 5 carbon atoms which is substituted with a hydroxyl group, a di- (C_1-C_3) alkylamino group, a carbamoyl group, a mono- or di- (C_1-C_3) -alkyl-substituted aminocarbonyl group or a carboxyl group, or a pyridyl group, or R_{5-a} and R_{6-a} jointly represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1-C_3) -
 55 alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof, wherein the substituent for the cyclic amino group includes a (C_1-C_3) alkyl group, a carbamoyl group, a carboxyl group, a mono- or di- (C_1-C_3) alkyl-substituted aminocarbonyl group or a hydroxyl group; or a

group represented by the formula (4-a):



- 5 wherein R_{8-a} represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

The more preferred compounds of the formula (I) are those wherein R_1 is a 1-hydroxyethyl group; R_2 and R_3 are both hydrogen atoms, and Y is a group represented by the formula (2-b):

10



- 15 wherein R_{5-b} and R_{6-b} each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group; an alkyl group having 1 to 5 carbon atoms which is substituted with a hydroxyl group, a di-(C_1 - C_3)alkylamino group, a carbamoyl group, a mono- or di-(C_1 - C_3)-alkyl-substituted aminocarbonyl group or a carboxyl group, or a pyridyl group, or R_{5-b} and R_{6-b} jointly
20 represent an alkylene chain or alkylene chain containing an oxygen atom, a sulfur atom or a (C_1 - C_3) alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3-to 7-membered cyclic amino group which may contain double bond(s) in its ring, wherein the substituent for the cyclic amino group includes an alkyl group having 1 to 3 carbon atoms, a carbamoyl group or a hydroxyl group; or a group represented by the formula (4-a):

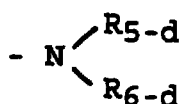
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wherein R_{8-a} has the same meaning as defined above.

Preferred examples of Y include a group represented by the formula:

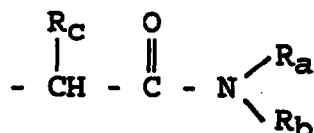
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wherein R_{5-d} represents a hydrogen atom or a methyl group, and R_{6-d} represents a group of the formula:

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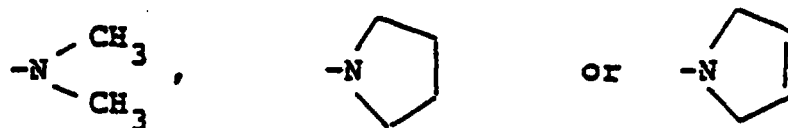


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wherein R_a , R_b and R_c each represents a hydrogen atom or a methyl group.

Other preferred examples of Y comprise a group of the formula:

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The most preferred compounds of the formula (I) are those wherein R_1 is a 1-hydroxyethyl group; R_2 and R_3 are both hydrogen atoms; and Y is a group represented by the formula (2-c):



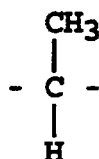
wherein R_{5-c} and R_{6-c} have one of the following meanings:

- (1) R_{5-c} represents an alkyl group having 1 to 5 carbon atoms which may be substituted with a carbamoyl group, a mono- or di-($\text{C}_1\text{-C}_3$)alkylaminocarbonyl group or a hydroxyl group, or a pyridyl group, and R_{6-c} represents a hydrogen atom or has the same meaning as described for R_{5-c} ;
- (2) R_{5-c} and R_{6-c} are directly taken together to represent an alkylene chain to form, together with the adjacent nitrogen atom, a 4- to 6-membered saturated cyclic amino group or a 5 to 6-membered unsaturated cyclic amino group having double bond(s) in its ring, such as a pyrrolinyl group, or the same saturated or unsaturated cyclic amino group as described above but having a substituent on its ring, such as a carbamoyl group or a hydroxyl group, and
- (3) R_{5-c} and R_{6-c} jointly represent an alkylene chain containing an oxygen atom or a ($\text{C}_1\text{-C}_3$)alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a 6-membered cyclic amino group.

Preferred examples of X, if positively enumerated, can include a sulfur atom, a methyl-substituted or unsubstituted methylene group as claimed in claims 7, more preferred as represented by the formula (1-a):

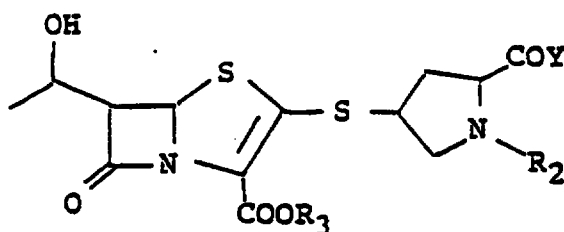


wherein R_{4-a} represents a hydrogen atom or a methyl group, with a group

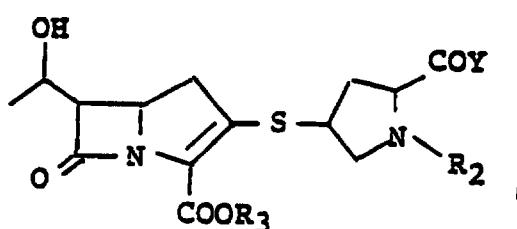


being particularly preferred.

Preferred compounds are (5R)-compounds, more preferred are (5R,6S,8R)-compounds and most preferred are (5R,6S,8R,2'S,4'S)-compounds of the formula

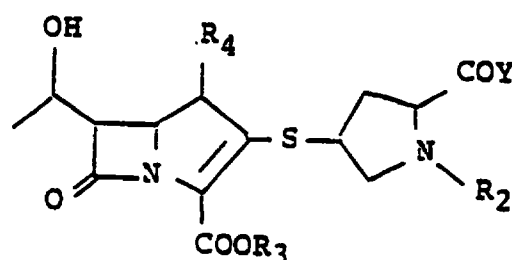


and preferred compounds are (5R)-compounds, more preferred are (5R,6S,8R)-compounds and most preferred are (5R,6S,8R,2'S,4'S)-compounds of the formula



wherein Y, R₂ and R₃ are as defined above.

Preferred compounds are also (5S)-compounds, more preferred are (5S,6S,8R)-compounds and most preferred are (5S,6S,8R,2'S,4'S)-compounds of the formula



wherein Y, R₂ and R₃ are as defined above and R₄ is an alkyl group having one to three carbon atoms. Especially preferred compounds are:

- 1.*) (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 2.*) (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 3.*) (5R)-3-[2-(Carbamoylpyrrolidin-4-ylthio)-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 4.*) (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 5.*) (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 6.*) (5R)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 7.*) (5R)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 8.*) (5R)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 9.*) (5R)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 10.*) (5R)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 11.*) (5R)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 12.*) (5R)-3-[2-(Carbamoylpyrrolidin-4-ylthio)-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 13.*) (5R)-3-[2-(4-Pyridylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 14.*) (5S)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 15.*) (5S)-3-[2-((1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;
- 16.*) (5S)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;

17.*) (5S)-3-[2-((1-Azatidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;

18.*) (5S)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;

19.*) (5S)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;

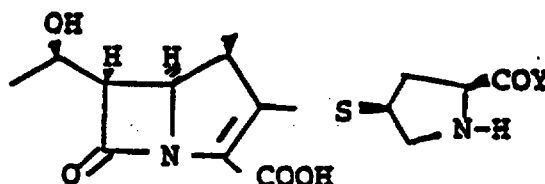
20.*) (5S)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;

21.*) (5S)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof;

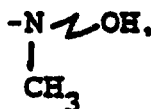
22.*) (5S)-3-[2-Carbamoylpyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.

The compounds 1* to 13* with (5R,6S,8R)-configuration are more and with (5R,6S,8R,2'S,4'S)-configuration are most preferred. Also the compounds 14* to 22* with (5S,6S,8R)-configuration are more and with (5S,6S,8R,2'S,4'S)-configuration are most preferred. Furthermore, subject matter of the present application are the following β -lactam compounds:

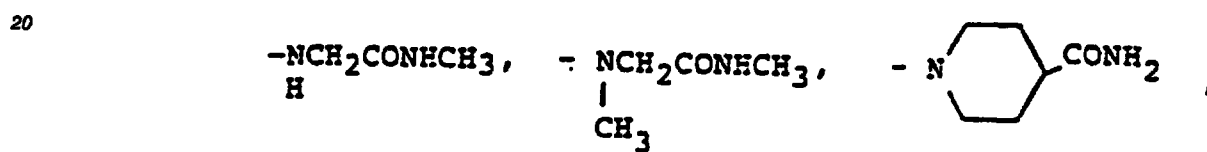
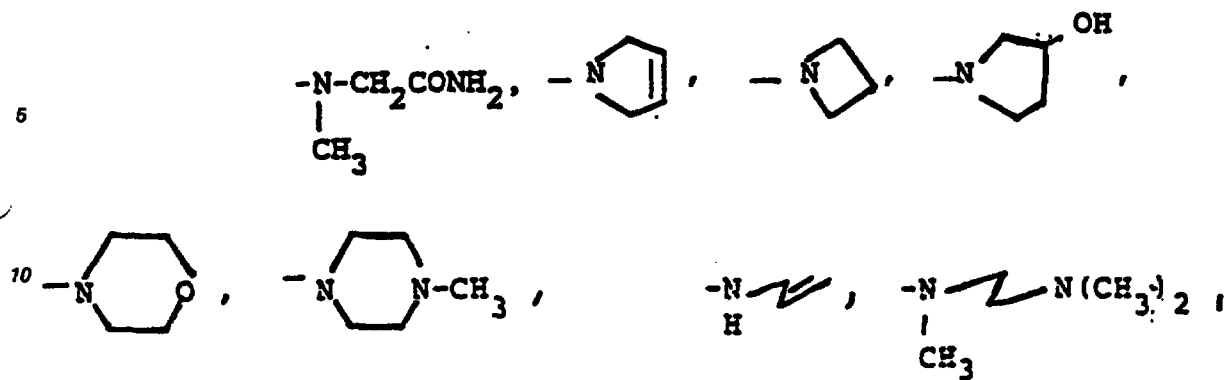
A β -lactam compound of the formula:



wherein Y is chosen from the group consisting of -NH₂,

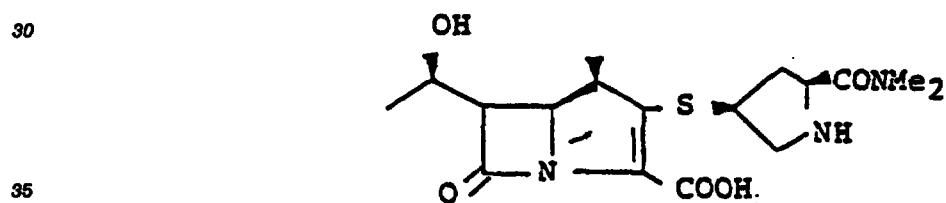


-NHCH₂CONH₂,



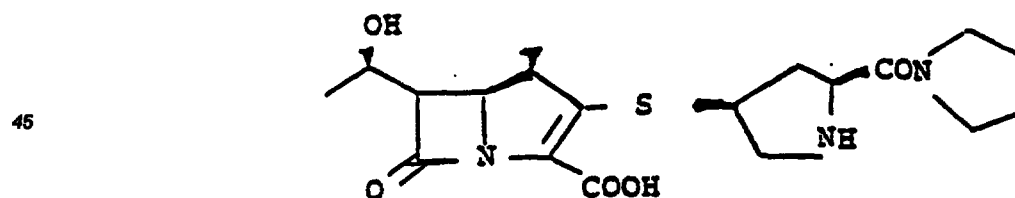
and the pharmaceutically acceptable salts thereof.

A β -lactam compound of the formula:



and the pharmaceutically acceptable salts thereof.

A β -lactam compound of the formula:

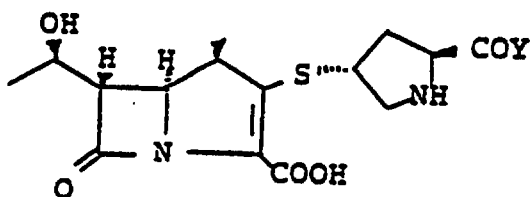


and the pharmaceutically acceptable salts thereof.

. A β -lactam compound of the formula:

5

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wherein Y is chosen from the group consisting of

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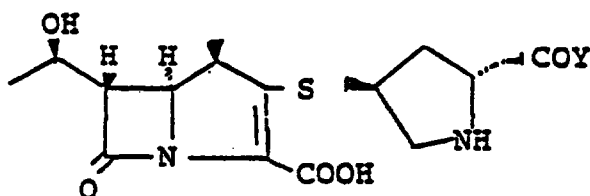
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and the pharmaceutically acceptable salts thereof.

. A β -lactam compound of the formula:

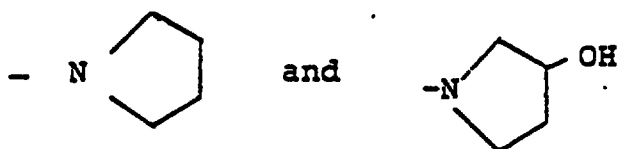
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wherein Y is chosen from the group consisting of

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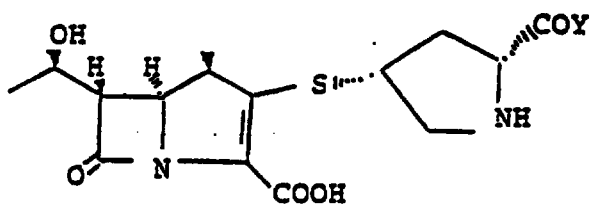
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and the pharmaceutically acceptable salts thereof.

. A β -lactam compound of the formula:

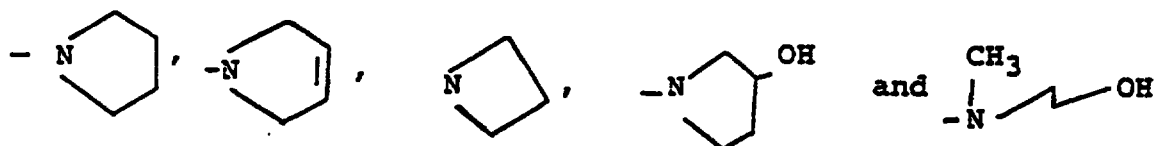
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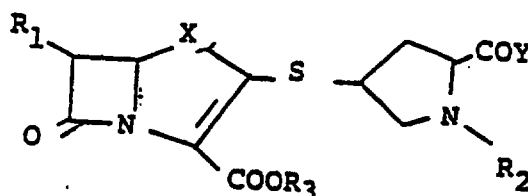
wherein Y is selected from the group consisting of

55



and the pharmaceutically acceptable salts thereof.

A β -lactam compound represented by the formula:



20 wherein R_1 represents a 1-hydroxyethyl group or a 1-hydroxyethyl group in which the hydroxy group is protected with a protecting group for a hydroxy group; R_2 represents a hydrogen atom or a protecting group for an amino group; R_3 represents a hydrogen atom or a protecting group for a carboxyl group; X represents a sulfur atom; and Y represents a group of the formula (2):



35 wherein R_5 and R_6 , which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a substituted alkyl group having 1 to 5 carbon atoms wherein said substituent is selected from the group consisting of hydroxyl, di-(C_1 - C_3)-alkylamino, carbamoyl, mono- or di-(C_1 - C_3)-alkyl-substituted aminocarbonyl and protected or unprotected carboxyl or a pyridyl group, or R_5 and R_6 taken together represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1 - C_3)-alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof, wherein said substituent is selected from the group consisting of C_1 - C_3 alkyl, carbamoyl, mono- or di-(C_1 - C_3)-alkyl-substituted aminocarbonyl and hydroxyl, or a group of the formula (4):

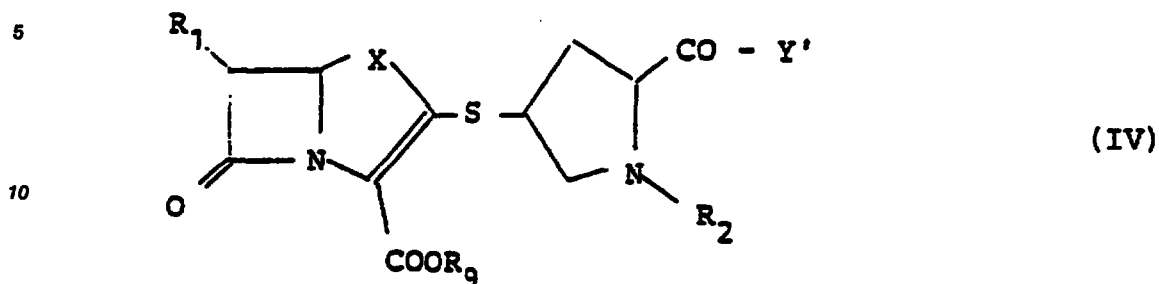


wherein R_8 represents a hydrogen atom, a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms, and a pharmaceutically acceptable salt thereof.

50 The β -lactam compounds represented by the formula (I) according to the present invention are novel compounds which are carbapenem (i.e., 1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid) derivatives or penem (i.e., 1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid) derivatives.

A process for producing the compounds of the formula (I) according to the present invention will be described below.

Of the β -lactam compounds of the formula (I), compounds represented by the formula (IV):

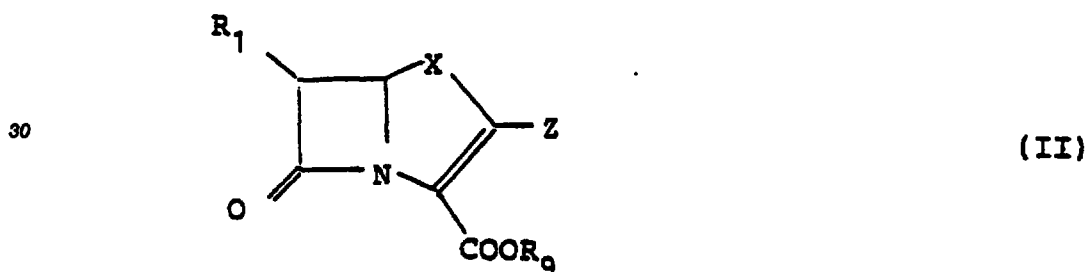


15 wherein R_1 , R_2 and X are as defined above; R_9 represents a protecting group for a carboxyl group; and Y' represents the group as represented by the aforesaid formula (2), or a group represented by the formula (4'):

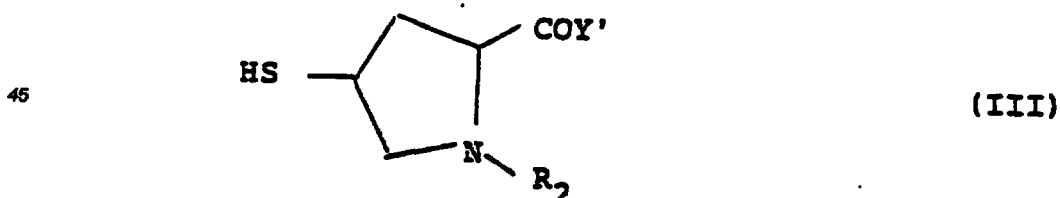


wherein R_8' represents a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms,

can be prepared by reacting a β -lactam derivative represented by the formula (II):



35 wherein R_1 , X and R_9 are as defined above, and Z represents a reactive ester group of an alcohol or a substituted or unsubstituted lower alkylsulfinyl group, with a mercaptan derivative represented by the formula (III):



50 wherein R_2 and Y' are as defined above, in an inert solvent in the presence of a base.

The term "reactive ester group of an alcohol" herein used means a group derived from a substituted or unsubstituted arylsulfonate, lower alkanesulfonate, halogeno-lower alkanesulfonate or diarylphosphoric acid ester or a halide, i.e., an ester with a hydrogen halide, of the alcohol represented by the formula (II). The substituted or unsubstituted arylsulfonate includes, for example, a benzenesulfonate, a *p*-toluenesulfonate, a *p*-nitrobenzenesulfonate or a *p*-bromobenzenesulfonate. The lower alkanesulfonate includes, for example, a methanesulfonate or an ethanesulfonate. The halogeno-lower alkanesulfonate includes, for example, a

trifluoromethanesulfonate. The diarylphosphoric acid ester includes, for example, a diphenylphosphoric acid ester. The halide includes, for example, a chloride, a bromide or an iodide. Of these reactive esters of an alcohol, preferred examples are a *p*-toluenesulfonate, a methanesulfonate and a diphenylphosphoric acid ester.

Further, in the substituted or unsubstituted lower alkylsulfinyl group, the lower alkyl group preferably includes a straight chain or branched chain alkyl group having 1 to 4 carbon atoms. The substituent for the substituted lower alkyl group can include a hydroxyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkoxy-carbonyloxy group having 2 to 5 carbon atoms, a lower alkanoyloxy group having 2 to 5 carbon atoms, an amino group, a mono- or di-lower alkylamino group, a lower alkanoylamino group having 2 to 5 carbon atoms, a lower alkoxy-carbonylamino group having 2 to 5 carbon atoms, an aralkyloxy-carbonyloxy group or an aralkyloxy-carbonylamino group.

The protecting group for a carboxyl group as represented by R_3 corresponds to the protecting group as represented by R_3 , and the same preferred groups as enumerated for R_3 can also be applied to R_3 .

Examples of the inert solvent which can be used in the above-described reaction are dioxane, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, acetonitrile, hexamethylphosphoramide and mixtures thereof, with acetonitrile and dimethylformamide being preferred.

The base also used in the reaction includes various organic or inorganic bases, such as sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, potassium *t*-butoxide, pyridine, various lutidines, 4-dimethylaminopyridine, triethylamine, diisopropylethylamine and the like, with the organic bases, e.g., diisopropylethylamine being preferred.

The amount of the base to be used should be enough for the reaction to sufficiently proceed and usually ranges from 1 to 2 equivalents per mole of the mercaptan derivative of the formula (III).

The mercaptan derivative (III) is used in an amount enough for the reaction to sufficiently proceed. It may be used in a large excess but usually in an amount of from 1 to 2 equivalents based on the compound of the formula (II).

The reaction can be carried out at a temperature ranging from about -78°C to 60°C , preferably from -40°C to 40°C .

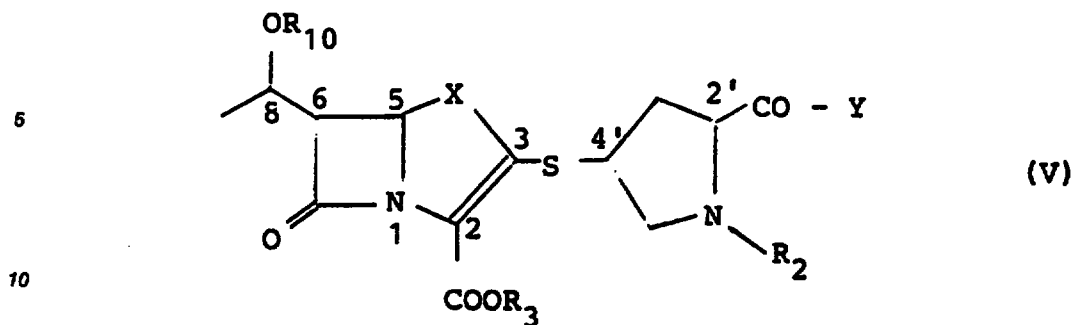
After completion of the reaction, the reaction product can be isolated by usual organochemical means.

Then, the thus obtained compound represented by the formula (IV) can be subjected, if necessary, to a reaction for removal of the hydroxyl-protecting group when R_1 contains a protected hydroxyl group, a reaction for removal of the amino-protecting group, a reaction for removal of the carboxyl-protecting group R_3 , a reaction for removal of the protecting group on Y' , or an appropriate combination thereof, thereby to obtain the β -lactam compound represented by the formula (I).

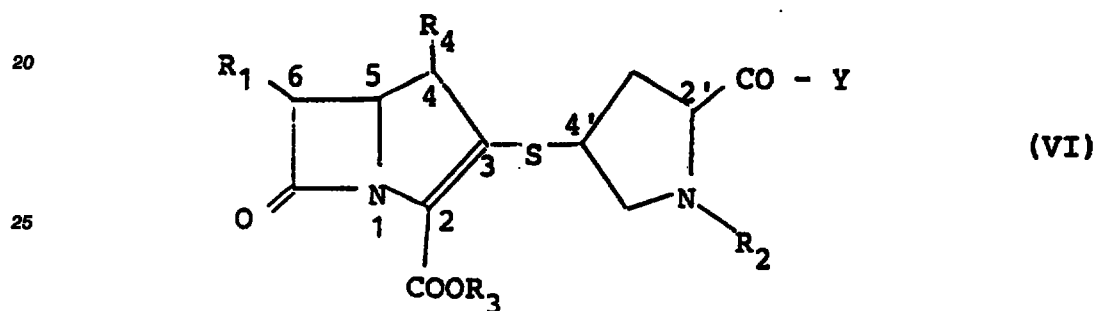
The reactions for removal of the protecting groups can be carried out by generally known methods selected depending on the type of the protecting groups. For example, those compounds of the formula (IV) wherein the hydroxyl-protecting group and/or the amino-protecting group in R_2 is/are a halogenoalkoxycarbonyl group(s) or an aralkyloxy-carbonyl group(s), and those compounds wherein the carboxyl-protecting group is a halogenoalkyl group, an aralkyl group or a benzhydryl group can be subjected to an appropriate reduction reaction to remove these protecting groups. Such reduction is preferably carried out by using an organic solvent, such as acetic acid, tetrahydrofuran or methanol and zinc in case when the protecting group to be removed is a halogenoalkoxycarbonyl group or a halogenoalkyl group, or by catalytic reduction using a catalyst, such as platinum or palladium-on-carbon, in case when the protecting group to be removed is an aralkyloxy-carbonyl group, an aralkyl group or a benzhydryl group. Solvents to be used in the catalytic reduction suitably include organic solvents, such as lower alcohols, e.g., methanol or ethanol; ethers, e.g., tetrahydrofuran or dioxane; and acetic acid, or mixed solvents of these organic solvents and water or buffer solutions, such as phosphoric acid, morpholinopropanesulfonic acid. The reaction can be conducted at a temperature of from about 0°C to 100°C , preferably 0°C to 40°C , in a hydrogen atmosphere under atmospheric pressure or under pressurized conditions.

In particular, when the protecting group to be removed is an *o*-nitrobenzyl group or an *o*-nitrobenzyloxy-carbonyl group, these groups can also be removed by photo reaction.

In the compounds according to the present invention, the 5- and 6-positions of the compounds of the above-described formula (I), the 8-position of the compounds represented by the formula (V):



15 wherein R_2 , R_3 , X and Y are as defined above, and R_{10} represents a hydrogen atom or a protecting group for a hydroxyl group,
the 4-position of the compounds represented by the formula (VI):



30 wherein R_1 , R_2 , R_3 , R_4 and Y are as defined above, and R_4 is an alkyl group,
and the 2'- and 4'-positions in the 3-side chain of the compounds of the formula (I), (V) and (VI) are all asymmetric carbons to form isomers. Therefore, the compounds represented by these formulae include optical isomers and steric isomers ascribed to these asymmetric carbon atoms. Although all of these isomers are represented by a respective single formula for the sake of convenience, the scope of the
35 present invention is not limited by such a single formula.

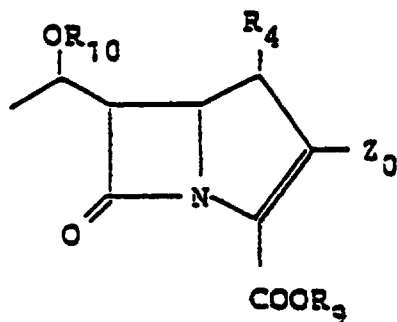
However, preferred isomers can include those having the same relative-configuration as thienamycin at the 5-positioned carbon atom. With respect to the 8-positioned carbon atom of the formula (V), those having an R-configuration are preferred. Further, with respect to the 4-position of the formula (VI), those wherein the lower alkyl group as represented by R_4 is in an R-configuration (i.e., (4R)-compounds) are preferred.

40 In addition, the 2'-substituted pyrrolidin-4'-ylthio group forms four isomers, of which the (2'S,4'S)- and (2'R,4'R)-compounds are preferred.

Particularly preferred compounds include those compounds of the formula (V), wherein X is a sulfur atom or a methylene group, having a (5R,6S,8R,2'S,4'S)-configuration, those compounds of the formula (V), wherein X is an alkylated methylene group having a (5S,6S,8R, 2'S,4'S)-configuration, and those compounds of the formula (VI) wherein R_1 is a 1-hydroxyethyl type substituent and R_4 is a lower alkyl group, having a (4R,5S,6S,8R,2'S,4'S)-configuration.

The isomers having the above-described steric configurations can be obtained by using the starting compounds of the formula (II) and/or (III) having the corresponding configurations.

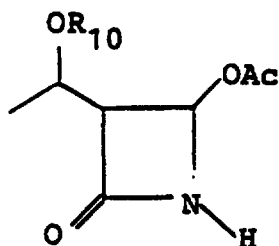
45 The starting compounds (II) can be prepared according to various known methods. For example, the
50 compounds represented by the formula (VII):



(VII)

wherein R₄, R₉ and R₁₀ are as defined above, and Z₀ represents a reactive ester group of an alcohol, and also wherein R₄ is a hydrogen atom are known *per se* in (1) Japanese Patent Application OPI (Open to Public Inspection) No. 27169/80, (2) J. Am. Chem. Soc., Vol. 103, 6765-6767 (1981) and (3) J. Chem. Soc., Perkin I, 964-968 (1981) and the compounds (VII) can be obtained according to the methods described in the above-described literatures (1) to (3).

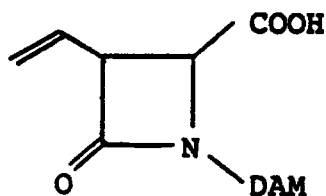
Further, the compounds (VII) can also be synthesized in accordance with the methods described in the above-described literatures (1) to (3) starting with compounds represented by the formula (a):



(a)

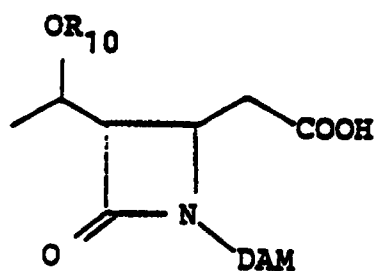
wherein R₁₀ is as defined above, and Ac represents an acetyl group, which can be obtained by the method described in Tetrahedron Letters, 2293-2296 (1982) or the method described in EPC Publication No. 70204.

Furthermore, the compounds (VII) can also be obtained by subjecting a compound represented by the formula (b):



(b)

wherein DAM represents a di-p-anisylmethyl group, which is obtained by the method disclosed in EPC Publication No. 70204 to a carbon-increasing reaction such as Arndt-Eistert reaction or the like and then to an oxymercuration reaction or the like according to the method of EPC Publication No. 70204, thereby converting the ethenyl group into a 1-hydroxyethyl group, subjecting the resulting product, if necessary, to an appropriate combination of a reaction for protecting or deprotecting the carboxyl group and a reaction for protecting the hydroxyl group to obtain a compound represented by the formula (c):



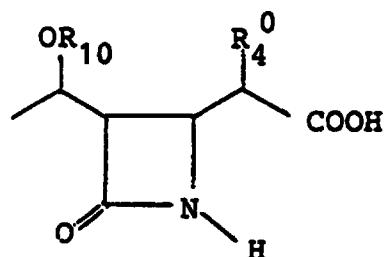
(c)

wherein R₁₀ and DAM are as defined above,
and then obtaining the compound (VII) from the compound (c) in accordance with the method described in Japanese Patent Application OPI No. 167964/82.

The DAM group on the nitrogen atom in the compound (c) can be removed by reacting with ceric ammonium nitrate in an inert solvent such as acetonitrile-water at 10 to 30°C. In this case, this reaction may be combined with a reaction for protecting or deprotecting the carboxyl group and/or a reaction for protecting the hydroxyl group, if necessary.

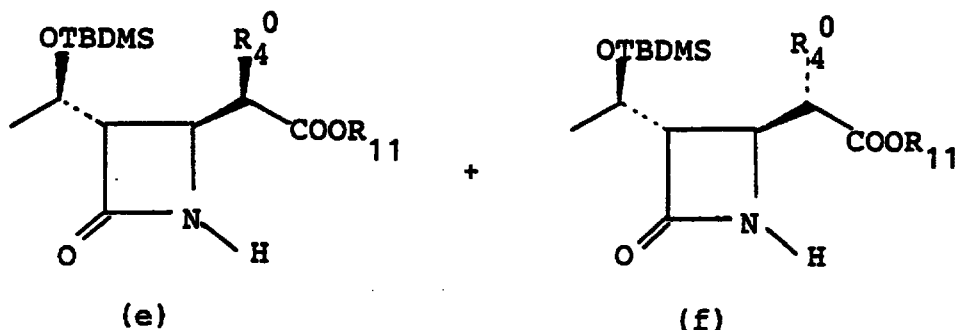
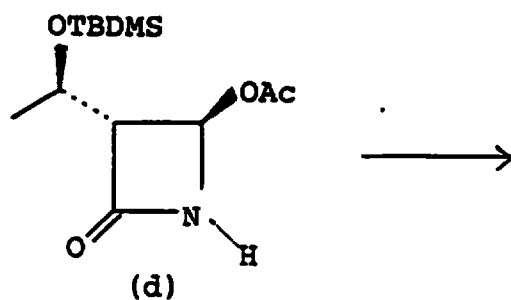
Further, the compound of the formula (VII) wherein R₄ is an alkyl group can be prepared by, for example, the known method as disclosed in Japanese Patent Application OPI No. 26887/83 or analogous methods thereof.

Compounds of the formula (VIII):



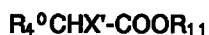
(VIII)

wherein R₁₀ is as defined above and R₄⁰ represents an alkyl group having 1 to 3 carbon atoms, which can be used as a starting material for preparing the compound (VII) wherein R₄ is an alkyl group, can be produced, for example, according to the following reaction scheme:



wherein R_4^0 is as defined above; R_{11} represents a protecting group for a carboxyl group; and TBDMS represents a t-butyldimethylsilyl group.

The compounds of the formulae (e) and (f) can be obtained as an isomeric mixture by a method described in Japanese Patent Application OPI No. 73656/80 which comprises reacting (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone of the formula (d) disclosed in Chem. Pharm. Bull., Vol. 29, 2899-2909 (1981) with a halogenofatty acid ester represented by the formula:

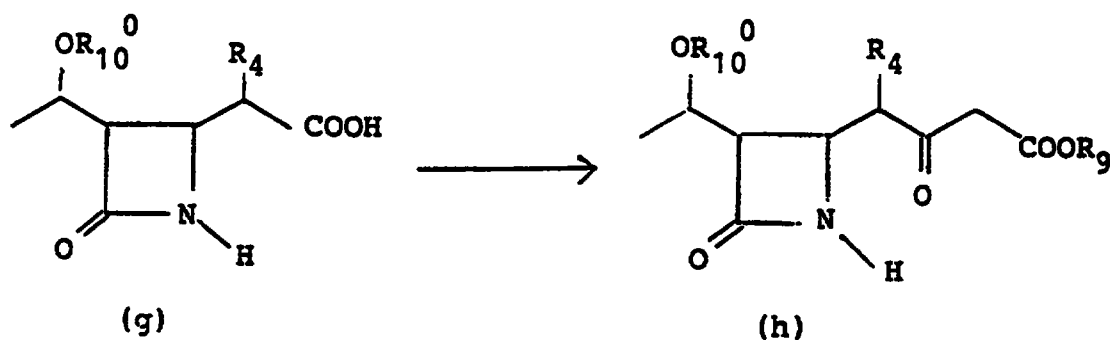


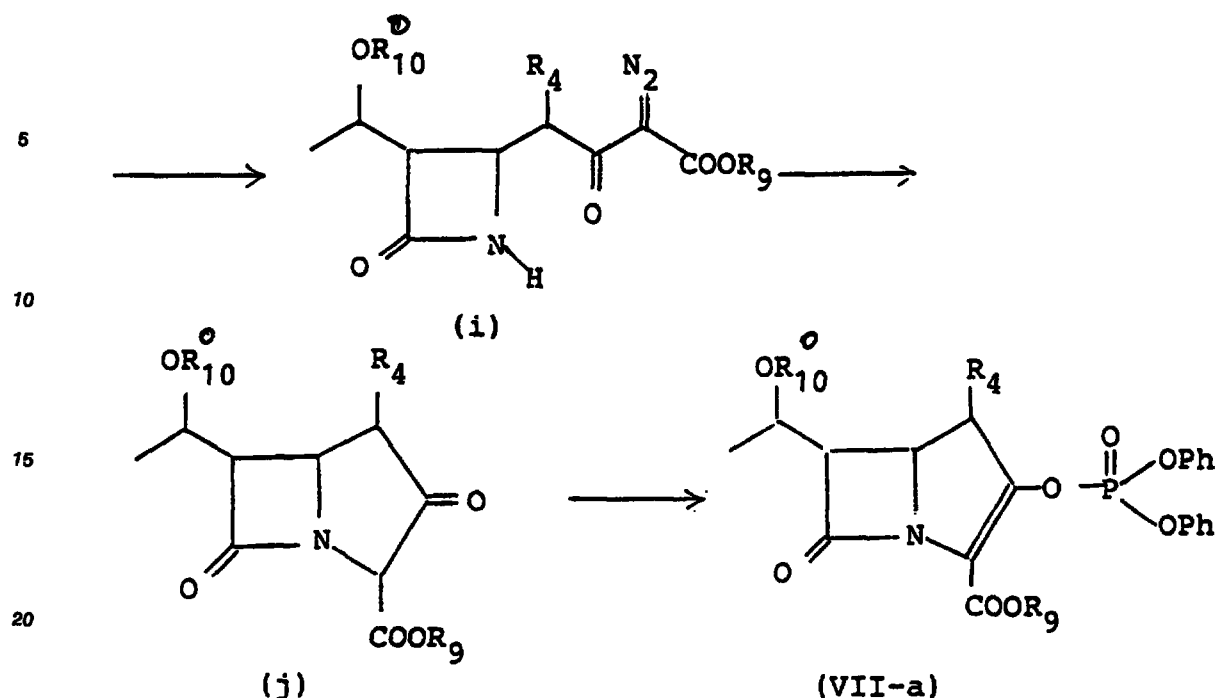
wherein R_4^0 and R_{11} are as defined above, and X' represents a halogen atom, in a solvent, such as an ether (e.g., tetrahydrofuran, dioxane or diethyl ether), an aromatic hydrocarbon (e.g., benzene or toluene), and the like, or a mixed solvent of these solvents and hexane in the presence of diethylaluminium chloride and zinc.

Separation and purification of the isomers (e) and (f) can be carried out by silica gel column chromatography.

The compounds (e) and (f) can be led to the compound (VIII) by appropriately combining reactions for protecting or deprotecting the hydroxyl group, the carboxyl group or the nitrogen atom.

One example for the production of the starting compound (VII) will be illustrated in the following reaction scheme:





25 wherein R_4 , R_9 and R_{10} are as defined above; R_{10}^0 represents a protecting group for a hydroxyl group; and Ph represents a phenyl group.

More specifically, the compound (g) obtainable by the aforesaid methods can be led to the compound (h) through the reaction described in Japanese Patent Application OPI No. 167964/82 or Heterocycles, Vol. 14, 1305-1306 (1980).

30 The compound (h) is then reacted with a diazotizing agent, e.g., carboxybenzenesulfonazide, in the presence of a base to obtain the compound (i) as disclosed in Tetrahedron Letters, 31-34 (1980).

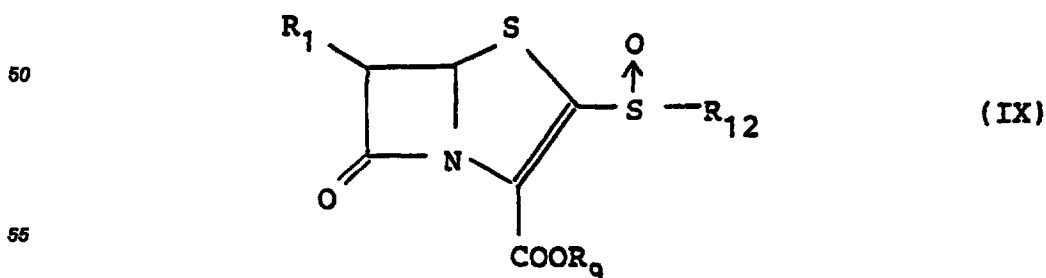
The compound (i) is then subjected to cyclization in the presence of a metal salt catalyst, e.g., dirhodium tetrakisacetate, or to photo reaction to obtain the compound (j).

35 Finally, the compound (j) is reacted with diphenyl-phosphoryl chloride in an inert solvent in the presence of a base such as diisopropyl ethyl amine or 4-dimethylaminopyridine to obtain the compound of the formula (VII-a).

In general, the starting compound (VII-a) as prepared from the compound (j) is subsequently subjected to the reaction with various mercaptans without being isolated to produce carbapenem derivatives, but the starting compound (VII-a) may also be once isolated from the reaction mixture and then reacted with the mercaptan derivative (III) to obtain the desired compound of the formula (IV).

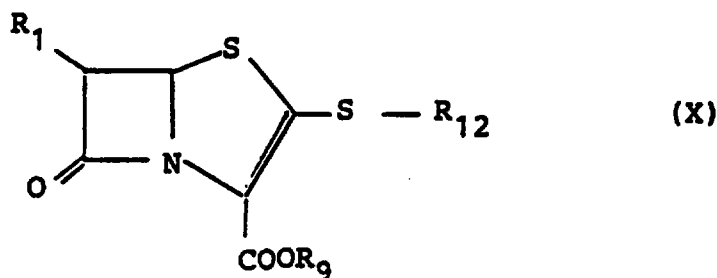
Optically active reactive esters, for example, the compound (VII-a), can be obtained in the same manner as described above but starting with the β -lactam derivative (g) having the corresponding steric configuration.

45 Further, of the above-described compounds of the formula (II), the compounds, for example, of the compound (IX):



wherein R_1 and R_9 are as defined above, and R_{12} represents a substituted or unsubstituted lower alkyl group,

can be prepared by subjecting a compound of the formula (X):

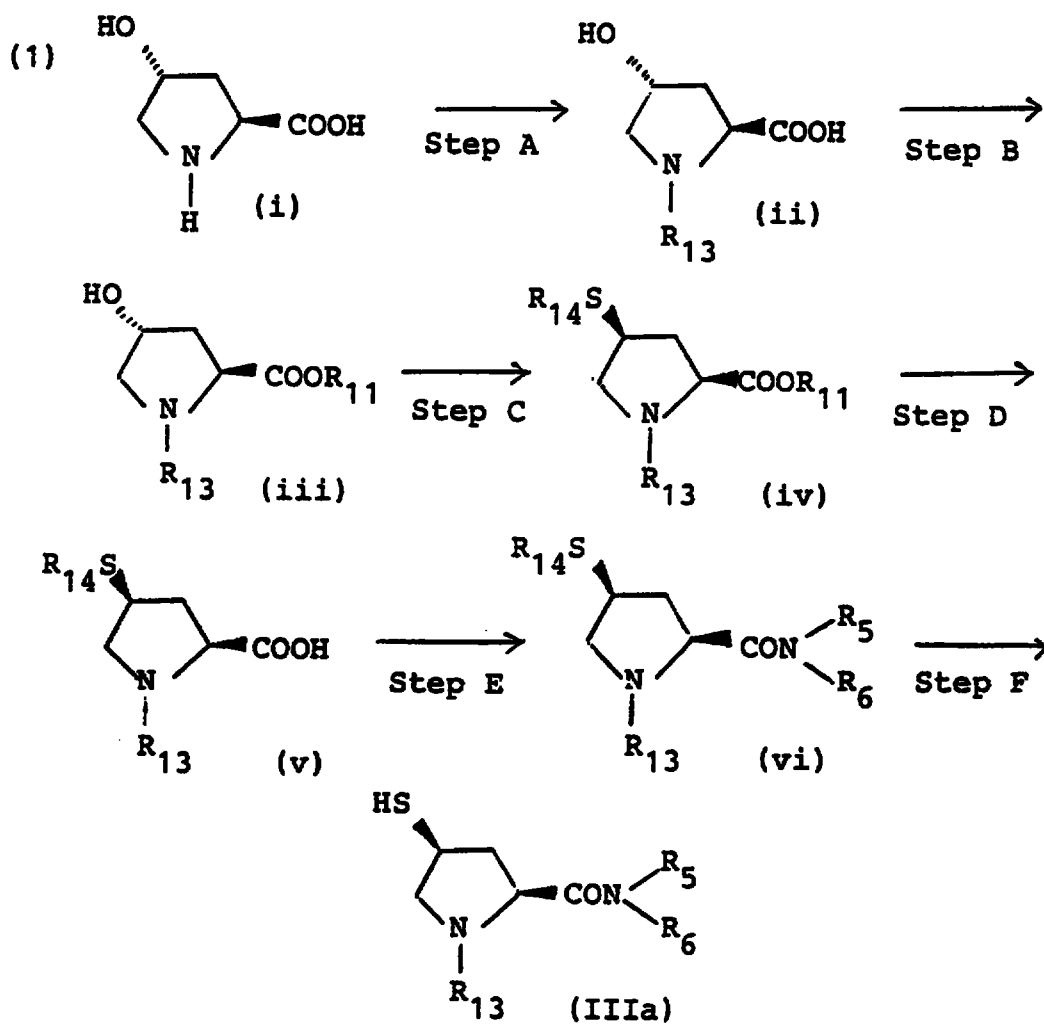


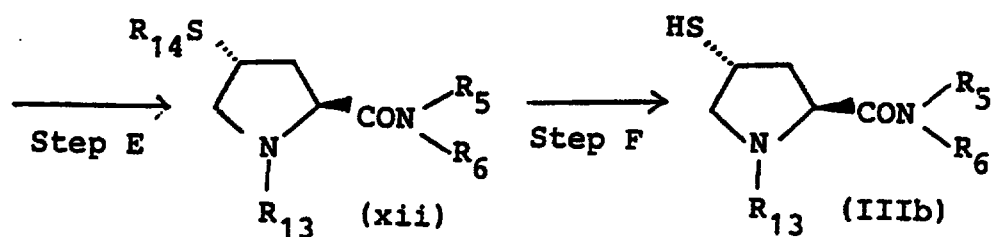
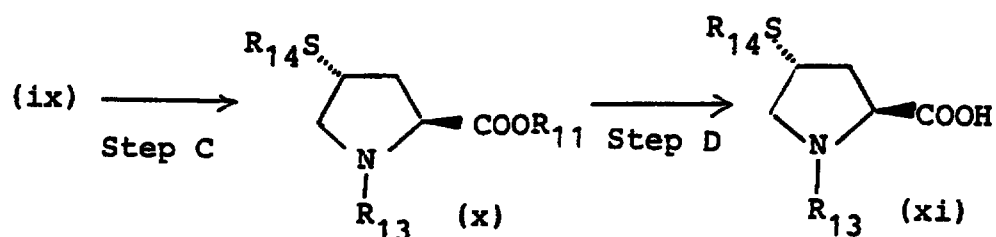
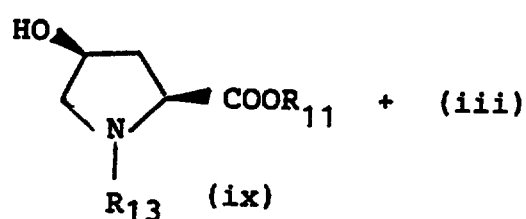
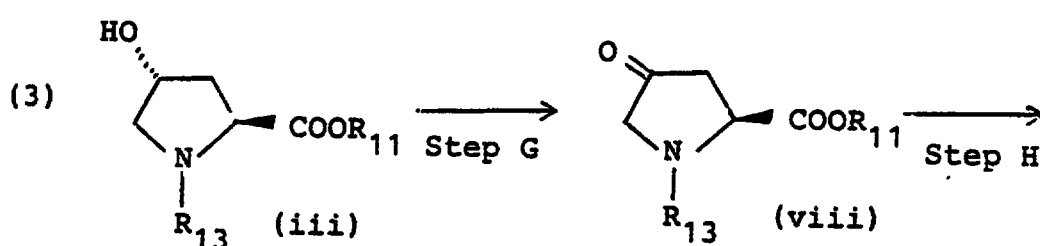
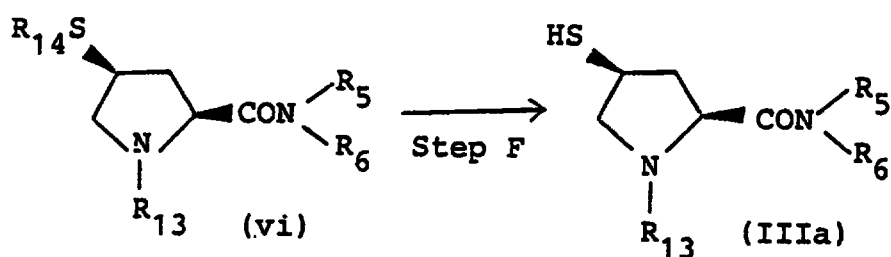
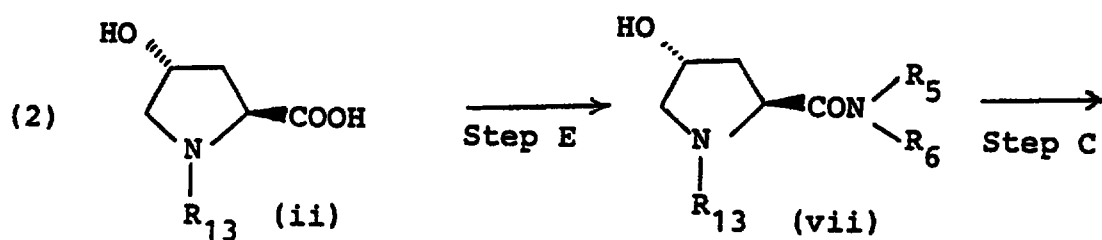
wherein R_1 , R_9 and R_{12} are as defined above,

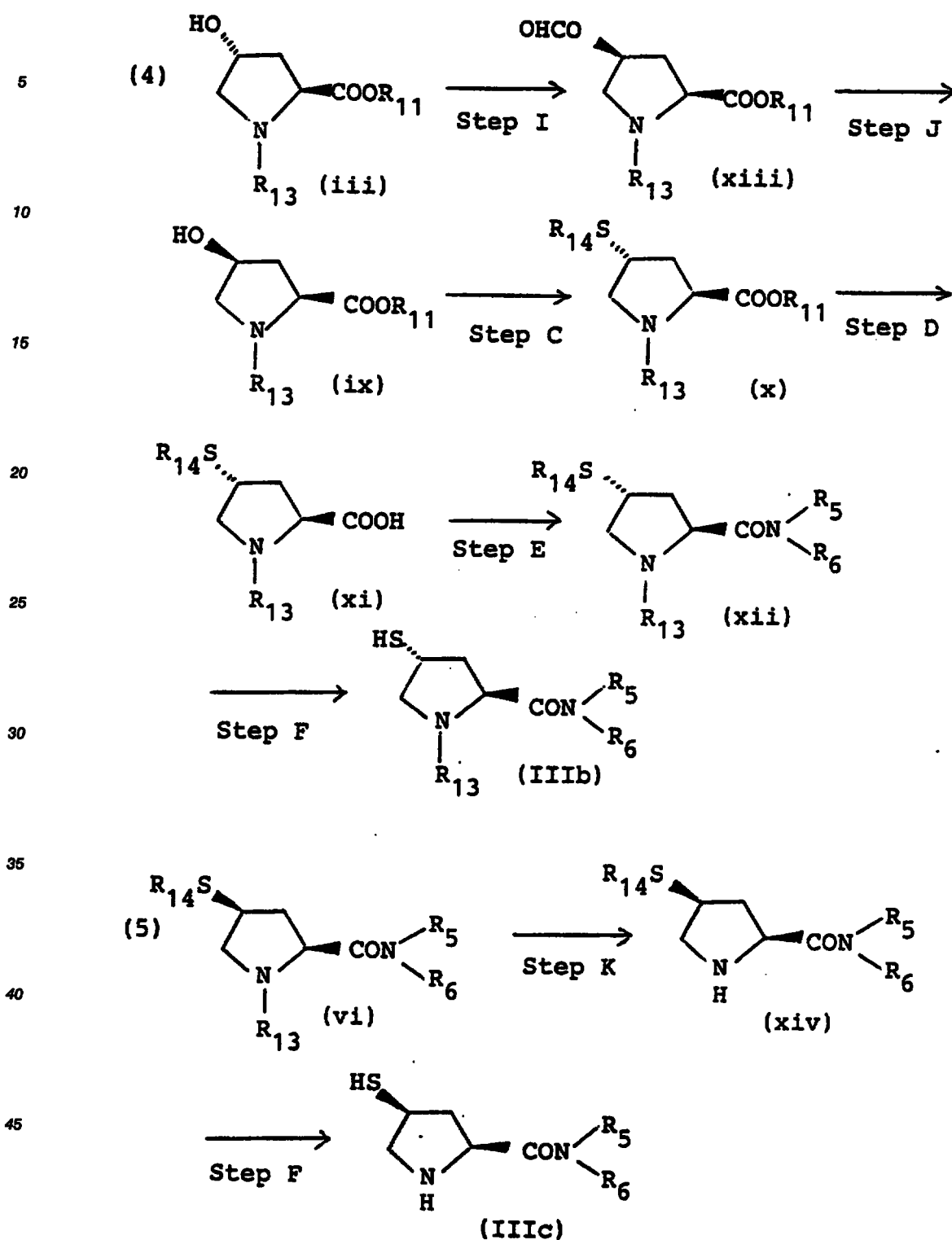
to S-oxidation using a mild oxidizing agent. The mild oxidizing agent includes perbenzoic acid, *m*-chloroperbenzoic acid, hydrogen peroxide, selenium dioxide, sodium *m*-periodate and the like, with substituted perbenzoic acids, e.g., *m*-chloroperbenzoic acid being preferred.

The starting compound represented by the formula (X) can be prepared by various methods already reported, for example, the methods as disclosed in Japanese Patent Applications OPI Nos. 9034/80, 105686/80 and 81591/81.

On the other hand, the starting mercaptan derivative of the formula (III) can be prepared by various methods. For example, mercaptan derivatives (IIIa), (IIIb) and (IIIc) having a 2'S-configuration can be obtained from *trans*-4-hydroxy-L-proline (i) in accordance with the reaction scheme shown below:







In the above formulae, R_5 , R_6 and R_{11} are as defined above; R_{13} represents a protecting group for an amino group; and R_{14} represents a protecting group for a thiol group.

55 Step A:

The reaction can easily be accomplished by various known methods generally employed for protecting an amino group of amino acids, for example, a method comprising reacting with an arylmethoxycarbonyl

chloride in the presence of a base, a method comprising using an S-acyl-4,6-dimethyl-2-mercapto-
pyrimidine and the like.

Step B:

The reaction can be carried out by various methods for obtaining esters from carboxylic acids, for
example, by reacting the carboxylic acid (ii) with various alkyl halides or aralkyl halides in the presence of a
base.

Step C:

The reaction can be accomplished by various known methods for converting a hydroxyl group into a
protected thiol group, for example, by a method comprising converting the carboxylic acid ester (iii) into an
active ester of a hydroxyl group and then reacting with various thionizing reagents, e.g., thioacetic acid,
thiobenzoic acid or tritylmercaptan in the presence of a base.

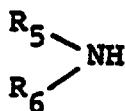
This step may also be conducted by reacting the alcohol derivative with a thionizing reagent, e.g.,
thioacetic acid in an inert solvent, e.g., tetrahydrofuran in the presence of triphenylphosphine and diethyl
azodicarboxylate.

Step D:

This step can be carried out by various known methods for converting an ester group into a carboxyl
group, for example, alkali-hydrolysis, a method of using trifluoroacetic acid or hydrobromic acid or a
reductive method of using zinc.

Step E:

The reaction can be achieved by various known methods for converting a carboxyl group to an amido
group, for example, by a method comprising reaction with a halogenating agent, an acylating agent to form
an active ester derivative and then treating the resulting ester with an amine represented by the formula:



wherein R₅ and R₆ are as defined above.

Step F:

The thiol-protecting group can be removed by various known methods for deprotection. For example,
an acyl group as the thiol-protecting group can be removed by alkali-hydrolysis or the like.

Step G:

The reaction can be accomplished by various known oxidation methods for converting a hydroxyl group
into a carbonyl group, for example, an oxidation reaction using chromic acid-sulfuric acid in acetone.

Step H:

The step can be conducted by various known reduction reactions for converting a carbonyl group to a
hydroxyl group. For example, treatment with sodium borohydride gives a mixture of the compound (iii) and
the compound (ix) having different steric configurations at the hydroxyl group. The production proportion of
(iii) and (ix) varies depending on reaction conditions, but each compound can be isolated as a single
compound by purification procedures, such as recrystallization, chromatography or the like.

Isomerization of the 4-hydroxyl group can be accomplished through the above-described steps G and
H, and may also be achieved through hereinafter described steps I and J.

Steps I & J:

The alcohol derivative is reacted with formic acid in an inert solvent, e.g., tetrahydrofuran in the presence of triphenylphosphine and diethyl azodicarboxylate to form a formyloxy derivative (xii), which is then subjected to alkali-hydrolysis to remove the formyl group.

Step K:

This step can be conducted by commonly employed various known methods for deprotecting amino groups, for example, a method of using an acid, e.g., trifluoroacetic acid or hydrobromic acid, a reducing method of using zinc or lithium-liquid ammonia or a catalytically reducing method.

The starting mercaptan derivatives (III) to be used for the production of the β -lactam compounds (I) wherein Y is a protected or unprotected hydroxyl group or an alkoxy group having 1 to 3 carbon atoms can be obtained by subjecting the compound (iv) or (x) to Step F.

The 2'R-mercaptan (III) can be prepared by using cis-4-hydroxy-D-proline as a starting compound in accordance with the above-described method for producing 2'S-compounds, i.e., by combining various reactions described in the production of the 2'S-compounds.

Of the novel β -lactam compounds represented by the formula (I) according to the present invention, those compounds in which R_2 and R_3 are hydrogen atoms exhibit excellent antimicrobial activity against a wide variety of disease-causing bacteria including Gram positive bacteria, such as Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes or Streptococcus faecalis and Gram negative bacteria, such as Escherichia coli, Proteus mirabilis, Serratia marcescens or Pseudomonas aeruginosa and are useful, therefore, as antimicrobial agents. Further, these compounds have a characteristic of exhibiting excellent antimicrobial activity against β -lactamase-producing strains. Other compounds according to the present invention are important intermediates for synthesizing the above-mentioned compounds having antimicrobial activity.

In addition, the compounds according to the present invention are also characterized in general by their high physiochemical stability and excellent water solubility, although varying depending on the respective compound.

The compounds of the present invention can be used as antimicrobial agents for treating bacteria-caused infectious diseases in the form of oral preparations, such as tablets, capsules, powders or syrups or non-oral preparations, such as intravenous injections, intramuscular injections or rectal preparations.

The dosage of the antimicrobial agent varies depending upon the symptoms, ages, body weights, dosage forms, times of doses and the like, but usually ranges from about 100 mg to 3,000 mg per day in a single dose or several divided doses for adults. The above dose level can be increased or decreased according to necessity.

Besides, the antimicrobial agent of the present invention can be administered, if necessary, in combination with dehydrodipeptidase-inhibitors, e.g., sodium Z-7-(L-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxyamido)-2-heptenoate (a series of compounds disclosed in Japanese Patent Application OPI No. 81518/81).

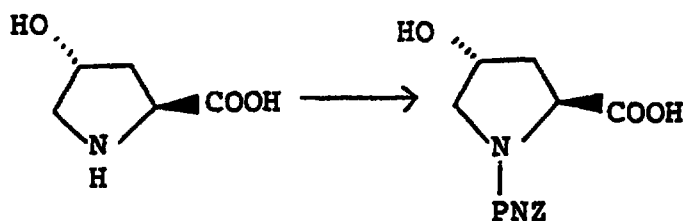
The present invention will now be illustrated in greater detail with reference to the following Reference Examples and Examples, which are given only for illustration.

"Nujol" is a paraffinic solvent.

In Reference Examples and Examples, the following abbreviations are used:

45	DAM:	Di-(p-anisyl)methyl group
	TBDMS:	t-Butyldimethylsilyl group
	PNZ:	p-Nitrobenzyloxycarbonyl group
	PMZ:	p-Methoxybenzyloxycarbonyl group
	PMB:	p-Methoxybenzyl group
50	PNB:	p-Nitrobenzyl group
	Ph :	Phenyl group
	Ac :	Acetyl group
	Ms :	Methanesulfonyl group
	tBu:	t-Butyl group
55	Me :	Methyl group
	Et :	Ethyl group

Reference Example 1-1



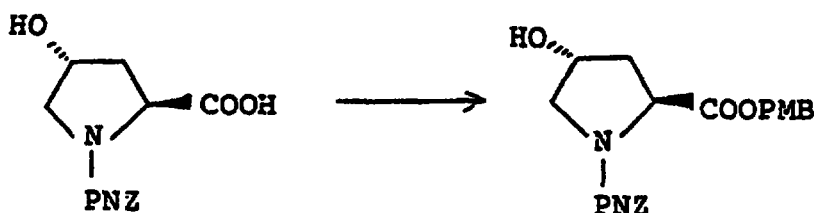
6.55 g of trans-4-hydroxy-L-proline and 7.5 ml of triethylamine were dissolved in 15 ml of water, and a solution of 15.95 g of S-p-nitrobenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine in 35 ml of dioxane was added thereto dropwise. The resulting mixture was stirred at room temperature for 1.5 hours and allowed to stand overnight. To the reaction mixture was added 30 ml of a 2N sodium hydroxide aqueous solution under ice-cooling, and the resulting mixture was extracted with diethyl ether. The ethereal layer was washed with 20 ml of a 1N sodium hydroxide aqueous solution and combined with the alkaline aqueous layer. The combined mixture was made acidic with 100 ml of a 2N hydrochloric acid aqueous solution and extracted with ethyl acetate. The ethyl acetate layer was washed with a 2N aqueous solution of hydrochloric acid, dried over sodium sulfate and distilled off to remove the solvent. The resulting crude crystals were washed with warm ethyl acetate to obtain trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline.

Melting Point: 134.3-135.5 °C

IR_{max}^{Nujol} (cm⁻¹):

3300 (br.), 1738, 1660, 1605, 1520, 1340, 1205, 1172, 1070, 965

Reference Example 1-2



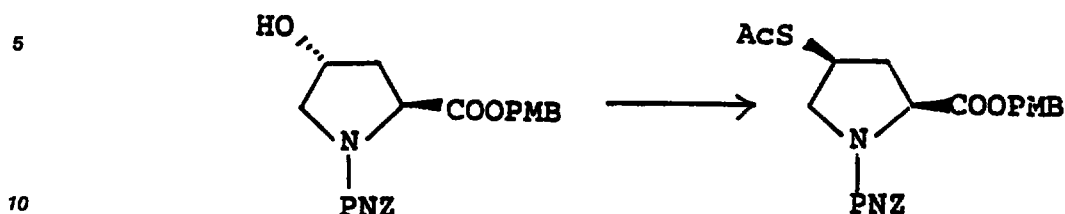
15.0 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline and 13.5 ml of triethylamine were dissolved in 150 ml of dried dimethylformamide, and 12.66 ml of p-methoxybenzyl chloride was added dropwise to the solution under a nitrogen stream, followed by stirring at 70 °C for 10 hours. The reaction mixture was diluted with 500 ml of ethyl acetate, washed with water, dried over sodium sulfate and distilled off to remove the solvent. Recrystallization of the residue from diethyl ether gave trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline-p-methoxybenzyl ester.

Melting Point: 83-85 °C

IR_{max}^{neat} (cm⁻¹):

3430, 1735, 1705, 1510, 1340, 1245, 1160

Reference Example 1-3



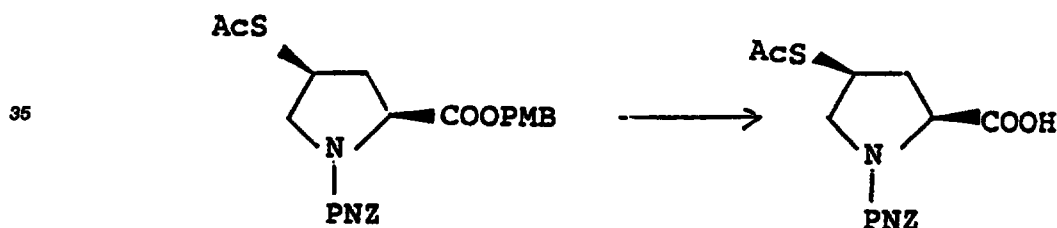
8.6 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline-p-methoxybenzyl ester and 7.86 g of triphenylphosphine were dissolved in 20 ml of dried tetrahydrofuran. To the resulting solution was added dropwise a solution of 5.22 g of diethyl azodicarboxylate in 5 ml of dried tetrahydrofuran under ice-cooling in a nitrogen stream, followed by stirring for 30 minutes at that temperature. Thereafter, 2.28 g of thioacetic acid was added thereto dropwise, and the mixture was stirred for 1 hour under ice-cooling and then at room temperature for 3 hours, followed by concentration. The residue was purified by silica gel column chromatography to obtain cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline-p-methoxybenzyl ester.

IR_{max}^{neat} (cm⁻¹) :

1740 (sh.), 1715, 1520, 1405, 1348, 1120

NMR δ (CDCl₃): 2.31 (3H, s), 3.79 (3H, s), 5.10 (2H, s), 5.24 (2H, s), 7.49 (2H, d, J=9.0Hz), 8.18 (2H, d, J=9.0Hz)ppm

Reference Example 1-4



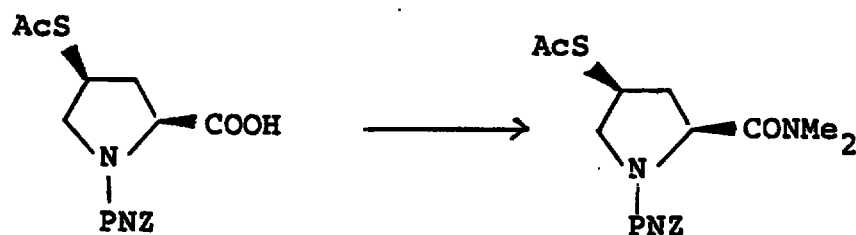
9.76 g of cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline-p-methoxybenzyl ester and 4.32 g of anisole were stirred together with 35 ml of trifluoroacetic acid at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to obtain cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline.

Melting Point : 107-109 °C

IR_{max}^{Nujol} (cm⁻¹) :

1725, 1685, 1660 (sh.), 1340, 1180, 1110

Reference Example 1-5



180 mg of *cis*-1-(*p*-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline was dissolved in 2 ml of dried tetrahydrofuran, and 48 mg of dimethylamine hydrochloride, 78 mg of *N,N*-dimethylaminopyridine and 152 mg of dicyclohexylcarbodiimide were successively added thereto, followed by stirring overnight. After any insoluble matter was removed by filtration, the filtrate was diluted with ethyl acetate, washed successively with dilute hydrochloric acid and water, dried over sodium sulfate and distilled off to remove the solvent. The residue was purified by silica gel chromatography to obtain (2*S*,4*S*)-*cis*-1-(*p*-nitrobenzyloxycarbonyl)-2-dimethylcarbamoyl-4-acetylthiopyrrolidine.

The above prepared compound could also be obtained by the following method:

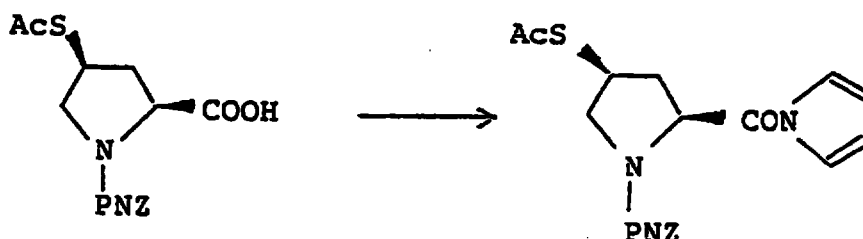
200 mg of the same starting carboxylic acid was dissolved in 1.8 ml of dried methylene chloride, and one drop of dimethylformamide was added thereto. 0.12 ml of oxalyl chloride was then added dropwise thereto under ice-cooling, followed by stirring at room temperature for 1 hour. The solvent was removed by distillation, and the residue was thoroughly dried in vacuo and dissolved in 1 ml of dried tetrahydrofuran. Under ice-cooling, 1.2 ml of a 1M solution of dimethylamine in tetrahydrofuran was added to the reaction mixture, followed by stirring at that temperature for 15 minutes. To the reaction mixture was added ice-water, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with dilute hydrochloric acid and water, dried over sodium sulfate and distilled off to remove the solvent.

$IR_{max}^{neat} (cm^{-1}) :$

1705, 1650, 1515, 1400, 1340, 1105

NMR δ (CDCl₃): 2.32 (3H, s), 2.97 (3H, s), 3.11 (3H, s), 5.21 (2H, s), 8.18 (2H, d, *J* = 8.5 Hz) ppm
 $[\alpha]_D^{20} + 5.21^\circ$ (*c* = 0.379, acetone)

Reference Example 1-6



277 mg of (2*S*,4*S*)-1-(*p*-nitrobenzyloxycarbonyl)-2-hydroxycarbonyl-4-acetylthiopyrrolidine was dissolved in 1.5 ml of dried methylene chloride, and 0.15 ml of oxalyl chloride and a catalytic amount of dimethylformamide were added thereto, followed by stirring at room temperature for 1.5 hours. The reaction mixture was distilled off to remove the solvent, and dried benzene was added to the residue. The benzene was then distilled off to remove any remaining oxalyl chloride. Separately, 51 mg of pyrrole was dissolved in 2 ml of dried tetrahydrofuran, and 0.47 ml of a 1.60 mmol/ml solution of *n*-butyl lithium in hexane was added thereto in a nitrogen stream under ice-cooling, followed by stirring at that temperature for 40 minutes. The

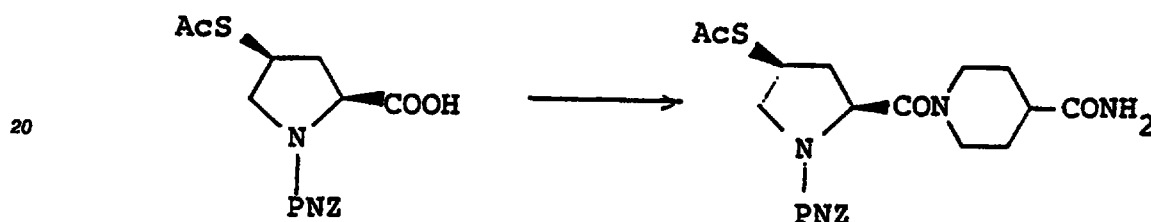
resulting mixture was then added in a nitrogen stream under ice-cooling to a solution of the above-described reaction residue dissolved in 2 ml of dried tetrahydrofuran, followed by stirring for 10 minutes. The resulting reaction mixture was diluted with methylene chloride, washed with water, dried over sodium sulfate and distilled off to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2S, 4S)-1-p-nitrobenzyloxycarbonyl-2-(1-pyrrolyl)carbonyl-4-acetylthiopyrrolidine.

IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm^{-1}):

1710, 1525, 1345, 1278, 1120

NMR δ (CDCl_3): 2.33 (3H, s), 5.23 (2H, s), 6.35 (2H, d, $J=2\text{Hz}$), 7.51 (2H, d, $J=9\text{Hz}$) ppm

Reference Example 1-7



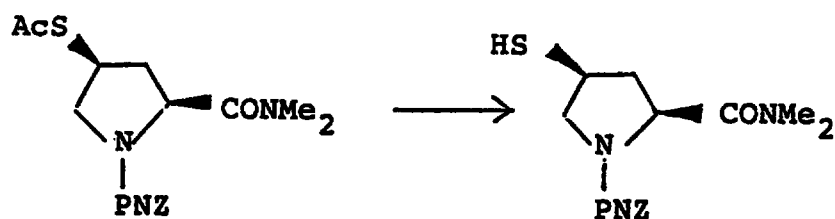
368 mg of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-hydroxycarbonyl-4-acetylthiopyrrolidine was dissolved in 3 ml of dried methylene chloride, and 0.3 ml of oxalyl chloride and a catalytic amount of dimethylformamide were added thereto, followed by stirring at room temperature for 1.5 hours. The reaction mixture was distilled off to remove the solvent, and to the residue was added dried benzene. The benzene was then distilled off to remove any remaining oxalyl chloride. Separately, 128 mg of 4-carbamoylpiperidine was dissolved in 3 ml of dried tetrahydrofuran, and 0.25 ml of bistrimethylsilylacetamide was added to the solution, followed by stirring for 3 hours in a nitrogen stream. Then, 101 mg of triethylamine was added thereto, and to the resulting mixture was added in a nitrogen stream under ice-cooling a solution of the above-obtained reaction residue dissolved in 3 ml of dried tetrahydrofuran, followed by stirring for 15 minutes under ice-cooling. Methylene chloride was added to the resulting reaction mixture. The mixture was washed successively with a sodium chloride aqueous solution, dilute hydrochloric acid, a sodium chloride aqueous solution, a sodium bicarbonate aqueous solution and a sodium chloride aqueous solution, dried over sodium sulfate and distilled off to remove the solvent. The residue was purified by silica gel thin layer chromatography to obtain (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(4-carbamoylpiperidinyl)carbonyl-4-acetylthiopyrrolidine.

IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm^{-1}):

3440, 1695, 1655, 1525, 1350, 1120

NMR δ (CDCl_3): 2.35 (3H, s), 5.21 (2H, s), 5.93 (2H, s), 7.52 (2H, d, $J=9\text{Hz}$), 8.22 (2H, d, $J=9\text{Hz}$) ppm

Reference Example 1-8



40 mg of (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylcarbamoyl-4-acetylthiopyrrolidine was dissolved in 4 ml of methanol, and 0.1 ml of a 1N sodium hydroxide aqueous solution was added thereto, followed by stirring at room temperature for 15 minutes. 0.11 ml of a 1N hydrochloric acid aqueous solution was then added thereto, followed by concentration under reduced pressure. The concentrate was diluted with ethyl acetate, washed with water, dried over sodium sulfate and distilled off to remove the solvent to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylcarbamoyl-4-mercaptopyrrolidine.

$IR_{max}^{neat} \text{ (cm}^{-1}\text{)} :$

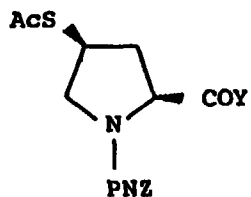
1705, 1650, 1515, 1400, 1340, 1165, 1105

$NMR \delta \text{ (CDCl}_3\text{)} :$ 1.90 (1H, d, $J=8\text{Hz}$), 2.97 (3H, s), 3.08 (3H, s), 5.19 (2H, s), 7.48 (2H, d, $J=9\text{Hz}$), 8.15 (2H, d, $J=9\text{Hz}$) ppm

In the same manner as described in Reference Example 1-5 but using the corresponding amines, the following thioacetate derivatives shown in Table 1 were obtained.

55 50 45 40 35 30 25 20 15 10 5

Table 1



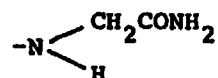
Reference Example No.	Y	Spectral Data
1-9	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1700, 1660(\text{sh}), 1520, 1405, 1345, 1115$
1-10	$\begin{array}{c} \text{CH} \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{H} \end{array} \begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH}_3 \end{array}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 3300, 1695, 1655, 1525, 1415, 1348, 1265, 1105$ $\text{NMR}_{\delta} (\text{CDCl}_3): 1.13(3\text{H}, \text{d}, \text{J}=6\text{Hz}), 1.15(3\text{H}, \text{d}, \text{J}=6\text{Hz}), 2.34(3\text{H}, \text{s}), 5.26(2\text{H}, \text{s}), 7.53(2\text{H}, \text{d}, \text{J}=9\text{Hz}), 8.21(2\text{H}, \text{d}, \text{J}=9\text{Hz})$
1-11	$\begin{array}{c} \text{CH}_2\text{CH}=\text{CH}_2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{H} \end{array}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1700, 1652, 1518, 1400, 1342, 1110$

Reference
Example No.

Y

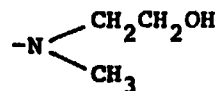
Spectral Data

1-12

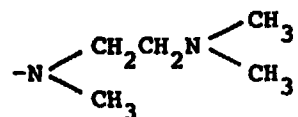

 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 3320, 1680, 1520, 1430, 1405, 1345, 1120$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.32(3\text{H}, \text{s}), 5.17(2\text{H}, \text{br}, \text{s}), 7.43(2\text{H}, \text{d}, J=9\text{Hz})$
 $8.10(2\text{H}, \text{d}, J=9\text{Hz})$

m.p. 163-167°C

1-13


 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 3400(\text{br}), 1685, 1640(\text{sh}), 1517, 1403, 1342, 1212$
 1115
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 2.97(3\text{H}, \text{s}), 5.20(2\text{H}, \text{s}), 7.49(2\text{H}, \text{d}, J=9\text{Hz}), 8.19(2\text{H}, \text{d}, J=9\text{Hz})$

1-14


 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1710, 1660, 1525, 1400, 1345, 1255, 1110$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.28(3\text{H}, \text{s}), 2.30(6\text{H}, \text{s}), 2.50(3\text{H}, \text{s}), 5.17(2\text{H}, \text{s}), 7.42(2\text{H}, \text{d}, J=8.5\text{Hz}), 8.13(2\text{H}, \text{d}, J=8.5\text{Hz})$

65 50 45 40 35 30 25 20 15 10 5

Reference
Example No.

Y

Spectral Data



IR $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹): 3320, 1700, 1650, 1520, 1405, 1345, 1220, 1110

NMR δ (CDCl₃): 2.33(3H, s), 2.93(3H, s), 5.23(2H, s), 7.27(5H, br, s)



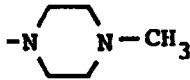
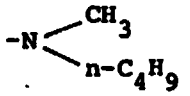
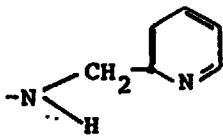
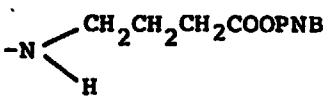
IR $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹): 1710, 1650, 1525, 1425, 1345, 1245, 1025, 962

NMR δ (CDCl₃): 1.58(6H, m), 2.32(3H, s), 5.22(2H, s)



IR $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹): 1710, 1655, 1520, 1430, 1400, 1345, 1115

NMR δ (CDCl₃): 2.31(3H, s), 5.20(2H, s), 7.47(2H, d, J=9Hz), 8.18(2H, d, J=9Hz)

Reference Example No.	Y	Spectral Data
1-18		IR _{max} ^{neat} (cm ⁻¹): 1700, 1650(sh), 1520, 1435, 1340, 1290, 1235, 1110, 1000
1-19		IR _{max} ^{neat} (cm ⁻¹): 1710, 1650, 1520, 1350, 1110 NMR δ (CDCl ₃): 2.33(3H, s), 4.68(1H, t, J=8Hz), 5.19(2H, s), 8.18(2H, d, J=8Hz)
1-20		IR _{max} ^{Nujol} (cm ⁻¹): 3320, 1700, 1660, 1170, 1110 m.p. 147-149°C
1-21		IR _{max} ^{neat} (cm ⁻¹): 1705, 1690, 1520, 1345, 1160, 1110 NMR δ (CDCl ₃): 2.32(3H, s), 5.22(2H, s), 7.50(2H, d, J=8.5Hz), 8.19(2H, d, J=8.5Hz)

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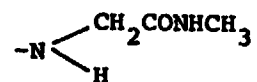
5

Reference
Example No.

Y

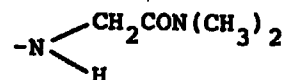
Spectral Data

1-22



IR_{max}^{Nujol} (cm⁻¹): 3310, 1710, 1635, 1520, 1170, 1120
m.p. 200-206°C

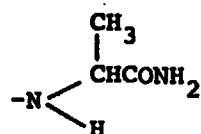
1-23



IR_{max}^{neat} (cm⁻¹): 3400, 1700, 1665, 1525, 1345, 1120

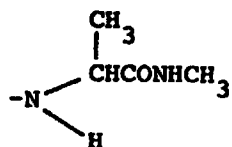
NMR δ (CDCl₃): 2.33(3H, s), 7.50(2H, d, J=9Hz), 8.20(2H, d, J=9Hz)

1-24



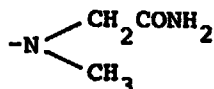
IR_{max}^{Nujol} (cm⁻¹): 3400, 3300, 3220, 1700, 1655, 1180, 1110
m.p. 203-209°C

1-25



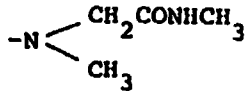
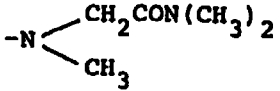
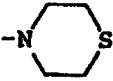
IR_{max}^{Nujol} (cm⁻¹): 3300, 1740, 1700, 1650, 1520, 1180
m.p. 185-188°C

1-26



IR_{max}^{neat} (cm⁻¹): 3350, 3230, 1695, 1525, 1410, 1350

NMR δ (CDCl₃): 2.37(3H, s), 3.23(3H, s), 5.20(2H, s), 7.50(2H, d, J=9Hz), 8.27(2H, d, J=9Hz)

Reference Example No.	Y	Spectral Data
1-27		CHCl_3 $\text{IR}_{\text{max}}^{\nu} (\text{cm}^{-1}): 3350, 1690, 1660, 1520, 1340, 1120$ $\text{NMR}_{\delta} (\text{CDCl}_3): 2.36(3\text{H}, \text{s}), 3.21(2\text{H}, \text{s}), 5.23(2\text{H}, \text{s}), 6.93(1\text{H}, \text{br.s}), 7.50(2\text{H}, \text{d}, J=9\text{Hz}), 8.25(2\text{H}, \text{d}, J=9\text{Hz})$
1-28		CHCl_3 $\text{IR}_{\text{max}}^{\nu} (\text{cm}^{-1}): 1700, 1650, 1520, 1340, 1110$ $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 7.43(2\text{H}, \text{d}, J=8\text{Hz}), 8.20(2\text{H}, \text{d}, J=8\text{Hz})$
1-29		$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1695, 1655, 1525, 1427, 1342, 1250, 1110, 1065, 955$ $\text{NMR}_{\delta} (\text{CDCl}_3): 2.32(3\text{H}, \text{s}), 5.21(2\text{H}, \text{s}), 7.48(2\text{H}, \text{d}, J=8.5\text{Hz}), 8.18(2\text{H}, \text{d}, J=8.5\text{Hz})$

55

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Reference
Example No.

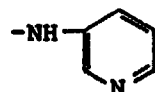
Y

Spectral Data

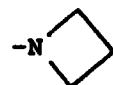
1-30


 CHCl_3
 $\text{IR}_{\text{max}} (\text{cm}^{-1}): 3400, 1700, 1520, 1440, 1345, 1115$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 8.20(2\text{H}, \text{d}, J=9\text{Hz})$
 m.p. 150-151°C

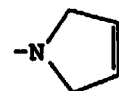
1-31


 CHCl_3
 $\text{IR}_{\text{max}} (\text{cm}^{-1}): 3300, 1700, 1525, 1345, 1120$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 5.25(2\text{H}, \text{s}), 7.47(2\text{H}, \text{d}, J=9\text{Hz}),$
 $8.58(1\text{H}, \text{d}, J=3\text{Hz}), 9.50(1\text{H}, \text{br.s})$

1-32


 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1705, 1655, 1520, 1430, 1400, 1342, 1112$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 5.20(2\text{H}, \text{s}), 7.47(2\text{H}, \text{d}, J=8.5\text{Hz}),$
 $8.17(2\text{H}, \text{d}, J=8.5\text{Hz})$

1-33


 CHCl_3
 $\text{IR}_{\text{max}} (\text{cm}^{-1}): 1705, 1660, 1525, 1345, 1120$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.35(3\text{H}, \text{s}), 5.23(2\text{H}, \text{s}), 7.55(2\text{H}, \text{d}, J=9\text{Hz})$

Reference
Example No.

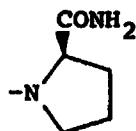
Y

Spectral Data

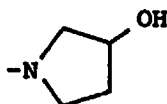
1-34


 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1705, 1640, 1516, 1430, 1400, 1342, 1110$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.31(3\text{H}, \text{s}), 4.03(2\text{H}, \text{dd}, J=6 \text{ and } 8\text{Hz}), 4.53(1\text{H}, \text{t}, J=8\text{Hz}), 5.19(2\text{H}, \text{s}), 7.48(2\text{H}, \text{d}, J=9\text{Hz}), 8.18(2\text{H}, \text{d}, J=9\text{Hz})$

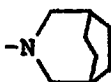
1-35


 $\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}): 3430, 1700, 1640, 1345, 1245, 1120$
 m.p. 173-175°C

1-36


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 3400, 1700, 1650, 1525, 1345, 1120$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 5.17(2\text{H}, \text{s}), 7.47(2\text{H}, \text{d}, J=9\text{Hz}), 8.18(2\text{H}, \text{d}, J=9\text{Hz})$

1-37


 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1700, 1640, 1520, 1400, 1335, 1100$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 5.22(2\text{H}, \text{s}), 7.50(2\text{H}, \text{d}, J=9\text{Hz}), 8.20(2\text{H}, \text{d}, J=9\text{Hz})$

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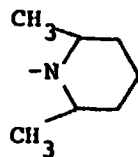
5

Reference
Example No.

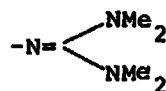
Y

Spectral Data

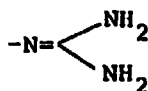
1-38


 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1710, 1640, 1525, 1345, 1120$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.35(3\text{H}, \text{s}), 5.25(2\text{H}, \text{s}), 7.53(2\text{H}, \text{d}, J=9\text{Hz}), 8.23(2\text{H}, \text{d}, J=9\text{Hz})$

1-39


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 1700, 1610, 1520, 1400, 1350, 1110$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 2.87(6\text{H}, \text{s}), 2.95(6\text{H}, \text{s}), 5.25(2\text{H}, \text{s}), 7.56(2\text{H}, \text{d}, J=9\text{Hz}), 8.22(2\text{H}, \text{d}, J=9\text{Hz})$

1-40


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 3350, 1705, 1610, 1525, 1345, 1120$
 $\text{NMR}_{\delta} (\text{CDCl}_3): 2.33(3\text{H}, \text{s}), 5.23(2\text{H}, \text{s}), 8.15(2\text{H}, \text{d}, J=8\text{Hz})$

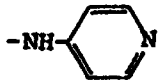
1-41


 $\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}): 1750, 1705, 1690, 1523, 1441, 1352, 1226, 1170, 1114$
 m.p. 92-93.5°C

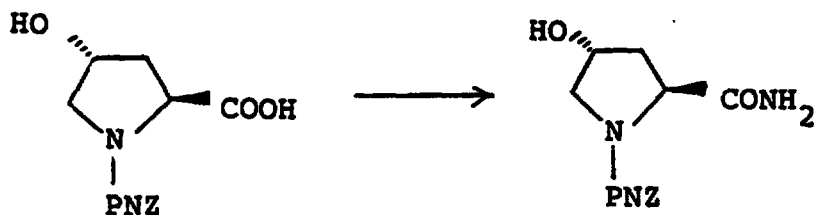
EP 0 126 587 B1

Reference Example No.	Y	Spectral Data
1-42	$-\text{OC}_2\text{H}_5$	IR _{max} ^{Nujol} (cm^{-1}): 1748, 1712, 1692, 1524, 1440, 1348, 1223, 1200 m.p. 80-81.5°C
1-43	$-\text{NHNH}_2$	IR _{max} ^{Nujol} (cm^{-1}): 3200, 1720, 1615, 1520, 1350, 1125 m.p. 208-213°C
1-44	$-\text{NHN}(\text{CH}_3)_2$	IR _{max} ^{Nujol} (cm^{-1}): 3200, 1710, 1660, 1520, 1340, 1175 m.p. 158-159°C
1-45	$-\text{N} \begin{array}{l} \text{CH}_3 \\ \text{N}(\text{CH}_3)_2 \end{array}$	IR _{max} ^{neat} (cm^{-1}): 1715, 1670, 1520, 1340, 1110 NMR δ (CDCl_3): 2.32(3H, s), 5.18(2H, s)
1-46	$-\text{NHOPNB}$	IR _{max} ^{Nujol} (cm^{-1}): 3200, 1730, 1700, 1680, 1520, 1340, 1120 m.p. 166-167°C
1-47	$-\text{NHOC}_2\text{H}_5$	IR _{max} ^{Nujol} (cm^{-1}): 3240, 1705, 1690, 1520, 1340, 1175 m.p. 178-179°C

55 50 45 40 35 30 25 20 15 10 5

Reference Example No.	Y	Spectral Data
1-48		$\text{IR}_{\text{vmax}}^{\text{neat}} (\text{cm}^{-1}): 1695, 1595, 1520, 1340, 1180, 1110$ $\text{NMR}_{\delta} (\text{CDCl}_3): 2.34(3\text{H}, \text{s}), 5.31(2\text{H}, \text{s}), 7.42(2\text{H}, \text{d}, J=6\text{Hz}), 8.48(2\text{H}, \text{d}, J=6\text{Hz})$
1-49		$\text{IR}_{\text{vmax}}^{\text{neat}} (\text{cm}^{-1}): 1695, 1600, 1520, 1340, 1110$ $\text{NMR}_{\delta} (\text{CDCl}_3): 2.34(4\text{H}, \text{s}), 2.39(3\text{H}, \text{s}), 5.18(2\text{H}, \text{s}), 7.48(2\text{H}, \text{d}, J=8.5\text{Hz}), 8.21(2\text{H}, \text{d}, J=8.5\text{Hz})$

Reference Example 2-1



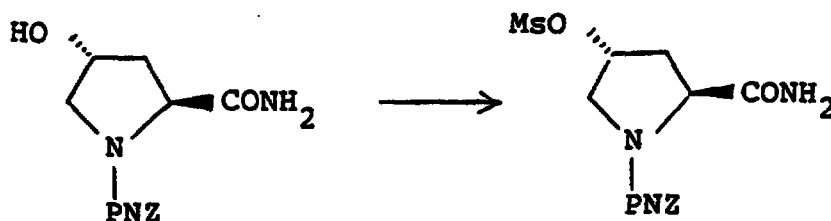
3.10 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline and 1.10 g of triethylamine were dissolved in 40 ml of dried tetrahydrofuran, and a solution of 1.20 g of ethyl chloroformate in 10 ml of dried tetrahydrofuran was added dropwise thereto at -25°C to -35°C . After stirring at the same temperature for 50 minutes, 10 ml of concentrated aqueous ammonia was added dropwise to the mixture at -25° to -40°C . The temperature was then gradually elevated to room temperature, and the reaction mixture was stirred for 1 hour, followed by concentration under reduced pressure. To the residue were added 20 ml of water and 50 ml of diethyl ether. After ice-cooling, the thus formed white crystals were separated by filtration, washed successively with cool water and cool diethyl ether, and dried under reduced pressure to yield trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-prolineamide.

Melting Point : $163.3\text{--}164.0^{\circ}\text{C}$

$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}) :$

3460, 3370, 3200, 1687, 1640, 1621, 1539, 1341, 1180, 1078

Reference Example 2-2



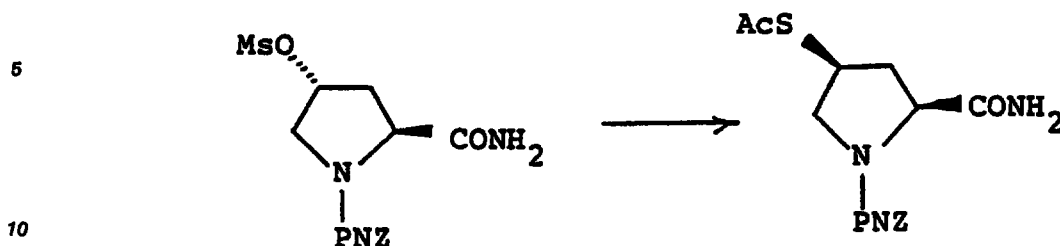
A solution of 1.89 g of methanesulfonyl chloride in 10 ml of dried tetrahydrofuran was added dropwise to a suspension of 2.32 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-prolineamide and 1.67 g of triethylamine in 40 ml of dried tetrahydrofuran at room temperature. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure, and to the residue were added 30 ml of water and 30 ml of diethyl ether. After cooling, the resulting white crystals were separated by filtration, washed successively with cool water and cool diethyl ether and dried under reduced pressure to obtain trans-1-(p-nitrobenzyloxycarbonyl)-4-methanesulfonyloxy-L-prolineamide.

Melting Point : $149.5\text{--}151^{\circ}\text{C}$

$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}) :$

3400, 3225, 1715, 1675, 1520, 1340, 1170, 1135

Reference Example 2-3



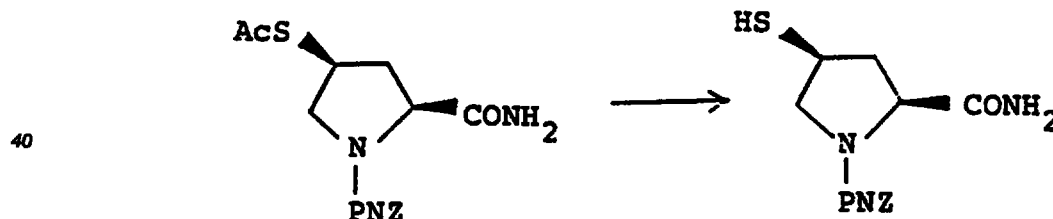
A solution of 642 mg of thioacetic acid in 14 ml of dried dimethylformamide was added to a suspension of 374 mg of 50% sodium hydride in 13 ml of dried dimethylformamide in a nitrogen stream, followed by stirring at room temperature for 25 minutes. To the mixture were added 975 mg of sodium iodide and then a solution of 2.52 g of trans-1-(p-nitrobenzyloxycarbonyl)-4-methanesulfonyloxy-L-prolineamide in 12 ml of dried dimethylformamide, and the resulting mixture was heated at 70°C for 6 hours while stirring. The reaction mixture was poured into a cool aqueous solution of sodium chloride and extracted with benzene. The extract was washed successively with a 10% aqueous solution of sodium sulfite and a sodium chloride aqueous solution, dried over sodium sulfate and distilled off to remove the solvent. The resulting crude crystals were washed with a warm mixed solvent of tetrahydrofuran and benzene to obtain cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-prolineamide.

Melting Point : 168.5-169.5°C

IR^{Nujol} (cm⁻¹) :
max

3350, 3180, 1715, 1690, 1638, 1510, 1330, 1100
[α]_D²⁰ -23° (c=0.334, DMF)

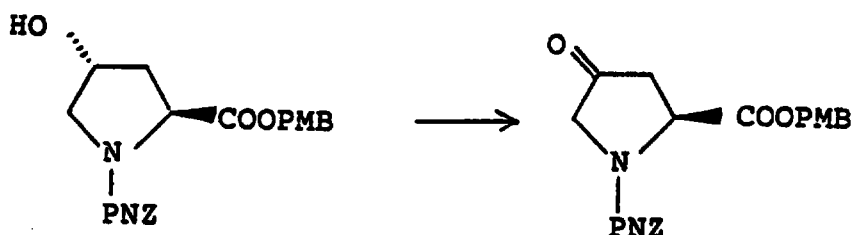
Reference Example 2-4



950 mg of (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carbamoyl-4-acetylthiopyrrolidine was dissolved in 95 ml of methanol, and 2.59 ml of a 1N aqueous solution of sodium hydroxide was added thereto at room temperature in an argon stream, followed by stirring at that temperature for 15 minutes. The reaction mixture was neutralized with 2.59 ml of a 1N aqueous solution of hydrochloric acid and distilled off under reduced pressure to remove the methanol. The thus precipitated crystals were filtered and washed with water to obtain (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carbamoyl-4-mercaptopyrrolidine.

Melting Point: 158-162°C

Reference Example 3-1



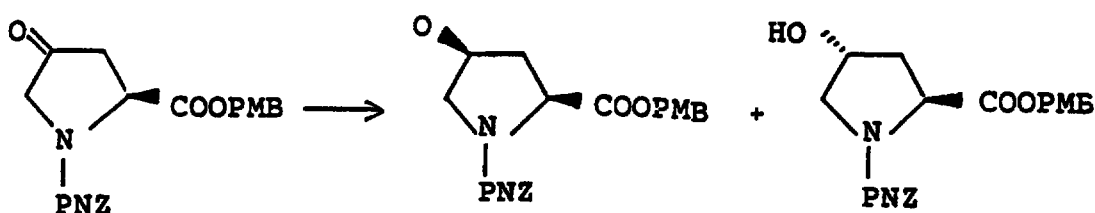
A solution of 0.35 ml of dimethyl sulfoxide in 1 ml of dried methylene chloride was added dropwise to a solution of 0.2 ml of oxalyl chloride in 5 ml of dried methylene chloride at -60° to -70° C. Ten minutes later, 10 ml of a dried methylene chloride solution of 860 mg of trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline p-methoxybenzyl ester was added dropwise to the above mixture at a temperature of -50° C or less, followed by stirring for 15 minutes. 1.01 g of triethylamine was then added dropwise thereto, and the resulting mixture was warmed to room temperature. The mixture was diluted with methylene chloride, washed with dilute hydrochloric acid aqueous solution and dried over sodium sulfate. The solvent was removed by distillation, and the residue was purified by silica gel column chromatography to yield 1-(p-nitrobenzyloxycarbonyl)-4-oxo-L-proline-p-methoxybenzyl ester.

IR_{max}^{neat} (cm^{-1}):

1762, 1740, 1710, 1512, 1345, 1245, 1155

NMR δ (CDCl_3): 3.78 (3H, s), 3.95 (2H, s), 5.08 (2H, s), 6.85 (2H, d, $J=9\text{Hz}$), 8.12 (2H, d, $J=9\text{Hz}$) ppm

Reference Example 3-2



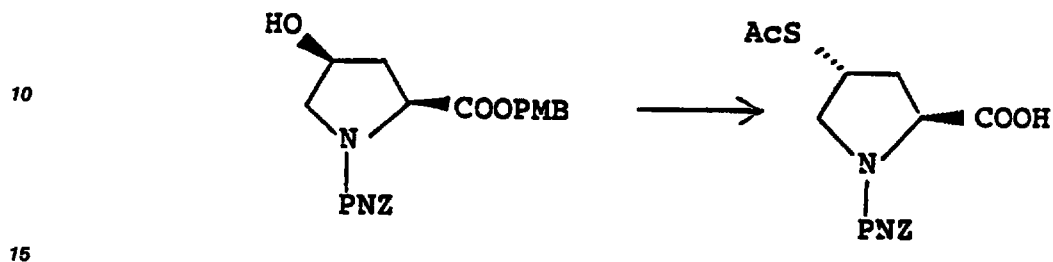
650 mg of 1-(p-nitrobenzyloxycarbonyl)-4-oxo-L-proline-p-methoxybenzyl ester was dissolved in 45 ml of ethanol, and 86 mg of sodium borohydride was added thereto in two divided portions at room temperature. After 30 minutes, the reaction mixture was concentrated under reduced pressure at 30° C or below, and the concentrate was diluted with ethyl acetate, washed with water, dried over sodium sulfate and distilled off to remove the solvent. The residue was purified by silica gel column chromatography to obtain cis-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline-p-methoxybenzyl ester (450 mg) and trans-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline-p-methoxybenzyl ester (190 mg).

Trans-compound: The IR and NMR data were consistent with those obtained for the compound of Reference Example 1-2.

Cis-compound:

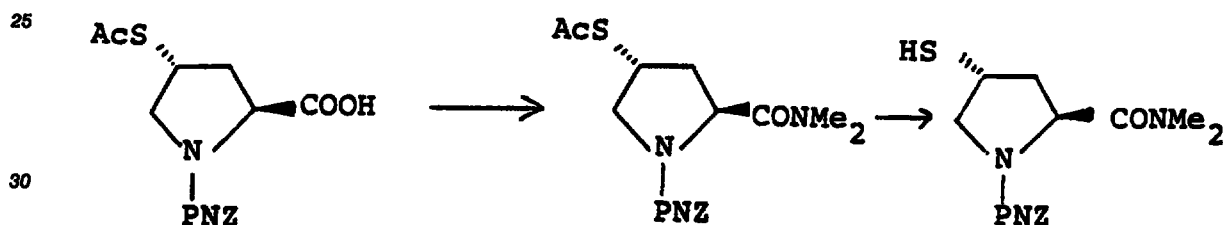
IR_{max}^{neat} (cm^{-1}):

3400 (br.), 1725, 1515, 1405, 1350, 1250, 1170, 1120

NMR δ (CDCl₃): 3.78 (3H, s), 5.08 (2H, s), 6.82 (2H, d, J=9Hz), 8.12 (2H, d, J=9Hz) ppm5 Reference Example 3-3

In the same manner as described in Reference Examples 1-3 and 1-4 but using 610 mg of cis-1-(p-nitrobenzyloxycarbonyl)-4-hydroxy-L-proline-p-methoxybenzyl ester, trans-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline was obtained.

20

Reference Example 3-4

35 a) In the same manner as described in Reference Example 1-5 but using 180 mg of trans-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline, 100 mg of (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylcarbamoyl-4-acetylthiopyrrolidine was obtained.

40 $IR_{max}^{neat} (cm^{-1}) :$

1700, 1655, 1515, 1400, 1340, 1115

 $[\alpha]_D^{30} +32.8^{\circ}$ (c=0.375, acetone)

45 b) In the same manner as described in Reference Example 1-8 but using 80 mg of the thioacetate derivative prepared as in a) above, (2S,4R)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylcarbamoyl-4-mercaptopyrrolidine was obtained.

50 $IR_{max}^{neat} (cm^{-1}) :$

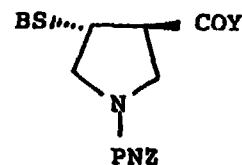
1700, 1650, 1510, 1420, 1400, 1340, 1120

55 NMR δ (CDCl₃): 1.77 (1H, d, J=7Hz), 2.97 (3H, s), 3.16 (3H, s), 5.22 (2H, s), 8.16 (2H, d, J=8.5Hz) ppm

In the same manner as described in Reference Example 3-4 but using the corresponding amines, the following thioacetates and mercaptans as shown in Table 2 were obtained.

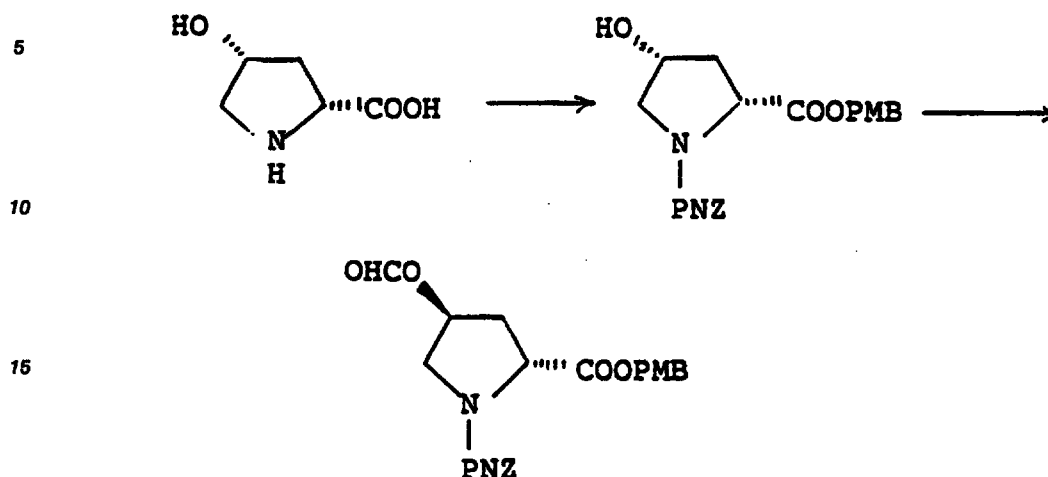
55 50 45 40 35 30 25 20 15 10 5

Table 2



Reference Example No.	B	Y	Spectral Data
3-5	Ac	-NH ₂	IR _v ^{neat} _{max} (cm ⁻¹): 3300(br), 1700(sh), 1685, 1512, 1430, 1400, 1345, 1175, 1115
			[α] _D ³⁰ + 7.36° (c=0.625, acetone)
3-6	H	-NH ₂	IR _v ^{neat} _{max} (cm ⁻¹): 1700, 1685, 1515, 1435, 1400, 1342, 1118
			NMRδ (CDCl ₃): 2.26(1H, d, J=7Hz), 5.22(2H, s), 8.11(2H, d, J=8.5Hz)
	Ac		IR _v ^{KBr} _{max} (cm ⁻¹): 1705, 1645, 1517, 1435, 1400, 1340, 1115
			NMRδ (CDCl ₃): 2.33(3H, s), 5.22(2H, s), 8.16(2H, d, J=9Hz)
	H		IR _v ^{neat} _{max} (cm ⁻¹): 1705, 1640, 1515, 1430, 1110

Reference Example 4-1



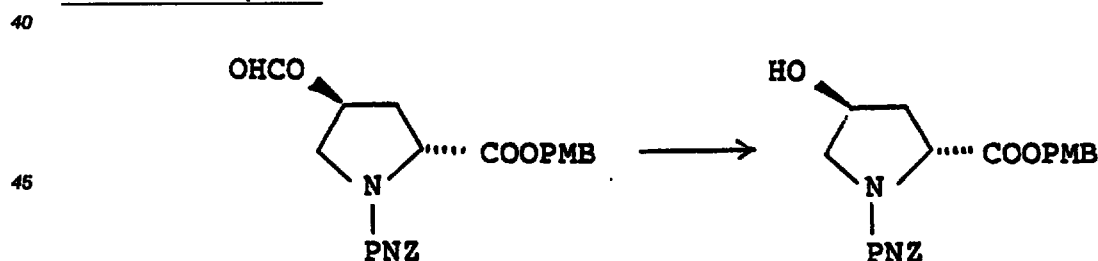
166 mg of cis-1-p-nitrobenzyloxycarbonyl-4-hydroxy-D-proline-p-methoxybenzyl ester, which was obtained from cis-4-hydroxy-D-proline in the same manner as in Reference Examples 1-1 and 1-2, and 202 mg of triphenylphosphine were dissolved in 1.5 ml of dried tetrahydrofuran, and 27 mg of formic acid was added to the solution. 134 mg of diethyl azodicarboxylate further added thereto at room temperature in a nitrogen stream. After stirring for 30 minutes, the solvent was removed by distillation. The residue was purified by silica gel chromatography to obtain trans-1-p-nitrobenzyloxycarbonyl-4-formyloxy-D-proline-p-methoxybenzyl ester.

IR^{neat}_{max} (cm⁻¹) :

1720, 1515, 1402, 1342, 1245, 1165, 1120

NMR δ (CDCl₃): 3.76 (3H, s), 4.50 (2H, t, J = 8Hz), 5.08 (2H, s), 5.15 (2H, ABq., J = 16Hz), 5.41 (1H, m), 7.97 (1H, s) ppm

Reference Example 4-2



215 mg of trans-1-p-nitrobenzyloxycarbonyl-4-formyloxy-D-proline-p-methoxybenzyl ester was dissolved in 1.1 ml of tetrahydrofuran, and 0.93 ml of a 1N aqueous solution of sodium hydroxide was added to the resulting solution. After stirring for 10 minutes, the reaction mixture was diluted with ethyl acetate, washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and distilled off to remove the solvent. The resulting residue was purified by silica gel thin layer chromatography to obtain trans-1-p-nitrobenzyloxycarbonyl-4-hydroxy-D-proline-p-methoxybenzyl ester.

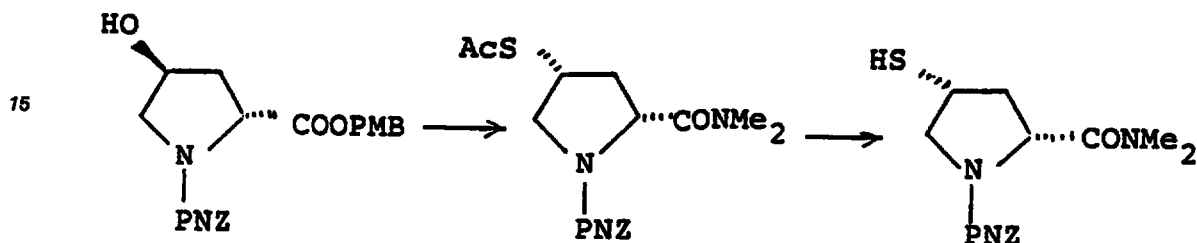
$IR_{max}^{neat} (cm^{-1}) :$

5 3425 (br.), 1735, 1705, 1510, 1400, 1340, 1240, 1162

NMR δ ($CDCl_3$): 2.33 (2H, m), 3.58 (2H, d, $J=3.5Hz$), 3.73 (3H, s), 5.03 (2H, s), 5.07 (2H, ABq., $J=18Hz$), 6.73 (2H, d, $J=9Hz$), 6.77 (2H, d, $J=9Hz$), 8.00 (2H, d, $J=8.5Hz$), 8.07 (2H, d, $J=8.5Hz$)ppm

Reference Example 4-3

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20

a) In the same manner as described in Reference Examples 1-3, 1-4 and 1-5 but using 110 mg of trans-1-p-nitrobenzyloxycarbonyl-4-hydroxy-D-proline-p-methoxybenzyl ester, (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-dimethylcarbamoyl-4-acetylthiopyrrolidine was obtained.

25

$IR_{max}^{neat} (cm^{-1}) :$

30

1705, 1650, 1515, 1435, 1340, 1115

$[\alpha]_D^{30} -7.38^\circ$ ($c=0.210$, acetone)

b) In the same manner as described in Reference Example 1-8 but using 42 mg of the thioacetate derivative as obtained in a) above, (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-dimethylcarbamoyl-4-mercapthiopyrrolidine was obtained.

35

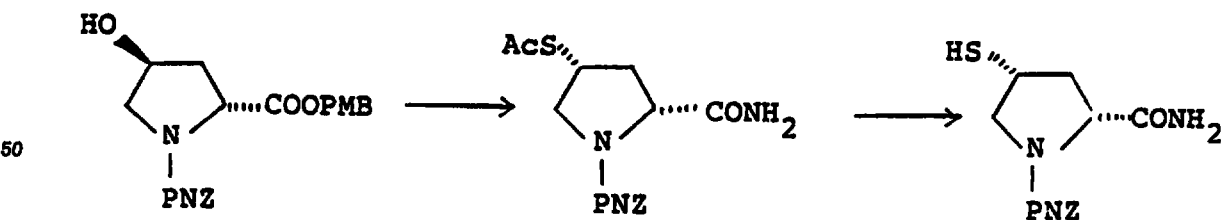
$IR_{max}^{neat} (cm^{-1}) :$

40

1710, 1660, 1525, 1440, 1347, 1180, 1122

Reference Example 4-4

45



a) In the same manner as described in Reference Examples 1-3, 1-4 and 2-1 but using 110 mg of trans-1-p-nitrobenzyloxycarbonyl-4-hydroxy-D-proline-p-methoxybenzyl ester, 40 mg of (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-carbamoyl-4-acetylthiopyrrolidine was obtained.

$IR_{max}^{neat} (cm^{-1}) :$

5 1685, 1515, 1400, 1340, 1110

$[\alpha]_D^{30} + 39.6^{\circ}$ ($c=0.293$, DMF)

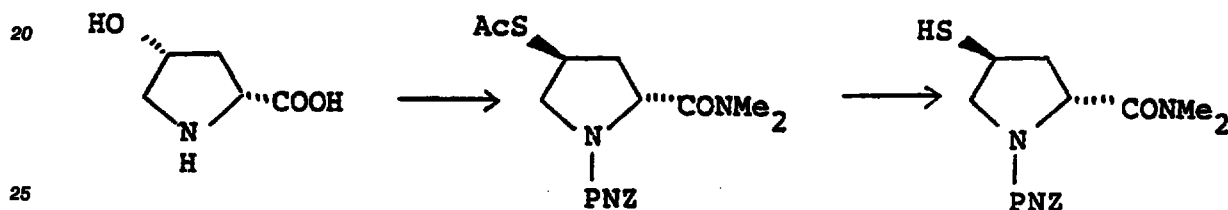
b) In the same manner as described in Reference Example 1-8 but using 40 mg of the thioacetate derivative as obtained in a) above, (2R,4R)-1-p-nitrobenzyloxycarbonyl-2-carbamoyl-4-mercaptopyrrolidine was obtained.

10

$IR_{max}^{Nujol} (cm^{-1}) :$

15 3200, 1710, 1655, 1512, 1340, 1115

Reference Example 5-1



30 a) In the same manner as described in Reference Examples 1-1, 1-2, 1-3, 1-4 and 1-5 but using 300 mg of cis-4-hydroxy-D-proline, 45 mg of (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylcarbamoyl-4-acetylthiopyrrolidine was obtained.

35 $IR_{max}^{neat} (cm^{-1}) :$

1700, 1650, 1520, 1400, 1345, 1120

$[\alpha]_D^{30} -29.6^{\circ}$ ($c=0.215$, acetone)

40 b) In the same manner as described in Reference Example 1-8 but using 30 mg of the thioacetate derivative as obtained in a) above, (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-dimethylcarbamoyl-4-mercaptopyrrolidine was obtained.

45 $IR_{max}^{neat} (cm^{-1}) :$

1710, 1655, 1520, 1430, 1405, 1347, 1122

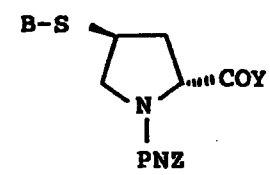
In the same manner as described in Reference Example 5-1 but using the corresponding amines, the following thioacetate derivatives and mercaptan derivatives as shown in Table 3 were obtained.

50

55

65 50 45 40 35 30 25 20 15 10 5

Table 3



Reference Example No.	B	Y	Spectral Data
5-2	Ac	-NH ₂	IR _v ^{neat} _{max} (cm ⁻¹): 1705(sh), 1685, 1520, 1425, 1402, 1342, 1122 [α] _D ³⁰ - 6.92° (c=0.665, acetone)
	H	-NH ₂	IR _v ^{CHCl₃} _{max} (cm ⁻¹): 1695(sh), 1682, 1515, 1395, 1340, 1115
5-3	Ac		IR _v ^{neat} _{max} (cm ⁻¹): 1695, 1635, 1515, 1430, 1395, 1340, 1115
	H		IR _v ^{CHCl₃} _{max} (cm ⁻¹): 1700, 1640, 1520, 1422, 1345, 1120

65 60 45 40 36 30 25 20 15 10 5

Reference
Example No.

B

Y

Spectral Data

IR_{max}^{neat} (cm⁻¹): 1700, 1655, 1620, 1605, 1520, 1340, 1115

Ac



NMR_δ (CDCl₃): 2.33(3H, s), 5.22(2H, s), 7.49(2H, d, J=8.5Hz),
8.21(2H, d, J=8.5Hz)

5-4

[α]_D²³ -21° (c=0.25, acetone)

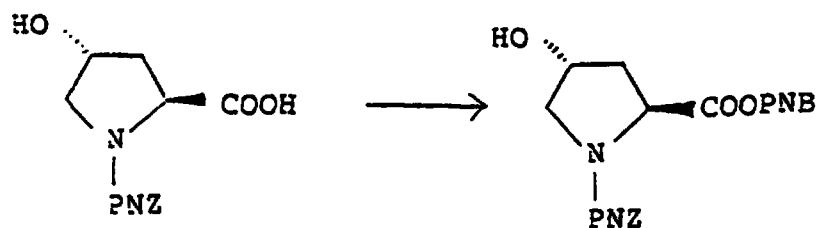
H



IR_{max}^{CHCl₃} (cm⁻¹): 1705, 1660, 1525, 1340, 1120

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Reference Example 6-1



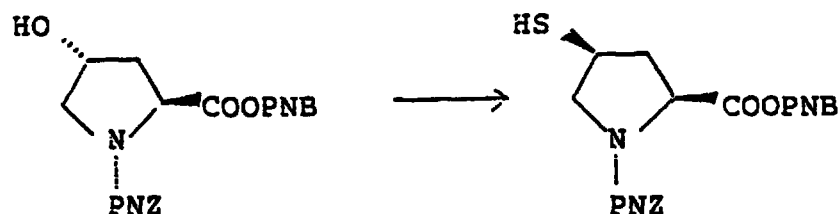
In the same manner as described in Reference Example 1-2 but using 500 mg of trans-1-p-nitrobenzyloxycarbonyl-4-hydroxy-L-proline and 383 mg of p-nitrobenzyl bromide, trans-1-p-nitrobenzyloxycarbonyl-4-hydroxy-L-proline-p-nitrobenzyl ester was obtained.

$IR_{max}^{CHCl_3} (cm^{-1}) :$

3380 (br.), 1750, 1705, 1520, 1425, 1400, 1342, 1160

NMR δ ($CDCl_3$) : 2.20 (3H, m), 3.67 (2H, d, $J=3Hz$), 4.60 (2H, t, $J=8Hz$), 5.15 (2H, s), 5.23 (2H, ABq.), 7.47 (4H, d, $J=8.5Hz$), 8.15 (4H, d, $J=8.5Hz$) ppm

Reference Example 6-2

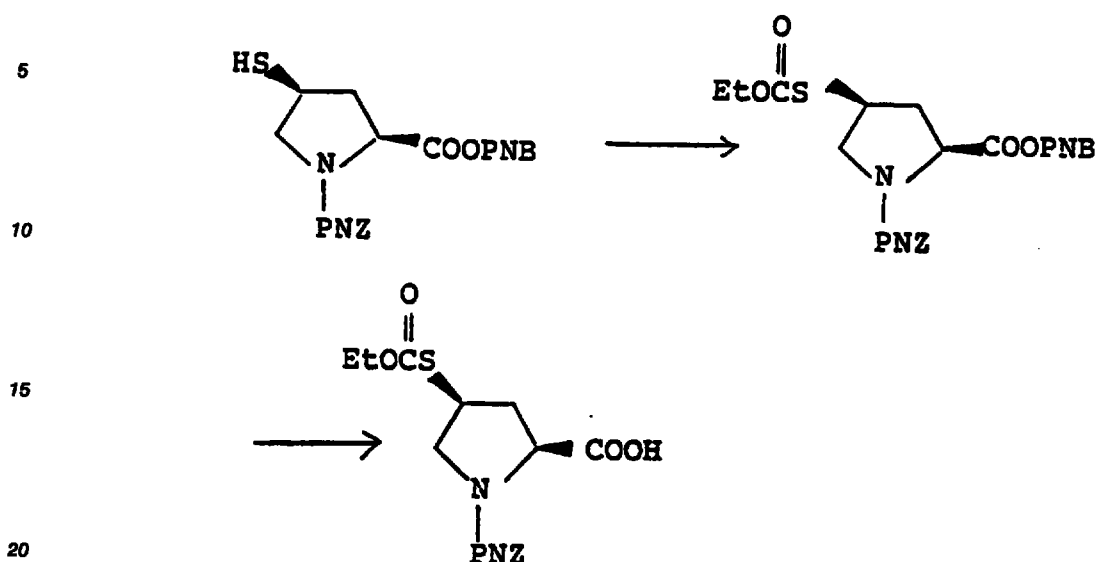


In the same manner as described in Reference Examples 1-3 and 1-8 but using trans-1-p-nitrobenzyloxycarbonyl-4-hydroxy-L-proline-p-nitrobenzyl ester, cis-1-p-nitrobenzyloxycarbonyl-4-mercapto-L-proline-p-nitrobenzyl ester was obtained.

$IR_{max}^{neat} (cm^{-1}) :$

1700, 1685, 1600, 1510, 1430, 1400, 1340, 1105

Reference Example 6-3



25 a) 115 mg of cis-1-p-nitrobenzyloxycarbonyl-4-mercapto-L-proline-p-nitrobenzyl ester was dissolved in 3 ml of dried tetrahydrofuran, and 30 mg of triethylamine was added thereto. Then, 28.5 mg of ethyl chloroformate was added dropwise thereto under ice-cooling, followed by stirring for 10 minutes. The reaction mixture was diluted with ethyl acetate, washed successively with dilute hydrochloric acid and water, and dried over sodium sulfate. The solvent was removed by distillation to give 133 mg of cis-1-p-nitrobenzyloxycarbonyl-4-ethoxycarbonylthio-L-proline-p-nitrobenzyl ester.

30

$IR_{max}^{neat} (cm^{-1}) :$

35 1755, 1710, 1610, 1525, 1405, 1350, 1160, 1015, 850

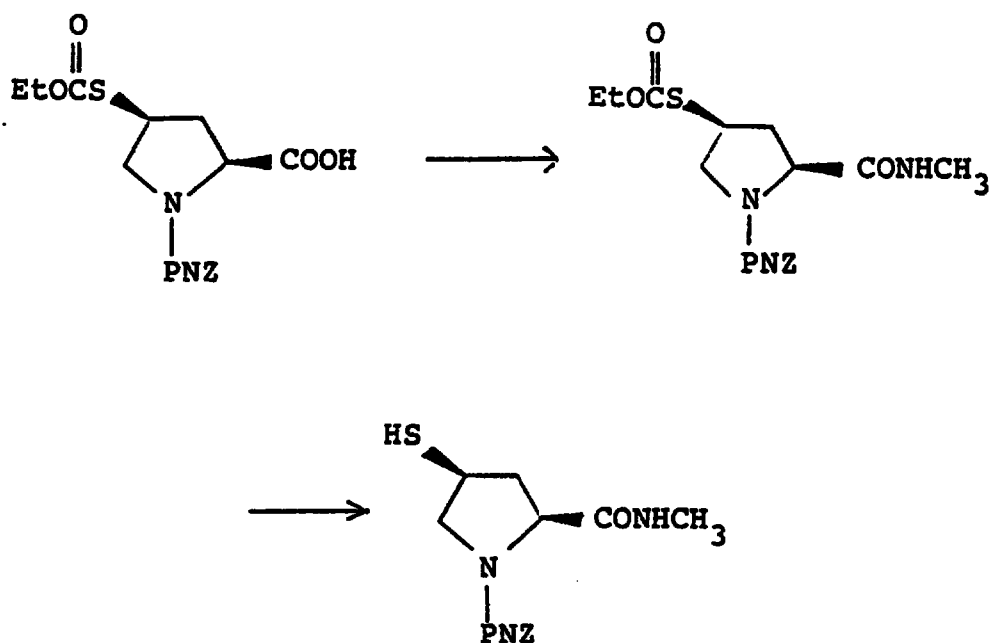
40 b) 133 mg of the thus obtained ester derivative was dissolved in 5 ml of a mixture of tetrahydrofuran and water (1:1 by volume), and 0.26 ml of a 1N aqueous solution of sodium hydroxide was added thereto. After stirring at room temperature for 2.5 hours, 0.3 ml of a 1N hydrochloric acid aqueous solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and distilled off to remove the solvent. The residue was subjected to silica gel thin layer chromatography to obtain cis-1-p-nitrobenzyloxycarbonyl-4-ethoxycarbonylthio-L-proline.

45 $IR_{max}^{neat} (cm^{-1}) :$

1700, 1520, 1400, 1340, 1165, 1145

50 NMR δ (CDCl₃): 1.30 (3H, t, J=7Hz), 4.28 (2H, q, J=7Hz), 5.24 (2H, s), 7.50 (2H, d, J=9Hz), 8.17 (2H, d, J=9Hz) ppm

Reference Example 6-4



a) 72 mg of *cis*-1-*p*-nitrobenzyloxycarbonyl-4-ethoxycarbonylthio-L-proline was dissolved in 3 ml of dried tetrahydrofuran, and 40 mg of triethylamine was added thereto. Under ice-cooling, 41 mg of ethyl chloroformate was added dropwise thereto, followed by stirring for 15 minutes. 1.5 ml of a 40% aqueous solution of methylamine was added dropwise to the mixture, followed by stirring for 15 minutes. The reaction mixture was diluted with ethyl acetate, washed successively with dilute hydrochloric acid and water, dried over sodium sulfate and distilled off to remove the solvent, thereby to obtain (2*S*,4*S*)-1-*p*-nitrobenzyloxycarbonyl-2-methylcarbamoyl-4-ethoxycarbonylthiopyrrolidine.

$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}) :$

3290, 1705, 1660, 1520, 1425, 1405, 1345, 1180, 1160

$\text{NMR } \delta (\text{CDCl}_3) : 1.30 (3\text{H}, \text{t}, J=8\text{Hz}), 2.80 (3\text{H}, \text{d}, J=5\text{Hz}), 4.27 (2\text{H}, \text{q}, J=8\text{Hz}), 5.22 (2\text{H}, \text{s}), 7.48 (2\text{H}, \text{d}, J=9\text{Hz}), 8.18 (2\text{H}, \text{d}, J=9\text{Hz}) \text{ ppm}$

b) 82 mg of the methylcarbamoyl derivative as prepared in a) above was dissolved in 4 ml of a mixture of methanol and water (1:1 by volume), and 0.25 ml of a 1N aqueous solution of sodium hydroxide was added thereto. After stirring at room temperature for 30 minutes, 0.27 ml of a 1N hydrochloric acid aqueous solution was added thereto. The resulting mixture was extracted with ethyl acetate, and the extract was washed with water, dried over sodium sulfate and distilled off to remove the solvent, thereby to obtain (2*S*,4*S*)-1-*p*-nitrobenzyloxycarbonyl-2-methylcarbamoyl-4-mercaptopyrrolidine.

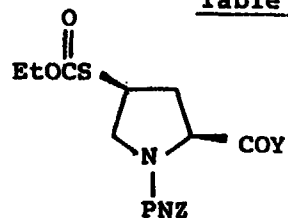
$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}) :$

3280, 1710, 1650, 1510, 1340, 1165

$\text{NMR } \delta (\text{CDCl}_3) : 2.79 (3\text{H}, \text{d}, J=5\text{Hz}), 4.27 (2\text{H}, \text{t}, J=8\text{Hz}), 5.23 (2\text{H}, \text{s}), 7.50 (2\text{H}, \text{d}, J=9\text{Hz}), 8.20 (2\text{H}, \text{d}, J=9\text{Hz}) \text{ ppm}$

In the same manner as described in Reference Example 6-4(a) but using the corresponding amines, the following thiocarbonates as shown in Table 4 were obtained.

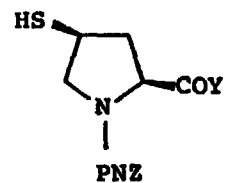
Table 4



Reference Example No.	Y	Spectral Data
6-5		$\text{IR}_{\text{vmax}}^{\text{neat}} (\text{cm}^{-1}): 3350, 1705, 1520, 1405, 1345, 1170, 1150$ $\text{NMR}_{\delta} (\text{CDCl}_3): 1.27(3\text{H}, \text{t}, \text{J}=7\text{Hz}), 4.23(2\text{H}, \text{q}, \text{J}=7\text{Hz}), 5.18(2\text{H}, \text{s}), 7.44(2\text{H}, \text{d}, \text{J}=9\text{Hz}), 8.13(2\text{H}, \text{d}, \text{J}=9\text{Hz})$
6-6		$\text{IR}_{\text{vmax}}^{\text{neat}} (\text{cm}^{-1}): 1710, 1520, 1400, 1345, 1170, 1148$ $\text{NMR}_{\delta} (\text{CDCl}_3): 1.28(3\text{H}, \text{t}, \text{J}=7\text{Hz}), 2.19(6\text{H}, \text{s}), 4.24(2\text{H}, \text{q}, \text{J}=7\text{Hz}), 5.20(2\text{H}, \text{s}), 7.47(2\text{H}, \text{d}, \text{J}=9\text{Hz}), 8.13(2\text{H}, \text{d}, \text{J}=9\text{Hz})$

The following mercaptans as shown in Table 5 were obtained in the same manner as described in Reference Example 1-8 or 6-4(b).

Table 5



Reference Example No.	Y	Spectral Data
7-1	$\text{-N} \begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1705, 1640, 1520, 1430, 1400, 1345, 1105$
7-2	$\text{-N} \begin{cases} \text{CH} \begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases} \\ \text{H} \end{cases}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 3290, 1710, 1650, 1520, 1403, 1340$
7-3	$\text{-N} \begin{cases} \text{CH}_2\text{CH}=\text{CH}_2 \\ \text{H} \end{cases}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 3290, 1717, 1660, 1520, 1410, 1350$
7-4	$\text{-N} \begin{cases} \text{CH}_2\text{CONH}_2 \\ \text{H} \end{cases}$	$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}): 3420, 3300, 1700(\text{sh}), 1675, 1640, 1510, 1340$

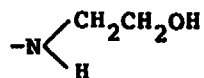
55 60 45 40 35 30 25 20 15 10 5

Reference
Example No.

Y

Spectral Data

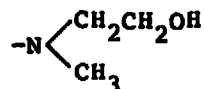
7-5



IR_v^{Nujol}_{max} (cm⁻¹): 3270, 1710, 1650, 1505, 1340

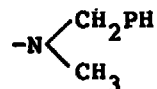
NMR δ (CDCl₃): 5.20(2H, s), 7.49(2H, q, J=8.5Hz), 8.16(2H, d, J=8.5Hz)

7-6



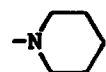
IR_v^{neat}_{max} (cm⁻¹): 3400, 1690, 1640, 1515, 1405, 1345

7-7



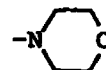
IR_v^{neat}_{max} (cm⁻¹): 1705, 1650, 1515, 1400, 1340

7-8



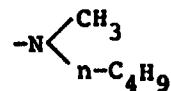
IR_v^{neat}_{max} (cm⁻¹): 1710, 1645, 1520, 1440, 1345, 1245, 1025

7-9



IR_v^{neat}_{max} (cm⁻¹): 1710, 1655, 1520, 1430, 1405, 1342, 1112

7-10



IR_v^{neat}_{max} (cm⁻¹): 1710, 1650, 1520, 1405, 1345, 1205

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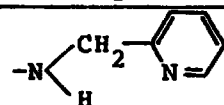
5

Reference
Example No.

Y

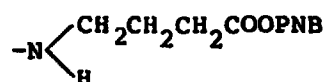
Spectral Data

7-11



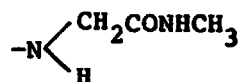
IR_ν^{Nujol}_{max} (cm⁻¹): 3300, 1725, 1660, 1520, 1345, 1110

7-12



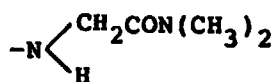
IR_ν^{neat}_{max} (cm⁻¹): 3280, 1730(sh), 1710, 1645, 1510, 1340

7-13



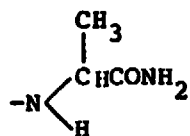
IR_ν^{Nujol}_{max} (cm⁻¹): 3320, 1725, 1640, 1520, 1405, 1345

7-14



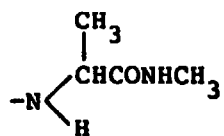
NMR δ (CDCl₃): 1.87(1H, d, J=7Hz), 2.96(3H, s), 2.98(3H, s), 4.33(1H, t, J=7.5Hz), 5.24(2H, s), 7.48(2H, d, J=9Hz), 8.18(2H, d, J=9Hz)

7-15



IR_ν^{Nujol}_{max} (cm⁻¹): 3300, 1700, 1680, 1655, 1520, 1345

7-16



IR_ν^{Nujol}_{max} (cm⁻¹): 3310, 1722, 1650, 1525, 1350

55 60 45 40 35 30 25 20 15 10 5

Reference
Example No.

Y

Spectral Data

7-17	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{N} \begin{array}{l} \text{CHCON}(\text{CH}_3)_2 \\ \text{H} \end{array} \end{array}$	IR _v ^{Nujol} _{max} (cm ⁻¹): 3325, 1710, 1640, 1520, 1345
7-18	$-\text{N} \begin{array}{l} \text{CH}_2\text{CONH}_2 \\ \text{CH}_3 \end{array}$	IR _v ^{neat} _{max} (cm ⁻¹): 3350(br), 1690, 1660(sh), 1520, 1405, 1345
7-19	$-\text{N} \begin{array}{l} \text{CH}_2\text{CONHCH}_3 \\ \text{CH}_3 \end{array}$	IR _v ^{neat} _{max} (cm ⁻¹): 3370, 1700, 1665, 1525, 1410, 1350
7-20	$-\text{N} \begin{array}{l} \text{CH}_2\text{CON}(\text{CH}_3)_2 \\ \text{CH}_3 \end{array}$	IR _v ^{neat} _{max} (cm ⁻¹): 3500, 1710, 1660, 1520, 1405, 1345
7-21	$-\text{N} \begin{array}{c} \text{ } \\ \text{ } \end{array} \text{S}$	IR _v ^{neat} _{max} (cm ⁻¹): 3245, 1700, 1645, 1520, 1340, 1190, 1165, 1107, 1065, 950, 850
7-22	$-\text{NH} \begin{array}{c} \text{ } \\ \text{ } \end{array}$	IR _v ^{CHCl₃} _{max} (cm ⁻¹): 3410, 1710, 1525, 1440, 1345, 1305

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Reference
Example No.

Y

Spectral Data

7-23


 $\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}): 3250, 1710, 1670, 1525, 1345, 1175$

7-24


 $\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1710, 1650, 1518, 1435, 1400, 1345, 1170, 1110$

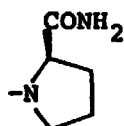
7-25


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 1710, 1660, 1520, 1345, 1170, 1110$

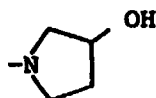
7-26


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 1720, 1525, 1470, 1340, 1170, 1110$

7-27


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 3470(\text{br}), 1700, 1640, 1520, 1340, 1120$

7-28


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 3420(\text{br}), 1700, 1645, 1520, 1340, 1165$

7-29


 $\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 1710, 1640, 1525, 1345, 1170, 1015$

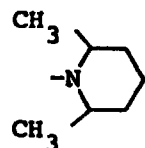
65 60 45 40 35 30 25 20 15 10 5

Reference
Example No.

Y

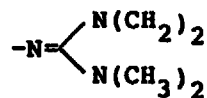
Spectral Data

7-30



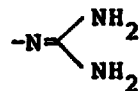
NMR δ (CDCl₃): 1.95(1H, d, J=8Hz), 5.25(2H, s), 7.52(2H, d, J=9Hz), 8.21(2H, d, J=9Hz)

7-31



IR $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹): 1705, 1600, 1520, 1400, 1340, 1160

7-32



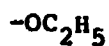
IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm⁻¹): 3420, 1695, 1610, 1522, 1350, 1110

7-33



IR $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹): 1745, 1710, 1605, 1520, 1430, 1400, 1345, 1205, 1167, 1110

7-34



IR $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹): 1740, 1710, 1522, 1430, 1402, 1342, 1200, 1170, 1110

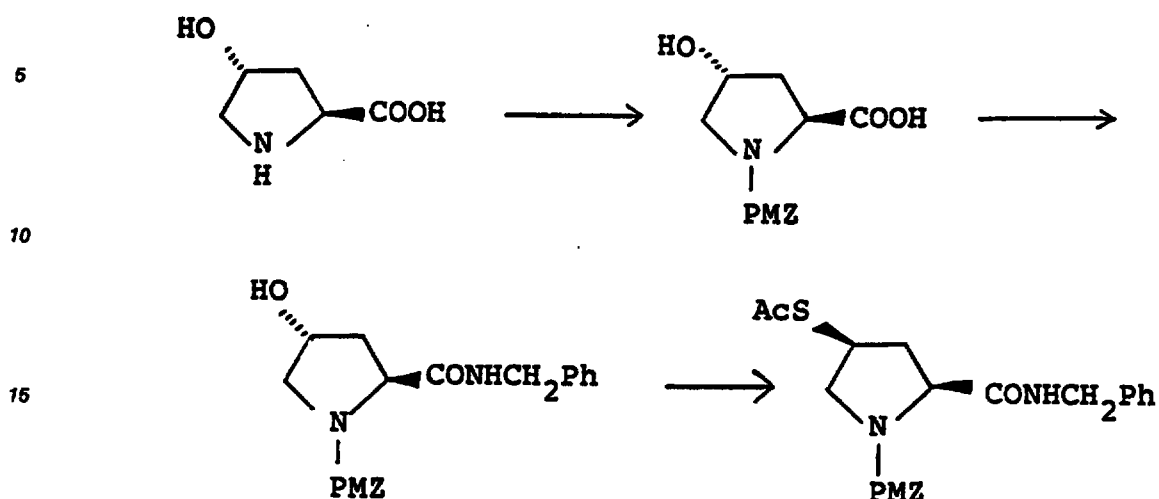
7-35



IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹): 3180, 3050, 1720, 1615, 1520, 1350

Reference Example No.	Y	Spectral Data
7-36	$-\text{NHN}(\text{CH}_3)_2$	$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}): 3205, 1720, 1660, 1520, 1345, 1180$
7-37	$-\text{N} \begin{array}{l} \text{CH}_3 \\ \text{N}(\text{CH}_3)_2 \end{array}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1706, 1662, 1520, 1340, 1165, 1105$
7-38	$-\text{NHOPNB}$	$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}): 3200, 1715, 1665, 1515, 1345, 1170$
7-39	$-\text{NHOCH}_3$	$\text{IR}_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1}): 3200, 1715, 1670, 1520, 1340, 1170$
7-40	$-\text{N} \begin{array}{c} \text{---} \end{array} \text{CONH}_2$	$\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 1690, 1650, 1525, 1405, 1345, 1170, 1110$
7-41	$-\text{N} \begin{array}{c} \text{---} \end{array}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1700, 1520, 1400, 1340, 1200, 1160, 1105$
7-42	$-\text{N} \begin{array}{c} \text{---} \end{array}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1708, 1645, 1520, 1440, 1405, 1350, 1170, 1115$
7-43	$-\text{NH} \begin{array}{c} \text{---} \end{array} \text{N}$	$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1700, 1600, 1515, 1105$

Reference Example 8-1



a) In the same manner as described in Reference Example 1-1 but using 10 g of trans-4-hydroxy-L-proline and 23.2 g of S-p-methoxybenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine, trans-1-(p-methoxybenzyloxycarbonyl)-4-hydroxy-L-proline was obtained.

$IR_{max}^{neat} (cm^{-1}) :$

3400 (br.), 1692, 1430, 1355, 1245, 1170, 1122

NMR δ ($CDCl_3$): 2.23 (2H, m), 3.73 (3H, s), 5.00 (2H, s), 6.78 (2H, d, $J=9$ Hz), 7.20 (2H, d, $J=9$ Hz) ppm

b) In the same manner as described in Reference Example 2-1 but using 0.57 g of the proline derivative as prepared in a) above and 0.215 g of benzylamine, trans-1-(p-methoxybenzyloxycarbonyl)-4-hydroxy-L-benzylprolineamide was obtained.

$IR_{max}^{Nujol} (cm^{-1}) :$

3375, 3300, 1665, 1248, 1165, 1120, 1025

NMR δ ($CDCl_3$) : 3.76 (3H, s), 4.35 (4H, m), 4.96 (2H, s), 6.79 (2H, d, $J=9$ Hz), 7.20 (5H, s) ppm

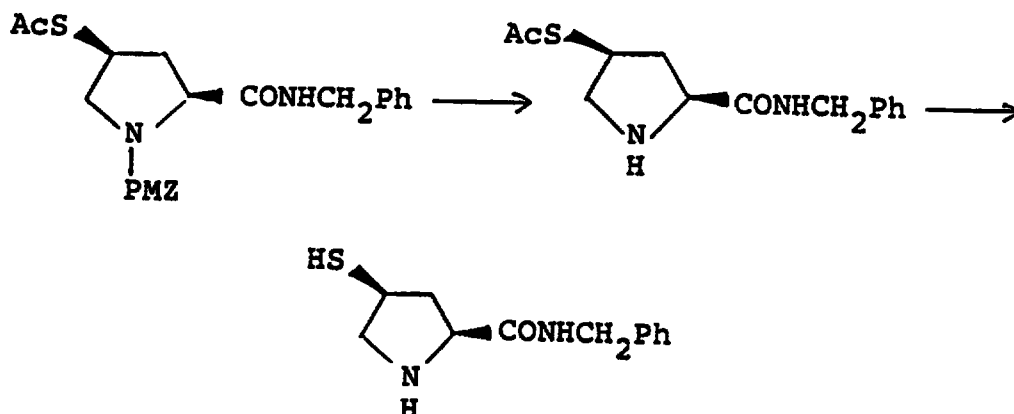
c) In the same manner as described in Reference Example 1-3 but using 0.5 g of the benzylprolineamide as prepared in b) above, (2S,4S)-1-(p-methoxybenzyloxycarbonyl)-2-benzylcarbamoyl-4-acetylthiopyrrolidine was obtained.

$IR_{max}^{Nujol} (cm^{-1}) :$

3280, 1690, 1675, 1240

NMR δ ($CDCl_3$) : 2.27 (3H, s), 3.82 (3H, s), 4.42 (2H, d, $J=6$ Hz), 5.05 (2H, s), 6.87 (2H, d, $J=8$ Hz), 7.23 (2H, d, $J=8$ Hz), 7.28 (5H, s) ppm

Reference Example 8-2



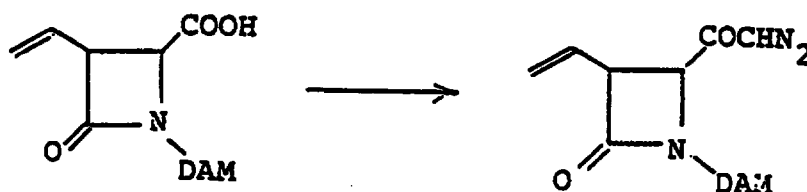
177 mg of (2S,4S)-1-p-methoxybenzyloxycarbonyl-2-benzylcarbamoyl-4-acetylthiopyrrolidine and 86 mg of anisole were dissolved in 0.5 ml of trifluoroacetic acid, followed by stirring at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate, washed successively with an aqueous solution of sodium bicarbonate and water and dried over sodium sulfate. The solvent was removed by distillation, and the residue was subjected to silica gel thin layer chromatography to obtain (2S,4S)-2-benzylcarbamoyl-4-acetylthiopyrrolidine.

$IR_{\max}^{\text{neat}}$ (cm^{-1}):

3325, 1690, 1510, 1400, 1350, 1120, 950

NMR δ (CDCl_3): 2.28 (3H, s), 3.83 (2H, m), 4.42 (2H, d, $J=6\text{Hz}$), 7.32 (5H, s) ppm

Reference Example 9-1



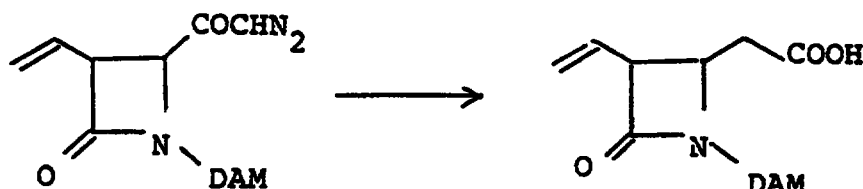
7 g of 1-(di-p-anisylmethyl)-3-ethenyl-4-carboxy-2-azetidinone was dissolved in 50 ml of dried methylene chloride, and 0.8 ml of dimethylformamide was added to the resulting solution. 2 ml of oxalyl chloride was added dropwise thereto under ice-cooling, followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and to the concentrate was added 50 ml of dried methylene chloride, followed by concentration again under reduced pressure. The resulting residue was dried in vacuo and then dissolved in 100 ml of dried diethyl ether. The resulting solution was added dropwise under ice-cooling to 120 ml of a 0.17M solution of diazomethane in diethyl ether to which 4 ml of triethylamine had been added, followed by stirring at the same temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed successively with a 1N aqueous solution of hydrochloric acid and water, dried over sodium sulfate and distilled off to remove the solvent. The resulting oily residue was purified by silica gel chromatography to obtain 1-(di-p-anisylmethyl)-3-ethenyl-4-diazoacetyl-2-azetidinone.

IR_{max}^{neat} (cm⁻¹) :

2110, 1755, 1640, 1612, 1505, 1240, 1177, 1030, 828

NMR δ (CDCl₃): 3.78 (6H, s), 5.00 (1H, s), 5.80 (1H, s), 6.84 (4H, d, J=8.5Hz) ppm

Reference Example 9-2



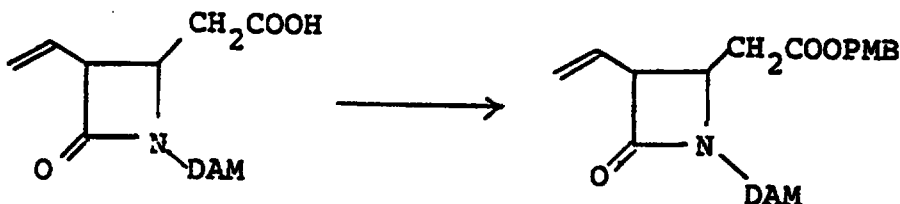
0.7 g of 1-(di-p-anisylmethyl)-3-ethenyl-4-diazoacetyl-2-azetidinone was dissolved in 300 ml of methylene chloride, and 1 ml of water was added thereto. The mixture was irradiated with light for 1 hour using a high pressure mercury lamp while removing oxygen from the system under ice-cooling. Then, the mixture was extracted with a 1N aqueous solution of sodium hydroxide. The aqueous layer was rendered acidic with hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and distilled off to remove the solvent thereby obtaining 1-(di-p-anisylmethyl)-3-ethenyl-4-carboxymethyl-2-azetidinone.

IR_{max}^{neat} (cm⁻¹) :

~3000, 1700, 1612, 1510, 1300, 1180, 1030, 820

NMR δ (CDCl₃): 2.35 (2H, d, J=6Hz), 3.73 (6H, s), 5.80 (1H, s), 6.78 (4H, d, J=9.0Hz), 7.08 (4H, d, J=9.0Hz) ppm

Reference Example 9-3



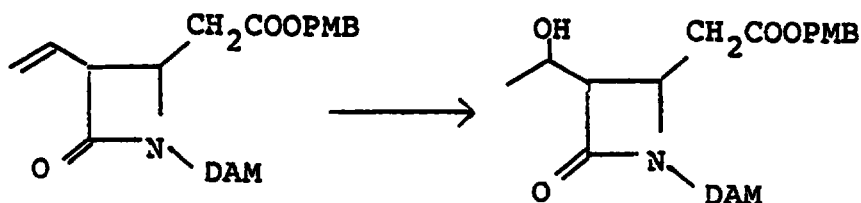
2.3 g of 1-(di-p-anisylmethyl)-3-ethenyl-4-carboxymethyl-2-azetidinone was dissolved in 50 ml of dried dimethylformamide, and 1.5 ml of triethylamine was added thereto. 1.3 g of p-methoxybenzyl chloride was then added dropwise to the mixture, followed by stirring at 70°C for 3 hours. The reaction mixture was diluted with ethyl acetate and diethyl ether, washed successively with dilute hydrochloric acid and water, dried over sodium sulfate and distilled off to remove the solvent thereby obtaining 1-(di-p-anisylmethyl)-3-ethenyl-4-p-methoxybenzyloxycarbonylmethyl-2-azetidinone.

IR_{max}^{neat} (cm⁻¹) :

1750, 1612, 1510, 1250, 1175, 1033

NMR δ (CDCl₃): 2.36 (2H, d, J=6.5Hz), 3.72 (6H, s), 3.75 (3H, s), 4.83 (2H, s), 5.78 (1H, s) ppm

Reference Example 9-4



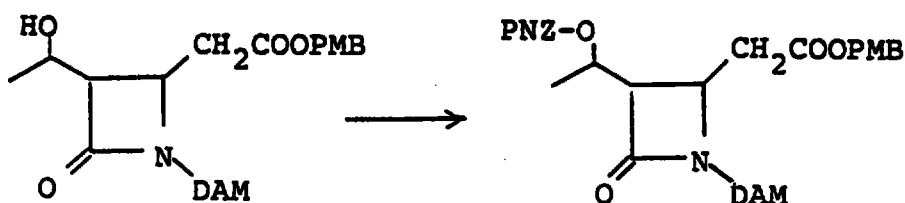
2.85 g of 1-(di-p-anisylmethyl)-3-ethenyl-4-p-methoxybenzyloxycarbonylmethyl-2-azetidinone was dissolved in 14 ml of tetrahydrofuran, and 7 ml of water and 2.0 g of mercury (II) acetate were added thereto, followed by stirring at 35°C for 5 hours. 12 ml of a 1N aqueous solution of sodium hydroxide was added thereto at 0°C, and to the resulting mixture was then added dropwise a solution of 0.25 g of sodium borohydride in 1 ml of a 1N aqueous solution of sodium hydroxide. After stirring at the same temperature for 15 minutes, the reaction mixture was neutralized with a 2N hydrochloric acid aqueous solution. Diethyl ether was added thereto, followed by filtration using Celite. The filtrate was extracted with diethyl ether, and the extract was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and distilled off to remove the solvent, thereby to obtain 2.6 g of 1-(di-p-anisylmethyl)-3-(1-hydroxyethyl)-4-p-methoxybenzyloxycarbonylmethyl-2-azetidinone.

IR_{max}^{neat} (cm⁻¹):

3430, 1730, 1615, 1510, 1247, 1178, 1030, 820

NMR δ (CDCl₃): 1.23 (3H, d, J=6.5Hz), 2.42 (2H, d, J=7Hz), 3.77 (9H, s), 4.95 (2H, s), 5.78 (1H, s) ppm

Reference Example 9-5



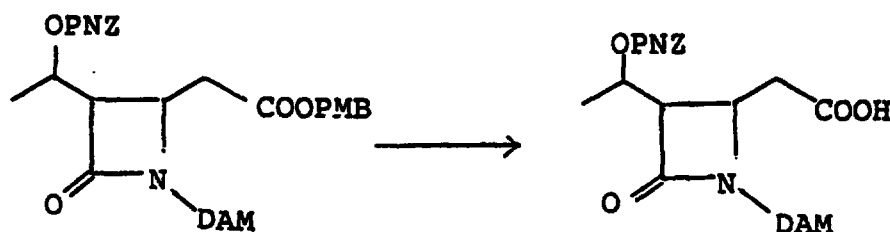
2.6 g of 1-(di-p-anisylmethyl)-3-(1-hydroxyethyl)-4-p-methoxybenzyloxycarbonylmethyl-2-azetidinone was dissolved in 15 ml of dried methylene chloride, and 1.22 g of 4-dimethylaminopyridine was added thereto. Under ice-cooling, a solution of 1.3 g of p-nitrobenzyl chloroformate in 7 ml of dried methylene chloride was added dropwise to the mixture, followed by stirring at room temperature for 1 hour. To the reaction mixture were added methylene chloride and water, and the methylene chloride layer was washed successively with a 1N hydrochloric acid aqueous solution, water, a 5% aqueous solution of sodium bicarbonate and water, and dried over sodium sulfate. The solvent was removed by distillation, and the residue was purified by silica gel chromatography to obtain 2.2 g of 1-(di-p-anisylmethyl)-3-(1-p-nitrobenzyloxyethyl)-4-p-methoxybenzyloxycarbonylmethyl-2-azetidinone.

IR_{max}^{neat} (cm⁻¹) :

1755, 1610, 1510, 1350, 1245, 1175, 1030

NMR δ (CDCl₃): 1.35 (3H, d, J=6.5Hz), 2.40 (2H, d, J=6.5Hz), 3.09 (1H, dd, J=2.5 and 6Hz), 3.73 (6H, s), 3.77 (3H, s), 4.91 (2H, s), 5.18 (2H, s), 5.71 (1H, s) ppm

Reference Example 9-6



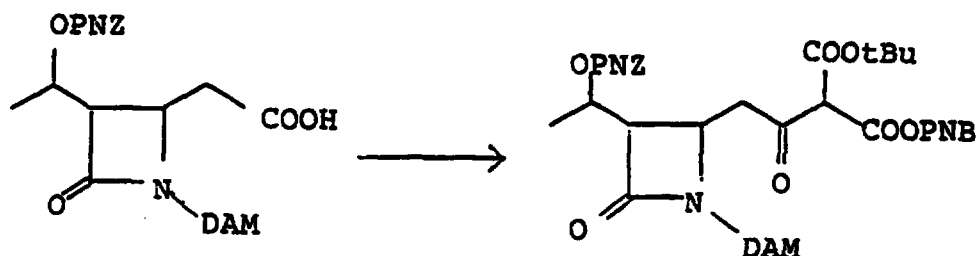
2.2 g of 1-(di-*p*-anisylmethyl)-3-(1-*p*-nitrobenzyloxycarbonyloxyethyl)-4-*p*-methoxybenzyloxycarbonylmethyl-2-azetidinone was dissolved in 20 ml of dried methylene chloride, and 0.88 g of *m*-dimethoxybenzene and 2.5 ml of trifluoroacetic acid were added to the solution, followed by stirring at room temperature for 4 hours. The solvent was removed by distillation, and the resulting oily residue was subjected to silica gel chromatography to obtain 1.75 g of 1-(di-*p*-anisylmethyl)-3-(1-*p*-nitrobenzyloxycarbonyloxyethyl)-4-carboxymethyl-2-azetidinone.

IR_{max}^{neat} (cm⁻¹) :

~3000, 1745, 1615, 1510, 1250, 1180, 1035

NMR δ (CDCl₃): 1.35 (3H, d, J=6.5Hz), 2.35 (2H, d, J=6.5Hz), 3.10 (1H, m), 3.73 (6H, s), 5.16 (2H, s), 5.75 (1H, s), 6.73 (4H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 8.10 (2H, d, J=9Hz) ppm

Reference Example 9-7



0.8 g of 1-(di-*p*-anisylmethyl)-3-(1-*p*-nitrobenzyloxycarbonyloxyethyl)-4-carboxymethyl-2-azetidinone was dissolved in 20 ml of dried methylene chloride, and 0.17 ml of *N*-methylmorpholine was added thereto. After cooling to -10°C or less, 0.15 ml of ethyl chloroformate was added dropwise thereto, followed by stirring for 30 minutes. Separately, 0.81 g of *t*-butyl-(*p*-nitrobenzyl)-malonate was dissolved in 15 ml of dried tetrahydrofuran, and 0.14 g of sodium hydride (50% purity) was added to the resulting solution in a nitrogen stream under ice-cooling, followed by stirring at that temperature for 30 minutes. The resulting solution was added dropwise to the above prepared solution of a mixed anhydride at a temperature of -10°C or less, followed by stirring for 1 hour. The reaction mixture was warmed to room temperature and concentrated

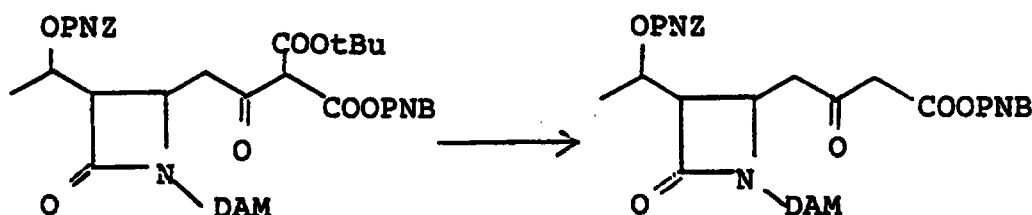
under reduced pressure. The concentrate was diluted with cool water and ethyl acetate, washed successively with a 1N aqueous solution of hydrochloric acid and water, dried over sodium sulfate and distilled off to remove the solvent. The resulting residue was purified by silica gel chromatography to obtain 1-(di-p-anisylmethyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-t-butoxycarbonyl-3-(p-nitrobenzyloxycarbonyl)-2-oxopropyl]-2-azetidinone.

$IR_{max}^{neat} (cm^{-1}) :$

1750, 1610, 1510, 1345, 1250

NMR δ ($CDCl_3$): 1.38 (9H, s), 3.75 (6H, s), 5.17 (4H, s), 5.77 (1H, br. s), 6.77 (4H, d, $J=8.5$ Hz), 7.45 (4H, d, $J=9$ Hz), 8.15 (4H, d, $J=9$ Hz) ppm

Reference Example 9-8



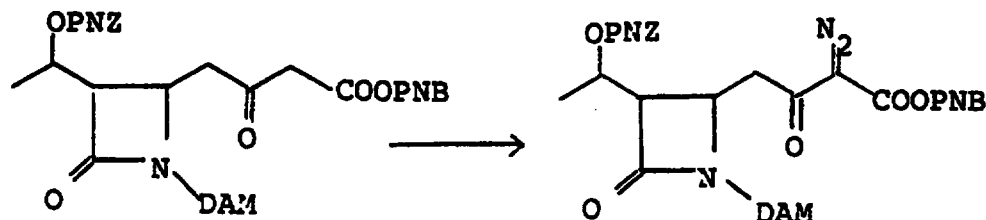
2.3 g of 1-(di-p-anisylmethyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-t-butoxycarbonyl-3-(p-nitrobenzyloxycarbonyl)-2-oxopropyl]-2-azetidinone was dissolved in 120 ml of dried methylene chloride, and 10 ml of trifluoroacetic acid was added to the solution, followed by stirring at room temperature for 1 hour. The reaction mixture was washed with an aqueous solution of sodium bicarbonate and then with water, dried over sodium sulfate and distilled off to remove the solvent. The residue was purified by silica gel chromatography to obtain 1-(di-p-anisylmethyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-(p-nitrobenzyloxycarbonyl)-2-oxopropyl]-2-azetidinone.

$IR_{max}^{neat} (cm^{-1}) :$

1748, 1720 (sh.), 1610, 1510, 1345, 1250

NMR δ ($CDCl_3$): 1.41 (3H, d, $J=6.5$ Hz), 2.61 (2H, d, $J=6.5$ Hz), 3.27 (2H, s), 3.76 (6H, s), 5.77 (1H, s), 6.82 (4H, d, $J=9$ Hz), 7.47 (2H, d, $J=9$ Hz), 7.53 (2H, d, $J=9$ Hz), 8.20 (4H, d, $J=9$ Hz) ppm

Reference Example 9-9



1.9 g of 1-(di-p-anisylmethyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-(p-nitrobenzyloxycarbonyl)-2-oxopropyl]-2-azetidinone and 660 mg of p-carboxybenzenesulfonyl azide were dissolved in 50 ml of dried acetonitrile, and 1.4 ml of triethylamine was added thereto dropwise in a nitrogen stream under ice-cooling. After stirring at that temperature for 15 minutes, the reaction mixture was diluted with ethyl acetate, and the

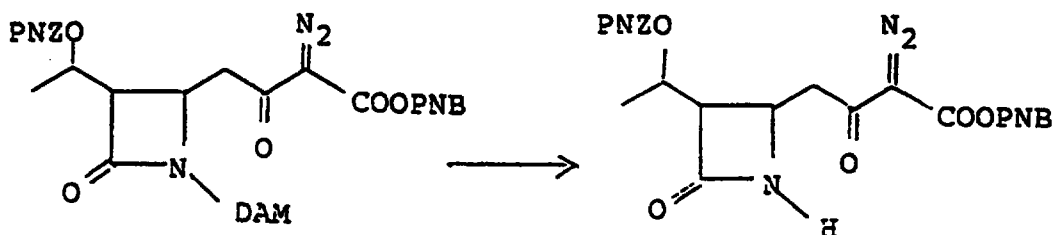
thus formed precipitate was filtered. The filtrate was concentrated under reduced pressure, and the resulting oily residue was subjected to silica gel chromatography to obtain 1-(di-p-anisylmethyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-(p-nitrobenzyloxycarbonyl)-2-oxo-3-diazopropyl]-2-azetidinone.

IR_{max}^{neat} (cm⁻¹) :

2150, 1750, 1720 (sh.), 1650, 1510, 1250, 1350

NMR δ (CDCl₃): 1.38 (3H, d, J=6.5Hz), 2.95 (2H, d, J=6.5Hz), 3.73 (6H, s), 5.17 (2H, s), 5.24 (2H, s), 5.74 (1H, s), 6.71 (2H, d, J=9Hz), 6.76 (2H, d, J=9Hz), 7.08 (2H, d, J=9Hz), 7.14 (2H, d, J=9Hz), 7.42 (4H, d, J=9Hz), 8.11 (2H, d, J=9Hz), 8.16 (2H, d, J=9Hz) ppm

Reference Example 9-10



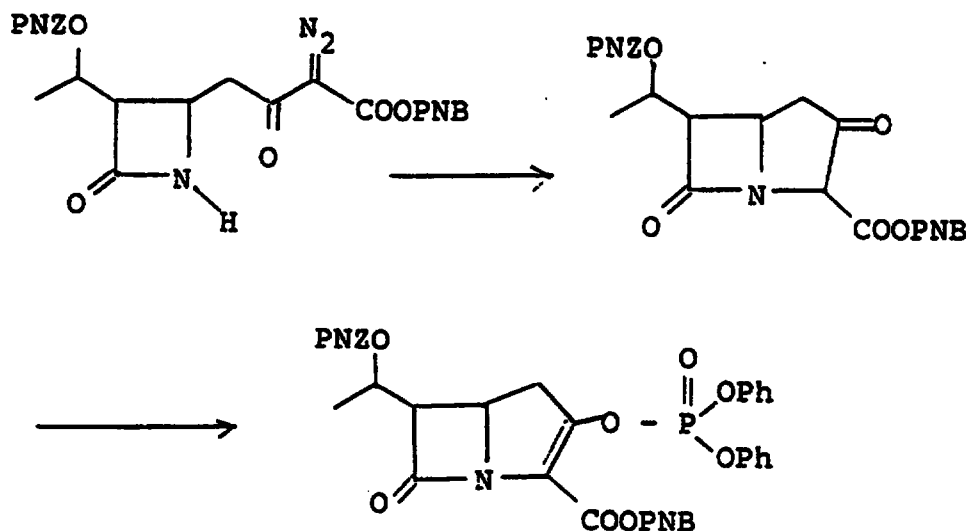
1.27 g 1-(di-p-anisylmethyl)-3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-(p-nitrobenzyloxycarbonyl)-2-oxo-3-diazopropyl]-2-azetidinone was dissolved in 50 ml of acetonitrile-water (9 : 1 by volume), and 2.7 g of ceric ammonium nitrate was added thereto all at once under ice-cooling. After vigorously stirring, the mixture was further stirred at room temperature for 30 minutes. Cool water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and dried over sodium sulfate. The solvent was distilled off, and the resulting residue was purified by silica gel chromatography to obtain 3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-(p-nitrobenzyloxycarbonyl)-2-oxo-3-diazopropyl]-2-azetidinone.

IR_{max}^{neat} (cm⁻¹) :

2145, 1750, 1720, 1650, 1520, 1345, 1260

NMR δ (CDCl₃): 1.45 (3H, d, J=6.5Hz), 3.01 (1H, dd, J=9 and 18Hz), 3.29 (1H, dd, J= 4.5 and 18Hz), 4.00 (1H, m), 5.24 (2H, s), 5.36 (2H, s), 6.12 (1H, s), 7.55 (4H, d, J=8.5Hz), 8.21 (2H, d, J=8.5Hz), 8.25 (2H, d, J=8.5Hz) ppm

Reference Example 9-11



a) 0.55 g of 3-(1-p-nitrobenzyloxycarbonyloxyethyl)-4-[3-(p-nitrobenzyloxycarbonyl)-2-oxo-3-diazopropyl]-2-azetidinone was dissolved in 25 ml of degassed dried benzene, and a catalytic amount of rhodium (II) acetate was added thereto. After blowing nitrogen gas into the mixture for about 3 minutes, the mixture was refluxed for 20 minutes, followed by cooling. The catalyst was separated by filtration and washed with benzene. The filtrate and the washing were combined and concentrated under reduced pressure to yield p-nitrobenzyl-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]heptan-3,7-dione-2-carboxylate.

$IR_{\max}^{\text{neat}}$ (cm^{-1}):

1770, 1745, 1520, 1350, 1260

NMR δ (CDCl_3): 1.50 (3H, d, $J=6.5\text{Hz}$), 2.50 (1H, dd, $J=8.0$ and 18Hz), 2.89 (1H, dd, $J=7.0$ and 18Hz), 3.39 (1H, dd, $J=2.0$ and 8.0Hz), 4.14 (1H, dt, $J=2.0$ and 7.0Hz), 4.77 (1H, s), 5.26 (4H, s), 7.52 (4H, d, $J=8.5\text{Hz}$), 8.21 (4H, d, $J=8.5\text{Hz}$) ppm

b) The keto ester derivative as obtained in a) above was dissolved in 25 ml of dried acetonitrile, and 195 mg of diisopronylethylamine was added thereto under ice-cooling. To the resulting mixture was added dropwise a solution of 300 mg of diphenyl chlorophosphate in 2 ml of dried acetonitrile, followed by stirring for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water, and dried over magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain p-nitrobenzyl-5,6-trans-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate.

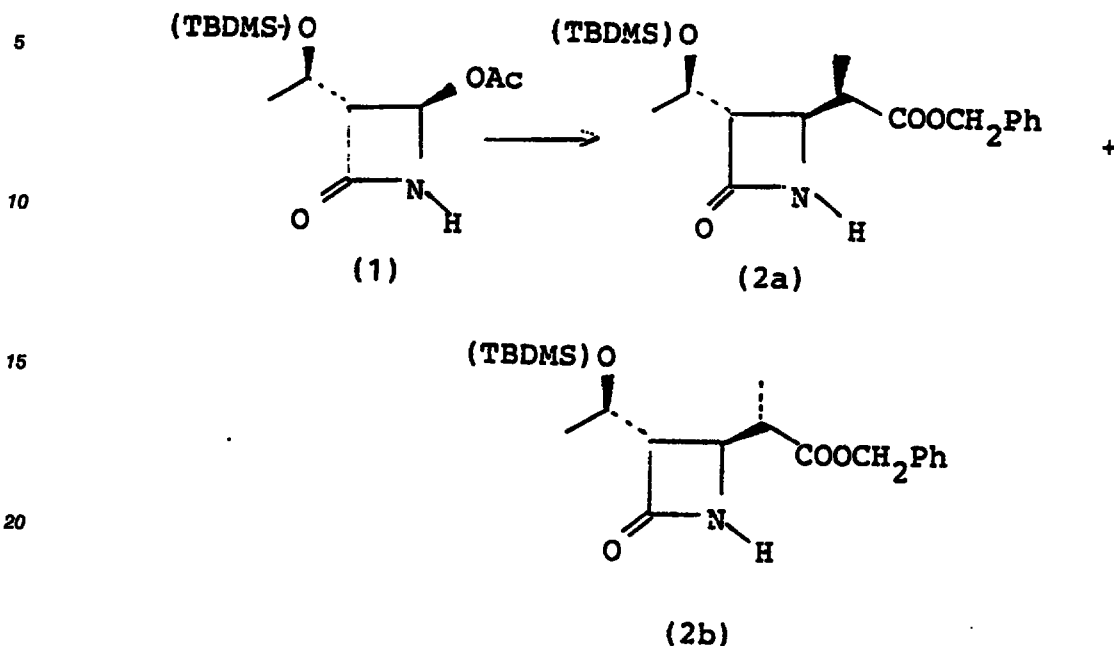
$IR_{\max}^{\text{neat}}$ (cm^{-1}):

1780, 1745, 1585, 1517, 1480, 1345, 1295, 1255, 1180, 1158, 965

NMR δ (CDCl_3): 1.46 (3H, d, $J=6.5\text{Hz}$), 3.24 (2H, br. d, $J=8.5\text{Hz}$), 3.40 (1H, dd, $J=3.0$ and 8.5Hz), 5.24 (2H, s), 5.32 (2H, ABq, $J=13\text{Hz}$), 7.28 (10H, s), 7.53 (4H, d, $J=8.5\text{Hz}$), 8.14 (2H, d, $J=8.5\text{Hz}$), 8.23 (2H, d, $J=8.5\text{Hz}$) ppm

Further, by using (3R,4S)-1-(di-p-anisylmethyl)-3-ethenyl-4-carboxy-2-azetidinone [optical rotation $[\alpha]_D^{22} = +63.3^\circ$ ($c=0.12$, CHCl_3)], (5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate was obtained.

Reference Example 10-1



To 1.33 g (20 mM) of activated zinc was added 20 ml of dried tetrahydrofuran, and 8.8 ml of a 15% *n*-hexane solution of diethylaluminium chloride was added thereto in a nitrogen stream under ice-cooling. A solution prepared by dissolving 1.49 g (5.2 mmol) of (3R,4R)-4-acetoxy-3-[(R)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (1) and 3.73 g (15.3 mmol) of benzyl α -bromopropionate in 13.3 ml of dried tetrahydrofuran was added dropwise to the mixture over a period of 30 to 40 minutes, followed by stirring for 1 hours. Under ice-cooling, 2.8 ml of pyridine, 13.2 ml of water, 26.5 ml of ethyl acetate and 13.2 ml of a 1N hydrochloric acid aqueous solution were successively added thereto, and the resulting mixture was filtered using Celite. The filtrate was washed with water, and the organic layer was dried over sodium sulfate and distilled off to remove the solvent. The resulting oily residue was subjected to silica gel column chromatography to obtain an isomeric mixture of 4-(1-benzyloxycarbonyl)ethyl-3-[(R)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone.

The isomeric mixture was separated into each compound by Lober column chromatography using silica gel and 1.5% isopropanol/*n*-hexane as an eluent to obtain the compound (2a) and the compound (2b) as oily substances.

Isomer (2b)

IR^{neat}_{max} (cm⁻¹) :

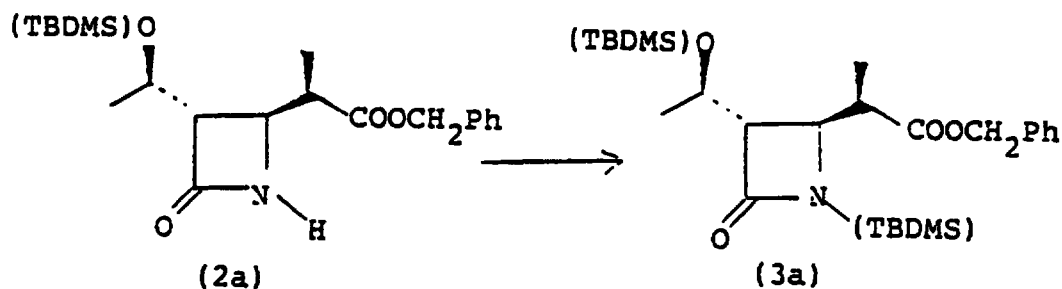
1755, 1460, 1377, 1252, 1100, 835

NMR δ (CDCl₃): 0.06 (6H, s), 0.87 (9H, s), 1.16 (3H, d, J=6.5Hz), 1.19 (3H, d, J=7.0Hz), 3.71 (1H, dd, J=2 and 10Hz), 5.14 (2H, s), 7.35 (5H, s) ppm

Isomer (2a)

NMR δ (CDCl₃): 0.06 (6H, s), 0.87 (9H, s), 1.08 (3H, d, J=6.5Hz), 1.18 (3H, d, J=7.0Hz), 3.91 (1H, dd, J=2.2 and 5.5Hz), 4.17 (2H, q, J=6Hz), 5.12 (2H, s), 7.35 (5H, s) ppm

Reference Example 10-2

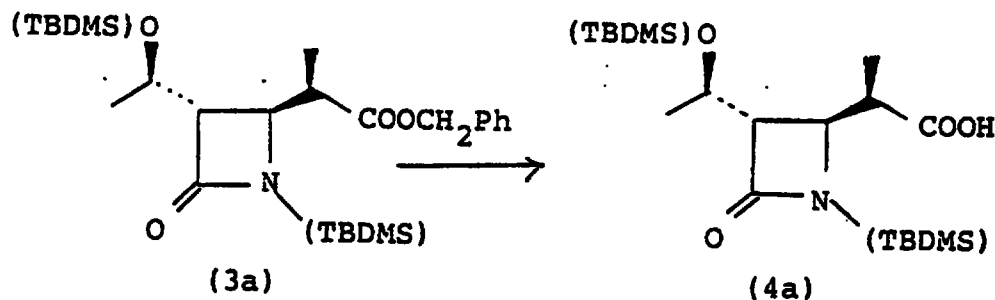


200 mg of 4-(1-benzyloxycarbonyl)-ethyl-3-[(R)-1-(t-butyl-dimethylsilyloxy)-ethyl]-2-azetidinone (2a) was dissolved in 2 ml of dried dimethylformamide. 126 mg of triethylamine was added to the resulting solution, and then 151 mg of t-butyl-dimethylsilyl chloride was added thereto, followed by stirring at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water, dried over sodium sulfate and purified by silica gel chromatography to obtain 4-(1-benzyloxycarbonyl)-ethyl-3-[(R)-1-(t-butyl-dimethylsilyloxy)-ethyl]-1-(t-butyl-dimethylsilyl)-2-azetidinone (3a).

$IR_{\text{max}}^{\text{neat}} (\text{cm}^{-1}) :$

1750, 1465, 1325, 1255, 835

Reference Example 10-3

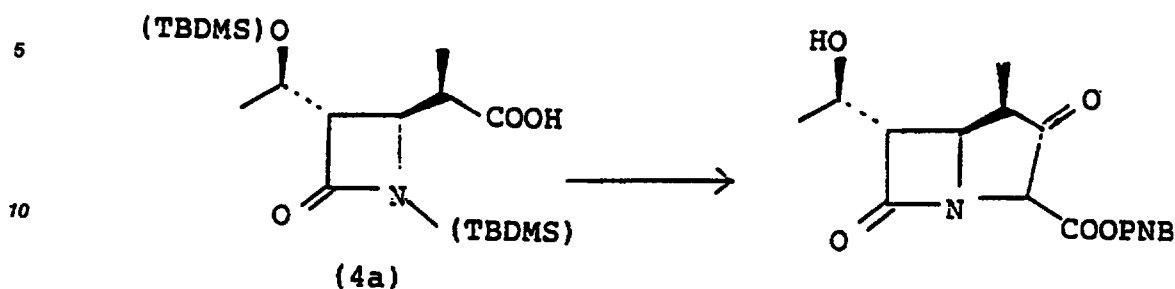


184 mg of 4-(1-benzyloxycarbonyl)-ethyl-3-[(R)-1-(t-butyl-dimethylsilyloxy)-ethyl]-1-(t-butyl-dimethylsilyl)-2-azetidinone (3a) was dissolved in 4 ml of methanol, and the resulting solution was stirred together with 20 mg of 10% palladium-on-carbon at an atmospheric pressure of hydrogen for 2 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 4-(1-carboxy)-ethyl-3-[(R)-1-(t-butyl-dimethylsilyloxy)-ethyl]-1-(t-butyl-dimethylsilyl)-2-azetidinone (4a).

$IR_{\text{max}}^{\text{neat}} (\text{cm}^{-1}) :$

1740, 1465, 1330, 1255, 1043, 837

Reference Example 10-4



15

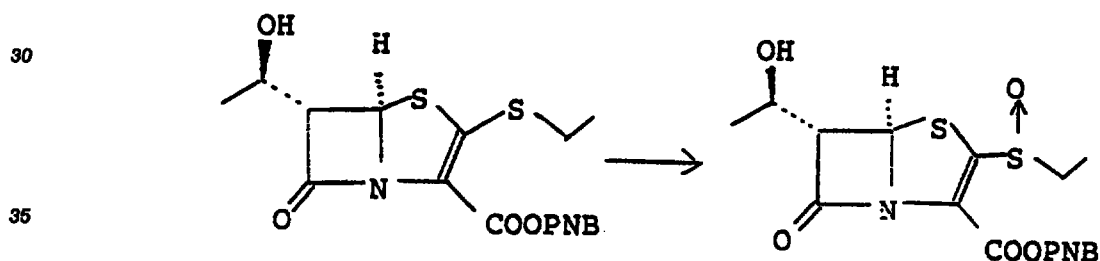
(4R,5R,6S,8R)-p-Nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate was obtained from 170 mg of 4-(1-carboxy)-ethyl-3-[(R)-1-(t-butyldimethylsilyloxy)-ethyl]-1-(t-butyldimethylsilyl)-2-azetidinone (4a) according to the method described in Japanese Patent Application OPI No. 26887/83, pages 64-65.

20

IR^{neat}_{max} (cm⁻¹) :

25 3450 (br.), 1770 (sh.), 1750, 1605, 1520, 1350, 1217, 1180

Reference Example 11



40 To a solution of 261 mg of (5R,6S,8R)-p-nitrobenzyl-3-ethylthio-6-(1-hydroxyethyl)-1-aza bicyclo[3.2.0]-hept-2-ene-7-one-4-thia-2-carboxylate in 28 ml of dried methylene chloride, 144 mg of m-chloroperbenzoic acid was added at -45°C in a nitrogen stream, followed by stirring at -20° to -40°C for 2 hours. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and then with water, dried over sodium sulfate and distilled off to remove the solvent. The resulting residue was purified by silica

45 gel chromatography to obtain (5R,6S,8R)-p-nitrobenzyl-3-ethylsulfinyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-ene-7-one-4-thia-2-carboxylate.

IR_v ^{CHCl₃}_{max} (cm⁻¹) :

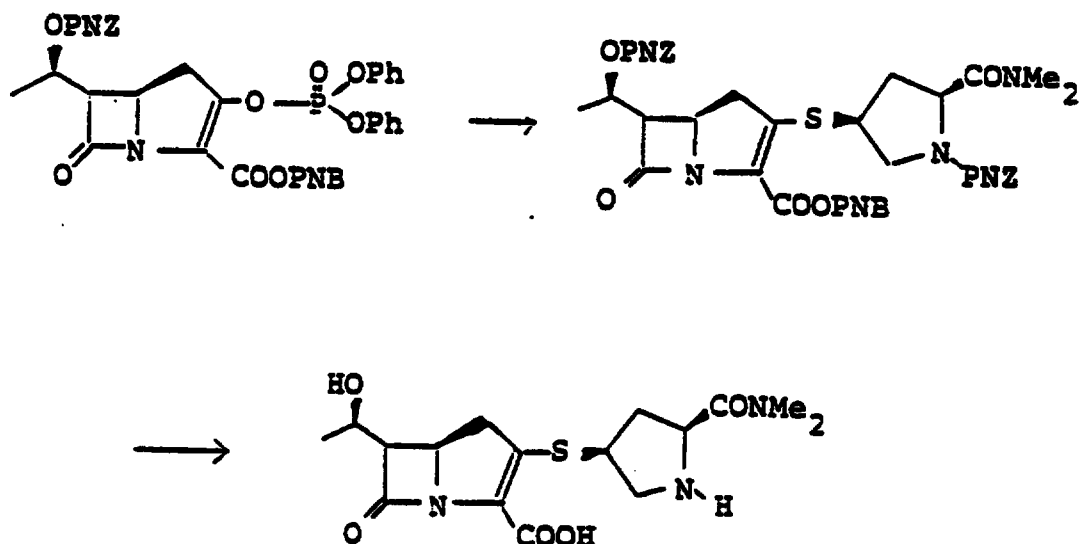
50

1793, 1703, 1605, 1517, 1447, 1377, 1344, 1315, 1172, 1112, 1043, 965, 824

NMR δ (CDCl₃): 5.74 (3/5H, d, J=1.5Hz), 5.87 (2/5H, d, J=1.5Hz) ppm

55

Example 1-1



a) 122 mg of (5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate was dissolved in 3 ml of dry acetonitrile, and 31 mg of diisopropylethylamine was added thereto in a nitrogen stream under ice-cooling. Then, 60 mg of [2S,4S]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4-mercaptopyrrolidine was added to the mixture, followed by stirring for 1 hour. The reaction solution was diluted with ethyl acetate, washed with water, dried over magnesium sulfate and the solvent was distilled off. The residue was purified by silica gel thin layer chromatography to obtain 95 mg of (5R,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate.

$IR_{max}^{neat} \text{ (cm}^{-1}\text{)} :$

1780, 1745, 1705, 1650, 1605, 1515, 1342, 1257

NMR δ (CDCl₃): 1.49 (3H, d, J=6Hz), 2.99 (3H, s), 3.11 (3H, s), 5.25 (4H, s), 5.23 and 5.46 (2H, ABq, J=14Hz), 7.53 (4H, d, J=8.5Hz), 7.62 (2H, d, J=8.5Hz), 8.18 (6H, d, J=8.5Hz)

$[\alpha]_D^{25} + 7.7^\circ$ (c=0.303, acetone)

b) 95 mg of (5R,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate was dissolved in 20 ml of dioxane, and a morpholinopropanesulfonic acid buffer solution (pH = 7.0, 10 ml) and platinum oxide (35 mg) were added thereto. The mixture was then hydrogenated under a hydrogen pressure of 3.5 atm. for 6.5 hours. The catalyst was filtered off and dioxane was distilled off under reduced pressure. The residual solution was washed with ethyl acetate, and the aqueous layer was again distilled under reduced pressure to remove the organic solvent. The residual solution was subjected to polymer chromatography (CHP-20P) to obtain (5R,6S,8R,2'S,4'S)-3-[4-(2-dimethylaminocarbonyl)pyrrolidinylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid from the fraction eluted with water.

$UV_{max}^{H_2O} \text{ nm:}$

297

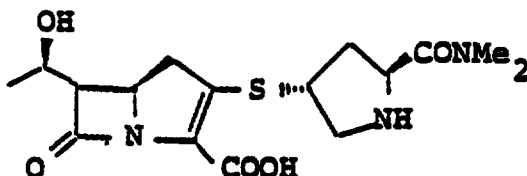
$$\text{IR}_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}:$$

5 1755, 1627, 1393, 1252, 1130

NMR δ (D_2O): 1.25 (3H, d, $J=6.4\text{Hz}$), 1.81-1.96 (1H, m), 2.96 (3H, s), 3.03 (3H, s), 3.14-3.20 (3H, m), 3.31-3.41 (2H, m), 3.62-3.72 (1H, m), 3.90-4.00 (1H, m), 4.14-4.26 (2H, m), 4.63 (1H, t, $J=8.5\text{Hz}$)

Example 1-2

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a) In the same manner as described in Example 1-1(a) but using 129 mg of (5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate and 67 mg of [2S,4R]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4-mercaptopyrrolidine, there was obtained 40 mg of (5R,6S,8R,2'S,4'R)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-carboxylate.

$$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}):$$

30

1775, 1745, 1705, 1650, 1520, 1400, 1345, 1260, 1130

NMR δ (CDCl_3): 1.48 (3H, d, $J=6\text{Hz}$), 2.96 (3H, s), 3.12 (3H, s), 5.22 (4H, s), 7.44, 7.50 and 7.58 (each 2H, d, $J=8.5\text{Hz}$), 8.17 (6H, d, $J=8.5\text{Hz}$)

35

$[\alpha]_{\text{D}}^{27} +31.1^\circ$ ($c=0.193$, acetone)

40

b) In the same manner as described in Example 1-1(b) but using 40 mg of (5R,6S,8R,2'S,4'R)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate, there was obtained (5R,6S,8R,2'S,4'R)-3-[4-(2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid.

$$\text{UV}_{\text{max}}^{\text{H}_2\text{O}} \text{ nm}:$$

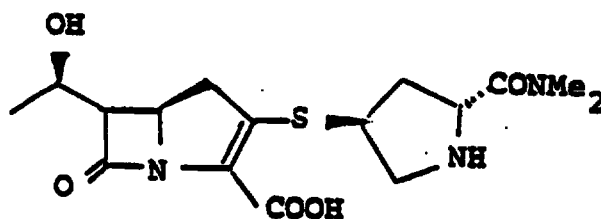
45

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Example 1-3



a) In the same manner as described in Example 1-1(a) but using 61 mg of (5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate and 31 mg of [2R,4S]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4-mercaptopyrrolidine, there was obtained 37 mg of (5R,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate.

$IR_{max}^{neat} \text{ (cm}^{-1}\text{)} :$

1775, 1745, 1705, 1650, 1520, 1400, 1345, 1260, 1130

NMR δ (CDCl₃): 1.49 (3H, d, J=6.5Hz), 2.98 (3H, s), 3.16 (3H, s), 5.27 (4H, s), 5.19 and 5.47 (2H, ABq, J=14Hz), 7.50, 7.55 and 7.64 (each 2H, d, J=8.5Hz), 8.20 (4H, d, J=8.5Hz), 8.22 (2H, d, J=8.5Hz)

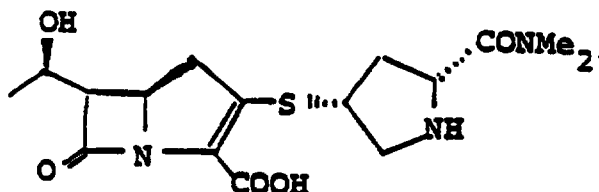
$[\alpha]_D^{29} + 26.8^\circ$ (c=0.243, acetone)

b) In the same manner as described in Example 1-1(b) but using 37 mg of (5R,6S,8R,2'R,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate, there was obtained (5R,6S,8R,2'R,4'S)-3-[4-(2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid.

$UV_{max}^{H_2O} \text{ nm:}$

297

Example 1-4



a) In the same manner as described in Example 1-1(a) but using 76 mg of (5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate and 39 mg of [2R,4R]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4-mercaptopyrrolidine, there was obtained 35 mg of (5R,6S,8R,2'R,4'R)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-

azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate.

$IR_{max}^{neat} (cm^{-1}) :$

1775, 1745, 1705, 1650, 1520, 1440, 1342, 1260, 1120

NMR δ ($CDCl_3$): 1.49 (3H, d, $J=6.5Hz$), 2.98 (3H, s), 3.09 (3H, s), 5.25 (4H, s), 5.26 and 5.44 (2H, ABq, $J=14Hz$), 8.20 (6H, d, $J=8.5Hz$)

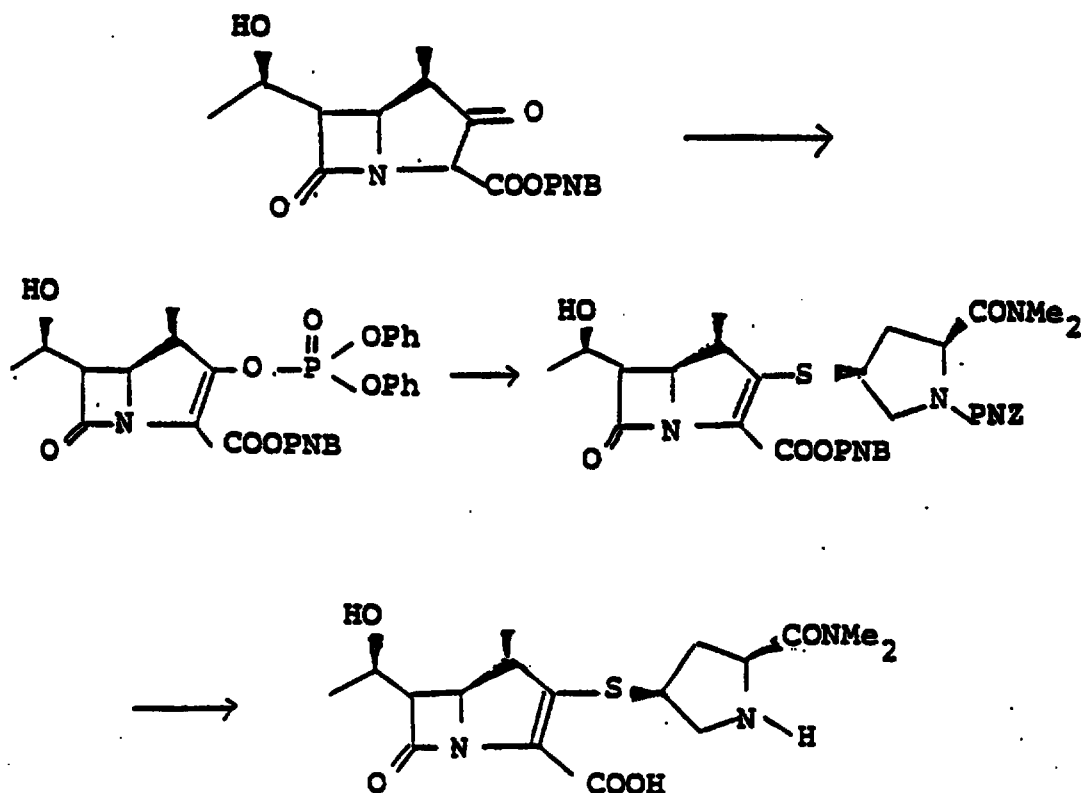
$[\alpha]_D^{30} +23.3^\circ$ ($c=0.329$, acetone)

b) In the same manner as described in Example 1-1(b) but using 35 mg of (5R,6S,8R,2'R,4'R)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate, there was obtained (5R,6S,8R,2'R,4'R)-3-[4-(2-dimethylaminocarbonyl)-pyrrolidinylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid.

$UV_{max}^{H_2O} nm:$

297

Example 2



a) 53 mg of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0] hept-3,7-dione-2-carboxylate was dissolved in 5 ml of dry acetonitrile, and 57 mg of diisopropylethylamine and then 43 mg of diphenyl chlorophosphate were added thereto. After stirring for 2.5 hours, 57 mg of [2S,4S]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4-mercaptopyrrolidine was added to the mixture, followed by stirring for 1 hour. The reaction solution was diluted with ethyl acetate, washed with water,

dried over magnesium sulfate and the solvent was distilled off. The residue was purified by silica gel thin layer chromatography to obtain 35 mg of (4R,5S,6S, 8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate.

$$\frac{I_{\text{max}}}{I_{\text{min}}} (\text{cm}^{-1}) :$$

1760, 1705, 1645, 1520, 1402, 1342, 1135, 1110

NMR δ (CDCl_3): 1.30 (3H, d, $J=7.0\text{Hz}$), 1.35 (3H, d, $J=6.5\text{Hz}$), 2.99 (3H, s), 3.02 (3H, d, $J=15\text{Hz}$), 5.21 (2H, s), 5.20 and 5.43 (2H, ABq, $J=14\text{Hz}$), 7.51 (2H, d, $J=8.5\text{Hz}$), 7.64 (2H, d, $J=8.5\text{Hz}$), 8.20 (4H, d, $J=8.5\text{Hz}$)

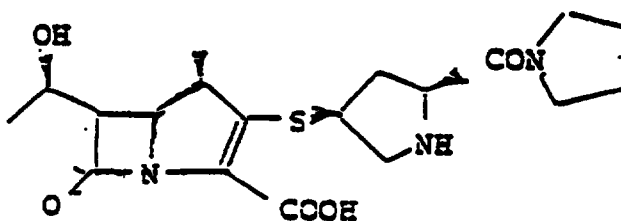
b) 25 mg of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidinylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate was dissolved in a mixture of 1.9 ml of tetrahydrofuran and 0.3 ml of ethanol, and the mixture was hydrogenated in a morpholinopropanesulfonic acid buffer solution ($\text{pH} = 7.0$, 1.9 ml) under atmospheric pressure of hydrogen for 3 hours at room temperature in the presence of 30 mg of 10% palladium-carbon, which had been activated in hydrogen atmosphere for 1 hour followed by washing with water. After filtering off the catalyst, tetrahydrofuran and ethanol were distilled off under reduced pressure, and the residual solution was washed with ethyl acetate. The aqueous layer was again distilled under reduced pressure to remove organic solvents, and the residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'S,4'S)-3-[4-(2-dimethylaminocarbonyl)-pyrrolidinylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid from the fraction eluted with water.

$$\frac{UV_{\text{max}}}{UV_{\text{min}}} \text{ nm} :$$

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NMR δ (D_2O): 1.21 (3H, d, $J=7.0\text{Hz}$), 1.29 (3H, d, $J=6.5\text{Hz}$), 1.92 (1H, m), 2.99 (3H, s), 3.06 (3H, s)

Example 3



a) 61 mg of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate was dissolved in 6 ml of dry acetonitrile, and 72 mg of diisopropylethylamine and then 55 mg of diphenyl chlorophosphate were added thereto in a nitrogen stream under ice-cooling, followed by stirring for 2.5 hours. 77 mg of [2S,4S]-1-p-nitrobenzyloxycarbonyl-2-(1-pyrrolidinocarbonyl)-4-mercaptopyrrolidine was added to the mixture, followed by stirring for 1 hour. The reaction solution was diluted with ethyl acetate, washed with water, dried over magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel thin layer chromatography to obtain 51 mg of (4R,5S, 6S,6R,2'S,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-(1-pyrrolidinocarbonyl)-pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate.

$$IR_{\max}^{\text{neat}} \text{ (cm}^{-1}\text{)} :$$

5 1760, 1710, 1640, 1525, 1440, 1350, 1210, 1110

NMR δ (CDCl_3) : 1.30 (3H, d, $J=7.0\text{Hz}$), 1.34 (3H, d, $J=6.5\text{Hz}$), 5.21 (2H, s), 5.20 and 5.44 (2H, ABq, $J=14\text{Hz}$), 7.50 (2H, d, $J=8.5\text{Hz}$), 7.64 (2H, d, $J=8.5\text{Hz}$), 8.20 (4H, d, $J=8.5\text{Hz}$)

b) 50 mg of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(1-pyrrolidinocarbonyl)-pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate was dissolved in a mixture of 3.9 ml of tetrahydrofuran and 0.6 ml of ethanol, and the mixture was hydrogenated in a morpholinopropanesulfonic acid buffer solution ($\text{pH} = 7.0$, 3.9 ml) under atmospheric pressure of hydrogen for 4.5 hours at room temperature in the presence of 60 mg of 10% palladium-carbon, which had been activated in hydrogen atmosphere for 1 hour followed by washing with water. After filtering off the catalyst, tetrahydrofuran and ethanol were distilled off under reduced pressure, and the residual solution was washed with ethyl acetate. The aqueous layer was again distilled under reduced pressure to remove organic solvents, and the residual solution was subjected to polymer chromatography (CHP-20P) to obtain (4R,5S,6S,8R,2'S,4'S)-3-[2-(1-pyrrolidinocarbonyl)-pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid from the fraction eluted with a 2% aqueous tetrahydrofuran solution.

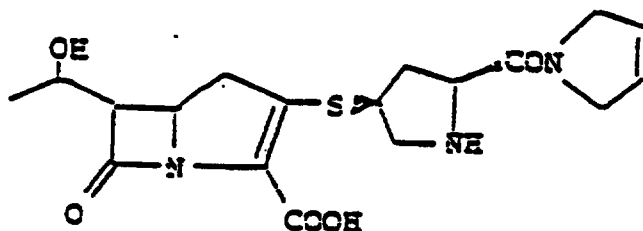
$$UV_{\max}^{\text{D}_2\text{O}} \text{ nm} :$$

25

297

NMR δ (D_2O) : 1.20 (3H, d, $J=7.0\text{Hz}$), 1.29 (3H, d, $J=6.5\text{Hz}$), 1.95 (6H, m), 3.46 (6H, m), 3.72 (1H, dd, $J=6.5$ and 12Hz), 4.02 (1H, quintet, $J=6.5\text{Hz}$)

30 Example 4



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a) 172 mg of (5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate was dissolved in 2.3 ml of dry acetonitrile, and to the solution were added a solution of 59 mg of diisopropylethylamine in 0.7 ml of dry acetonitrile and then a solution of 94 mg of [2S,4S]-1-p-nitrobenzyloxycarbonyl-2-(3-pyrroline-1-carbonyl)-4-mercaptopyrrolidine in 1 ml of dry acetonitrile, in a nitrogen stream and under ice-cooling, followed by stirring for 15 minutes. The reaction solution was diluted with diethyl ether, washed with water, and the insoluble material in the ether layer was dissolved with addition of methylene chloride. The methylene chloride and ether layer was dried over magnesium sulfate and the solvent was distilled off. The residue was purified by silica gel thin layer chromatography to obtain 182 mg of (5R,6S,8R,2'S,4'S)-p-nitrobenzyl-3-{4-[1-p-nitrobenzyloxycarbonyl-2-(3-pyrroline-1-carbonyl)]-pyrrolidinylthio}-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate.

55

$$IR_{\max}^{\text{CHCl}_3} \text{ (cm}^{-1}\text{)} :$$

1780, 1745, 1708, 1660, 1623, 1606, 1520, 1342

NMR δ (CDCl₃): 1.49 (3H, d, J = 6.2Hz), 5.26 (4H, s), 8.18 (6H, d, J = 8.8Hz)

b) 182 mg of (5R,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-[1-p-nitrobenzyloxycarbonyl-2-(3-pyrroline-1-carbonyl)]-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate was dissolved in a mixture of 12.6 ml of tetrahydrofuran and 2 ml of ethanol, and the solution was hydrogenated in a morpholinopropanesulfonic acid buffer solution (pH = 7.0, 12.6 ml) at room temperature under atmospheric pressure of hydrogen for 7 hours in the presence of 219 mg of 10% palladium-carbon, which had been activated in hydrogen atmosphere for 1 hour, followed by washing with water. After filtering off the catalyst, tetrahydrofuran and ethanol were distilled off under reduced pressure, and the residual solution was washed with ethyl acetate. The aqueous layer was again distilled under reduced pressure to remove organic solvents, and the residual solution was subjected to polymer chromatography (CHP-20P) to obtain (5R,6S,8R,2'S,4'S)-3-[4-[2-(3-pyrroline-1-carbonyl)-pyrrolidinylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid from the fraction eluted with a 2% aqueous tetrahydrofuran solution.

UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm:

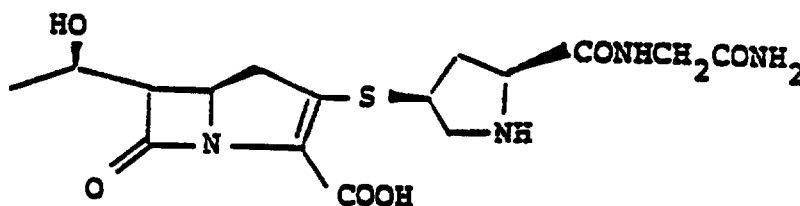
298

IR $_{\text{max}}^{\text{KBr}}$ (cm⁻¹):

1755, 1640, 1595, 1450, 1380, 1245

NMR δ (D₂O): 1.26 (3H, d, J = 6.4Hz), 3.18 (1H, dd, J = 2.1 and 9.0Hz), 3.77 (1H, dd, J = 7.0 and 12.0Hz), 5.89 (2H, br. s)

Example 5



a) Following the procedures as described in Example 1-1(a) using 68 mg of (5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate and 33 mg of [2S,4S]-1-p-nitrobenzyloxycarbonyl-2-carbamoylmethylaminocarbonyl-4-mercaptopyrrolidine, there was obtained 61 mg of crystalline (5R,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-carbamoylmethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate by filtration.

IR $_{\text{max}}^{\text{Nujol}}$ (cm⁻¹):

3445, 3300, 1790, 1745, 1710, 1670, 1635, 1510, 1345, 1270

NMR δ (CDCl₃): 1.50 (3H, d, J = 6.5Hz), 5.23 (4H, s), 7.50 (4H, d, J = 8.5Hz), 8.21 (6H, d, J = 8.5Hz)
m.p.: 184-189 °C (dec.)

b) 30 mg of (5R,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[4-(1-p-nitrobenzyloxycarbonyl-2-carbamoylmethylaminocarbonyl)-pyrrolidinylthio]-6-(1-p-nitrobenzyloxycarbonyloxyethyl)-1-azabicyclo[3.2.0]hept-2-

ene-7-one-2-carboxylate was dissolved in a mixture of 3.1 ml of tetrahydrofuran and 1 ml of dimethylformamide, and the solution was hydrogenated in the presence of a morpholinopropanesulfonic acid buffer solution (pH = 7.0, 3.1 ml) at room temperature under atmospheric pressure of hydrogen for 5 hours in the presence of 37 mg of 10% palladium-carbon which had been activated in hydrogen atmosphere for 1 hour followed by washing with water. After filtering off the catalyst, tetrahydrofuran was distilled off under reduced pressure, and the residual solution was washed with methylene chloride. The aqueous layer was distilled to remove the organic solvents, and the residual solution was subjected to polymer chromatography (CHP-20P) to obtain (5R,6S,8R,2'S,4'S)-3-[4-(2-carbamoylmethylaminocarbonyl)-pyrrolidinylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid from the fraction eluted with water.

UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm:

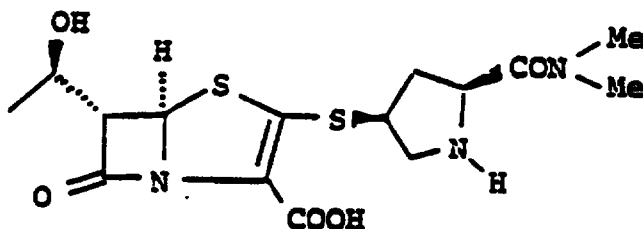
300

IR KBr ν_{max} (cm^{-1}):

1745, 1665, 1590, 1390, 1220, 1180, 1040

NMR δ (D_2O): 1.26 (3H, d, $J=6.6\text{Hz}$), 1.86 (1H, m), 3.20 (2H, dd, $J=7.5$ and 14.7Hz), 3.38 (1H, dd, $J=3.0$ and 6.7Hz), 4.02 (1H, t, $J=9.0\text{Hz}$)

Example 6



a) To a solution of 45 mg of (5R,6S,8R)-p-nitrobenzyl-3-ethylsulfinyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylate in 0.8 ml of dry acetonitrile were added a solution of 30 mg of diisopropylethylamine in 0.3 ml of dry acetonitrile and then a solution of 81 mg of (2'S,4'S)-1'-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4'-mercaptopyrrolidine in 0.6 ml of dry acetonitrile under nitrogen stream at -40°C , followed by stirring the mixture at -40°C to -45°C for 10 minutes. The reaction solution was diluted with ethyl acetate, washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and the solvent was distilled off. The resulting residue was purified by silica gel chromatography to obtain (5R,6S, 8R,2'S,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylate.

$[\alpha]_{\text{D}}^{20} + 52^\circ$ ($c=0.43$, CHCl_3)

IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm^{-1}):

1788, 1700, 1660, 1607, 1400, 1325, 1114, 1013

NMR δ (CDCl_3): 1.32 (3H, d, $J=6\text{Hz}$), 2.96 (3H, s), 3.08 (3H, s), 3.72 (1H, dd, $J=1.5\text{Hz}$ and $J=6\text{Hz}$),

5.20 (2H, s), 5.70 (1H, d, J=1.5Hz)

b) 204 mg of 5% palladium-carbon was suspended in a mixture of ethanol (3.8 ml) and water (3.8 ml) and hydrogenated at room temperature under atmospheric pressure for 1 hour. The catalyst was filtered, washed with water, suspended in a phosphate buffer (pH = 6.86, 5.1 ml), and added to a solution of 68 mg of (5R,6S,8R, 2'S,4'S)-p-nitrobenzyl-3-[(1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylate in 7.7 ml of tetrahydrofuran. The mixture was hydrogenated at room temperature and under atmospheric pressure for 3 hours. After filtering off the catalyst, tetrahydrofuran was distilled off under reduced pressure. The residual solution was washed with ethyl acetate, and the aqueous layer was again distilled under reduced pressure to remove the organic solvents. The resulting residual solution was purified by CHP-20P column chromatography to obtain (5R,6S,8R,2'S,4'S)-2-[(2-dimethylaminocarbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid.

UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm:

322, 255

IR $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}):

1765, 1645, 1580, 1508, 1367

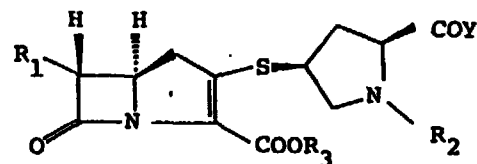
NMR δ (D_2O): 1.29 (3H, d, J=6.4Hz), 1.94 - 2.08 (1H, m), 2.93 - 3.15 (1H, m), 2.98 (3H, s), 3.05 (3H, s), 3.53-3.62 (1H, m), 3.83 - 3.93 (1H, m), 3.94 (1H, dd, J=1.4Hz and J=6Hz), 4.06 - 4.30 (3H, m), 5.71 (1H, d, J=1.4Hz)

Examples 7 to 67

The compounds shown in Table 6 below were prepared from the corresponding mercaptan derivatives. In Table 6, "HE" represents (R)-1-hydroxyethyl group, and "PNZE" represents (R)-1-p-nitrobenzyloxycarbonyloxyethyl group.

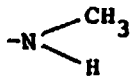
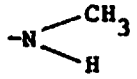
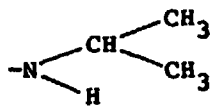
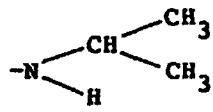
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Table 6



Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
	PNZE	PNZ	PNB		IR _ν ^{Nujol} _{max} (cm ⁻¹): 3420, 1785, 1742, 1710, 1677, 1510, 1342, 1255 m.p. 138-142°C [α] _D ³⁰ +44.4° (c=0.105, DMF) UVλ _{max} ^{H₂O} nm: 297
7	HE	H	H		IR _ν ^{KBr} _{max} (cm ⁻¹): 1752, 1687, 1595, 1385 NMR δ (D ₂ O): 1.24(3H, d, J=6.5Hz), 2.0-2.15(1H, m), 2.83-2.98(1H, m), 3.17(2H, d, J=9Hz), 3.32-3.42(2H, m), 3.71-3.80(1H, m), 3.98(1H, quintet, J=7Hz), 4.13-4.32(1H, m), 4.41(1H, t, J=8.5Hz) [α] _D ³⁰ -25° (c=0.05, H ₂ O)

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR _v ^{neat} _{max} (cm ⁻¹): 1775, 1745, 1700, 1665(sh), 1515, 1345, 1257
8	PNZE	PNZ	PNB		NMR δ (CDCl ₃): 1.48(3H, d, J=6.5Hz), 2.73(3H, s), 3.21(2H, d, J=9Hz), 5.25(4H, s), 5.25 and 5.43(2H, ABq, J=14Hz), 7.50, 7.54 and 7.62(each 2H, d, J=8.5Hz), 8.20(6H, d, J=8.5Hz)
	HE	H	H		UVλ ^{H₂O} _{max} nm: 297
					IR _v ^{Nujol} _{max} (cm ⁻¹): 1770, 1740, 1700, 1510, 1340, 1255
9	PNZE	PNZ	PNB		NMR δ (CDCl ₃): 1.08(3H, d, J=6.5Hz), 1.11(3H, d, J=6.5Hz), 1.48(3H, d, J=6Hz), 3.18(2H, br.d, J=9Hz), 5.25(4H, s), 5.26 and 5.44(2H, ABq, J=14Hz), 7.50, 7.54 and 7.62(each 2H, J=9Hz), 8.20(6H, d, J=8.5Hz)
	HE	H	H		UVλ ^{H₂O} _{max} nm: 296

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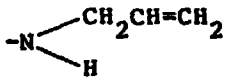
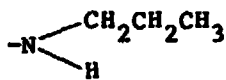
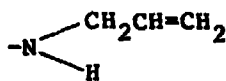
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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data	
					IR _ν ^{Nujol} _{max} (cm ⁻¹):	3275, 1782, 1740, 1700, 1650, 1515, 1340, 1260
	PNZE	PNZ	PNB		NMR _δ (CDCl ₃):	1.48(3H, d, J=6.5Hz), 3.18(2H, br, d, J=9Hz), 5.24(4H, s), 5.25 and 5.45(2H, ABq, J=14Hz), 7.50, 7.53 and 7.62(each 2H, d, J=8.5Hz), 8.19(6H, d, J=8.5Hz)
10	HE	H	H		NMR _δ (D ₂ O):	1.0(3H, t, J=7.5Hz), 1.23(3H, d, J=7Hz)
	HE	H	H		UVλ _{max} ^{H₂O} nm:	298
					NMR _δ (D ₂ O):	1.27(3H, d, J=7Hz), 5.68(3H, m)
					UVλ _{max} ^{H₂O} nm:	298

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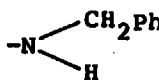
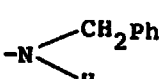
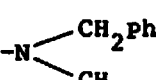
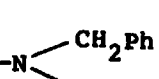
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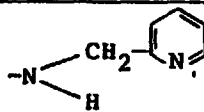
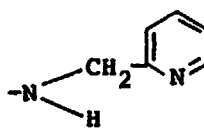
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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data	
					IR _v ^{neat} _{max} (cm ⁻¹):	
11	PNZE	PNZ	PNB	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$	1780, 1750, 1710, 1650, 1525, 1440, 1350, 1262	
	HE	H	H	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$	NMR δ (CDCl ₃):	1.06(3H, t, J=7Hz), 1.27(3H, t, J=7Hz), 1.49(3H, d, J=6Hz), 5.24(4H, s), 5.25 and 5.46(2H, ABq, J=14Hz), 7.46, 7.50 and 7.63(each 2H, d, J=8.5Hz), 8.20(6H, d, J=8.5Hz)
12	PNZE	PNZ	PNB	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{n-C}_4\text{H}_9 \end{array}$	IR _v ^{CHCl₃} _{max} (cm ⁻¹):	1780, 1746, 1708, 1656, 1610, 1525, 1350, 1260
	HE	H	H	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{n-C}_4\text{H}_9 \end{array}$	NMR δ (CDCl ₃):	1.48(3H, d, J=6Hz), 5.27(4H, s), 8.20(6H, d, J=9Hz)
					UV λ ^{H₂O} _{max} nm:	297
					IR _v ^{KBr} _{max} (cm ⁻¹):	1755, 1635, 1590, 1370, 1240
					NMR δ (D ₂ O):	0.88(3H, t, J=7.1Hz), 1.26(3H, d, J=6.4Hz), 1.91(1H, m), 2.94 and 3.02(3H, s)

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR ν_{max} Nujol (cm ⁻¹): 1770, 1735, 1640, 1510, 1340, 1250
13	PNZE	H	PNB		NMR δ (CDCl ₃): 1.49(3H, d, J=6.5Hz), 4.42(2H, d, J=7.0Hz), 5.25(4H, s), 5.27 and 5.43(2H, ABq, J=14Hz), 7.27(5H, s), 7.54, 7.62, 8.21 and 8.22(each 2H, d, J=8.5Hz)
	HE	H	H		UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297
					IR $\nu_{\text{max}}^{\text{neat}}$ (cm ⁻¹): 1780, 1750, 1715, 1660, 1525, 1442, 1350, 1265, 1122
14	PNZE	PNZ	PNB		NMR δ (CDCl ₃): 1.48(3H, d, J=6.5Hz), 2.92(3H, s), 4.56(2H, d, J=5Hz), 5.25(4H, s), 8.19(6H, d, J=9Hz)
	HE	H	H		UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
	PNZE	PNZ	PNB		IR _{max} ^{Nujol} (cm ⁻¹): 1790, 1745, 1714, 1652, 1605, 1520, 1347 m.p. 179-182°C (dec.)
15	HE	H	H		UV _{max} ^{H₂O} nm: 299, 266, 260 IR _{max} ^{KBr} (cm ⁻¹): 1745, 1590, 1490, 1210, 1090, 910 NMR _δ (D ₂ O): 1.26(3H, d, J=6.3Hz), 1.99(1H, m), 2.80(1H, m), 3.36(1H, dd, J=2.7 and 6.0Hz), 3.58(1H, dd, J=7.0 and 12.0Hz), 3.86(1H, m), 4.51(2H, d, J=4.4Hz), 7.82(1H, dt, J=1.8 and 7.7Hz), 8.42(1H, m)

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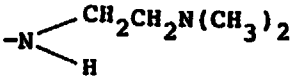
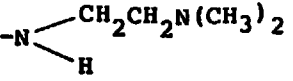
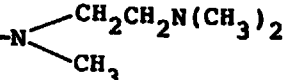
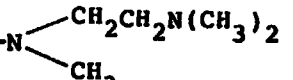
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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
16	PNZE	PNZ	PNB		IR _ν ^{neat} _{max} (cm ⁻¹): 1775, 1745, 1700, 1660(sh), 1515, 1345, 1260
					NMR _δ (CDCl ₃): 1.47(3H, d, J=6.5Hz), 2.24(3H, s), 2.27(3H, s), 5.25(4H, s), 7.49, 7.53 and 7.62(each 2H, d, J=8.5Hz), 8.20(6H, d, J=8.5Hz)
	HE	H	H		UV _λ ^{H₂O} _{max} nm: 297
17	PNZE	PNZ	PNB		IR _ν ^{neat} _{max} (cm ⁻¹): 1770, 1745, 1700, 1650, 1512, 1342, 1257
					NMR _δ (CDCl ₃): 1.49(3H, d, J=6.0Hz), 2.24(3H, s), 2.30(6H, s), 5.25(4H, s), 5.27 and 5.45(2H, ABq, J=13.5Hz), 7.54(4H, d, J=8.5Hz), 7.63(2H, d, J=8.5Hz), 8.20(6H, d, J=8.5Hz)
	HE	H	H		UV _λ ^{H₂O} _{max} nm: 298

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
18	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{neat}}$ (cm ⁻¹): 3350, 1770, 1740, 1695, 1510, 1340, 1250
	HE	H	H		NMR δ (CDCl ₃): 1.48(3H, d, J=6Hz), 5.25(4H, s), 5.18 and 5.43(2H, ABq, J=14Hz), 7.49, 7.53 and 7.61(each 2H, d, J=8.5Hz), 8.18(6H, d, J=8.5Hz)
19	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{neat}}$ (cm ⁻¹): 3400, 1778, 1745, 1700, 1650, 1520, 1345, 1260, 1120
	HE	H	H		NMR δ (CDCl ₃): 1.48(3H, d, J=6.5Hz), 3.00(3H, s), 5.20(2H, s), 5.25(2H, s), 5.25 and 5.45(2H, ABq, J=13.5Hz), 7.49, 7.51 and 7.63(each 2H, d, J=8.5Hz), 8.19(4H, d, J=8.5Hz), 8.21(2H, d, J=8.5Hz)
	HE	H	H		UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297

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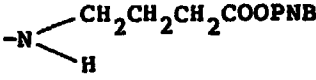
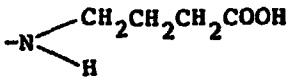
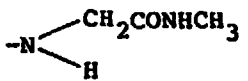
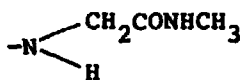
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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
20	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{neat}}$ (cm ⁻¹): 1770, 1730, 1695, 1650, 1600, 1505, 1340
					NMR δ (CDCl ₃): 1.48(3H, d, J=6.5Hz), 5.25(4H, s), 7.62(2H, d, J=8.6Hz), 8.20(6H, d, J=8.6Hz)
	HE	H	H		UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297
21	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm ⁻¹): 1795, 1747, 1712, 1640, 1608, 1517, 1350, 1275 m.p. 167-169°C (dec.)
					UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 300
	HE	H	H		IR $\nu_{\text{max}}^{\text{KBr}}$ (cm ⁻¹): 1752, 1650, 1590, 1388, 1255, 1150 NMR δ (D ₂ O): 1.26(3H, d, J=6.3Hz), 2.71(3H, s), 2.93(1H, q, J=7.4Hz), 3.88(2H, s)

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
22	PNZE	PNZ	PNB	$\begin{array}{c} \text{CH}_2\text{CON}(\text{CH}_3)_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{H} \end{array}$	IR ν_{max} ^{Nujol} (cm ⁻¹): 1800, 1750, 1707, 1675, 1650, 1610, 1520, 1350, 1280 m.p. 196-199°C (dec.) UV λ_{max} ^{H₂O} nm: 299
	HE	H	H	$\begin{array}{c} \text{CH}_2\text{CON}(\text{CH}_3)_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{H} \end{array}$	IR ν_{max} ^{KBr} (cm ⁻¹): 1750, 1640, 1590, 1380, 1250, 1145 NMR δ (D ₂ O): 1.26(3H, d, J=6.3Hz), 2.92(3H, s), 3.03(3H, s), 3.19(2H, dd, J=6.3 and 9.2Hz), 3.51(1H, dd, J=7.4 and 12Hz), 4.12(2H, s)
23	PNZE	PNZ	PNB	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CHCONH}_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{H} \end{array}$	IR ν_{max} ^{Nujol} (cm ⁻¹): 1795, 1750, 1700, 1680, 1655, 1610, 1525, 1350 m.p. 168-170°C (dec.)
	HE	H	H	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CHCONH}_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{H} \end{array}$	IR ν_{max} ^{KBr} (cm ⁻¹): 1745, 1665, 1590, 1390, 1180, 1037 UV λ_{max} ^{H₂O} nm: 300

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
24	PNZE	PNZ	PNB	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CONHCH}_3 \\ \\ \text{N} \\ \\ \text{H} \end{array} $	IR _{max} ^{Nujol} (cm ⁻¹): 1790, 1752, 1710, 1650, 1610, 1525, 1350 m.p. 98-101°C
	HE	H	H	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CONHCH}_3 \\ \\ \text{N} \\ \\ \text{H} \end{array} $	UV _{max} ^{H₂O} nm: 301 IR _{max} ^{KBr} (cm ⁻¹): 1750, 1650, 1590, 1385, 1170, 1040 NMR ^δ (D ₂ O): 1.26(3H, d, J=6.6Hz), 1.36(3H, d, J=8.1Hz), 2.71(3H, s), 3.19(1H, dd, J=6.6 and 9.0Hz), 3.98(1H, t, J=8.0Hz)

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
	PNZE	PNZ	PNB	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CON}(\text{CH}_3)_2 \\ \\ \text{N} \end{array} $	$\text{IR } \nu_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1780, 1745, 1705, 1640, 1605, 1520, 1346$ m.p. 172-175°C $\text{NMR } \delta (\text{D}_6\text{-DMCO}): 1.12(3\text{H}, \text{d}, J=7\text{Hz}), 1.34(3\text{H}, \text{d}, J=6.4\text{Hz}), 2.79(3\text{H}, \text{s}), 2.94(3\text{H}, \text{s}), 5.30(2\text{H}, \text{s}), 8.20(6\text{H}, \text{d}, J=8.8\text{Hz})$
25	HE	H	H	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CON}(\text{CH}_3)_2 \\ \\ \text{N} \end{array} $	$\text{UV } \lambda_{\text{max}}^{\text{H}_2\text{O}} \text{ nm}: 300$ $\text{IR } \nu_{\text{max}}^{\text{KBr}} (\text{cm}^{-1}): 1755, 1630, 1590, 1390, 1250, 1120$ $\text{NMR } \delta (\text{D}_2\text{O}): 1.26(3\text{H}, \text{d}, J=6.3\text{Hz}), 1.31(3\text{H}, \text{d}, J=6.9\text{Hz}), 2.92(3\text{H}, \text{s}), 3.13(3\text{H}, \text{s})$

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR $\nu_{\max}^{\text{CHCl}_3}$ (cm ⁻¹): 1783, 1746, 1705, 1680, 1608, 1524, 1345
	PNZE	PNZ	PNB	$\begin{array}{c} \text{CH}_2\text{CONH}_2 \\ \\ \text{-N} \\ \\ \text{CH}_3 \end{array}$	NMR δ (CDCl ₃): 1.48(3H, d, J=6.4Hz), 3.19(3H, s), 5.17(2H, s), 5.24(2H, s), 8.19(6H, d, J=8.6Hz)
26					UV $\lambda_{\max}^{\text{H}_2\text{O}}$ nm: 300
	HE	H	H	$\begin{array}{c} \text{CH}_2\text{CONH}_2 \\ \\ \text{-N} \\ \\ \text{CH}_3 \end{array}$	IR $\nu_{\max}^{\text{KBr}}$ (cm ⁻¹): 1750, 1654, 1590, 1395, 1250, 1060 NMR δ (D ₂ O): 1.26(3H, d, J=6.3Hz), 2.95(3H, s), 3.21(2H, dd, J=2.2 and 9.0Hz), 3.38(1H, dd, J=2.2 and 5.5Hz)

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
	PNZE	PNZ	PNB	$ \begin{array}{c} \text{CH}_2\text{CONHCH}_3 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{CH}_3 \end{array} $	$\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 1778, 1743, 1685, 1660, 1605, 1520, 1340$ $\text{NMR}_{\delta} (\text{CDCl}_3): 1.48(3\text{H}, \text{d}, J=6.2\text{Hz}), 2.72(3\text{H}, \text{d}, J=5\text{Hz}), 3.19(3\text{H}, \text{s}), 5.22(2\text{H}, \text{s}), 5.25(2\text{H}, \text{s}), 8.22(6\text{H}, \text{d}, J=8.8\text{Hz})$ $\text{UV}_{\lambda_{\text{max}}}^{\text{H}_2\text{O}} \text{ nm: } 300$
27	HE	H	H	$ \begin{array}{c} \text{CH}_2\text{CONHCH}_3 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{CH}_3 \end{array} $	$\text{IR}_{\text{max}}^{\text{KBr}} (\text{cm}^{-1}): 1750, 1640, 1585, 1382, 1250, 1125$ $\text{NMR}_{\delta} (\text{D}_2\text{O}): 1.26(3\text{H}, \text{d}, J=6.3\text{Hz}), 2.73(3\text{H}, \text{s}), 3.09(3\text{H}, \text{s}), 3.39(1\text{H}, \text{q}, J=2.6\text{Hz})$

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
28	PNZE	PNZ	PNB	$\begin{array}{c} \text{CH}_2\text{CON}(\text{CH}_3)_2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{CH}_3 \end{array}$	IR $\nu_{\text{max}}^{\text{neat}}$ (cm ⁻¹): 1778, 1745, 1705, 1650, 1605, 1520, 1345 NMR δ (CDCl ₃): 1.49(3H, d, J=6.2Hz), 2.93(3H, s), 2.99(3H, s), 3.10 and 3.15(3H, s), 5.25(4H, s), 8.21(6H, d, J=8.4Hz)
	HE	H	H	$\begin{array}{c} \text{CH}_2\text{CON}(\text{CH}_3)_2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{CH}_3 \end{array}$	UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297 IR $\nu_{\text{max}}^{\text{KBr}}$ (cm ⁻¹): 1760, 1650, 1500, 1380, 1240, 1130

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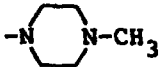
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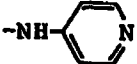
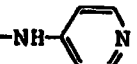
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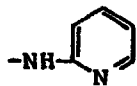
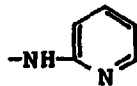
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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
29	PNZE	PNZ	PNB		IR _v ^{neat} _{max} (cm ⁻¹): 1778, 1750, 1705, 1650, 1518, 1430, 1345, 1258
					NMR δ (CDCl ₃): 1.49(3H, d, J=6.5Hz), 2.25(3H, s), 2.31(4H, s), 5.25(4H, s), 5.21 and 5.46(2H, ABq, J=13.5Hz), 7.53(4H, d, J=8.5Hz), 7.62(2H, d, J=8.5Hz), 8.20(6H, d, J=8.5Hz)
30	HE	H	H		UV λ _{max} ^{H₂O} nm: 298
					IR _v ^{neat} _{max} (cm ⁻¹): 1780, 1750, 1710, 1655, 1520, 1350, 1255, 1115
30	PNZE	PNZ	PNB		NMR δ (CDCl ₃): 1.48(3H, d, J=6.5Hz), 3.58 and 3.67(each 4H, s), 5.25(4H, s), 5.26 and 5.45(2H, ABq, J=14Hz), 7.53(4H, d, J=9Hz), 7.62(2H, d, J=9Hz), 8.19(6H, d, J=9Hz)
	HE	H	H		UV λ _{max} ^{H₂O} nm: 298

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
31	PNZE	PNZ	PNB		IR _v ^{CHCl₃} _{max} (cm ⁻¹): 1780, 1740, 1705, 1655, 1610, 1520, 1345
					NMR _δ (CDC ₃): 1.47(3H, d, J=6Hz), 5.22(4H, s), 8.13(6H, d, J=8Hz)
	HE	H	H		UV _λ ^{H₂O} _{max} nm: 298
32	PNZE	PNZ	PNB		IR _v ^{KBr} _{max} (cm ⁻¹): 1750, 1625, 1595, 1396, 1248, 1090
					IR _v ^{neat} _{max} (cm ⁻¹): 1780, 1740, 1700, 1590, 1520, 1340, 1255
	HE	H	H		NMR _δ (CDC ₃): 1.49(3H, d, J=6.6Hz), 5.26(4H, s), 5.35(2H, ABq, J=14.5Hz), 7.46(2H, d, J=5.5Hz), 8.48(2H, d, J=5.5Hz)
					UV _λ ^{H₂O} _{max} nm: 245, 300
					IR _v (cm ⁻¹): 1745, 1690, 1590, 1507, 1383, 1285

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
	PNZE	PNZ	PNB		IR _v ^{Nujol} (cm ⁻¹): 1785, 1745, 1705, 1605, 1520, 1350 max m.p. 181-183°C (dec.)
33	HE	H	H		UV _λ ^{H₂O} nm: 296, 276, 231 max IR _v ^{KBr} (cm ⁻¹): 1750, 1690, 1595, 1435, 1385, 1240, 1090 max NMR _δ (D ₂ O): 1.26(3H, d, J=6.3Hz), 1.95(1H, m), 3.20(1H, dd, J=4.0 and 9.0Hz), 3.37(1H, dd, J=2.6 and 6.1Hz), 8.32(1H, dd, J=1.3 and 5.0Hz), 8.60(1H, d, J=2.2Hz)

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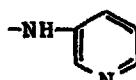
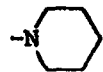
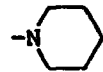
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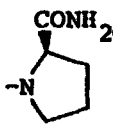
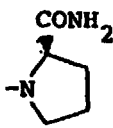
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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
34	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm ⁻¹): 1790, 1745, 1705, 1670, 1605, 1515, 1345 m.p. 189-191°C (dec.) UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 298, 286, 237
	HE	H	H		IR $\nu_{\text{max}}^{\text{KBr}}$ (cm ⁻¹): 1750, 1680, 1590, 1480, 1390, 1245, 1090 NMR δ (D ₂ O): 1.26(3H, d, J=6.3Hz), 1.95(1H, m), 3.20(1H, dd, J=4.0 and 9.0Hz), 3.37(1H, dd, J=2.6 and 6.1Hz), 8.32(1H, dd, J=1.3 and 4.9Hz), 8.60(1H, d, J=2.2Hz)
35	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{neat}}$ (cm ⁻¹): 1775, 1750, 1705, 1640, 1520, 1345, 1255, 1110 NMR δ (CDCl ₃): 1.48(3H, d, J=6.5Hz), 5.24(4H, s), 5.23 and 5.44(2H, ABq, J=14Hz), 8.19(6H, d, J=8.5Hz)
	HE	H	H		UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
36	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹): 1782, 1750, 1710, 1660, 1522, 1445, 1355, 1270, 1140 NMR δ (CDC₃): 1.48(3H, d, J=6Hz), 5.26(4H, s), 5.18 and 5.42(2H, ABq, J=14Hz), 7.50(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz), 7.62(2H, d, J=8.5Hz), 8.19(6H, d, J=8.5Hz) UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 298 IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹): 1755, 1630, 1600, 1440, 1382, 1240 NMR δ (D₂O): 1.26(3H, d, J=6.3Hz), 2.34(2H, m), 3.36(1H, dd, J=3.4 and 5.5Hz), 3.84(1H, m)
	HE	H	H		

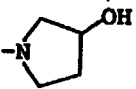
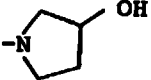
Example No.	R_1	R_2	R_3	Y	Spectral Data	
					CHCl ₃ IR _v _{max} (cm ⁻¹):	
37	PNZE	PNZ	PNB		1780, 1740(sh), 1710, 1605, 1520, 1340	NMR δ (CDCl ₃): 1.48(3H, d, J=6.4Hz), 5.25(4H, s), 6.32(2H, d, J=2Hz), 8.16(6H, d, J=8.8Hz)
	HE	H	H		UV λ _{H₂O} _{max} nm: 297, 241	IR _v _{max} ^{KBr} (cm ⁻¹): 1750, 1720, 1590, 1470, 1390, 1280
						NMR δ (D ₂ O): 1.26(3H, d, J=6.2Hz), 2.12(2H, m), 6.44(2H, t, J=2.2Hz), 7.39(2H, t, J=2.2Hz)

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
38	PNZE	PNZ	PNB		IR ν _{max} ^{CHCl₃} (cm ⁻¹): 1780, 1750, 1700, 1650(sh), 1610, 1525, 1350 NMR δ (CDCl ₃): 1.47(3H, d, J=6Hz), 5.22(4H, s), 8.12(6H, d, J=8.5Hz)
	HE	H	H		UV λ _{max} ^{H₂O} nm: 298 IR ν _{max} ^{KBr} (cm ⁻¹): 1750, 1650, 1600, 1440, 1395

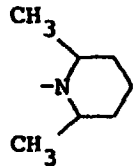
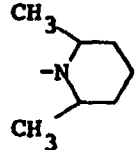
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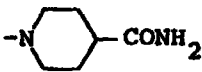
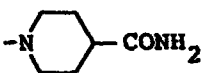
Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
39	PNZE	PNZ	PNB		IR _{max} ^{CHCl₃} (cm ⁻¹): 1783, 1750, 1715, 1660, 1615, 1530, 1350 NMR _δ (CDCl ₃): 1.48(3H, d, J=5.9Hz), 5.25(4H, s), 8.15(6H, d, J=8.6Hz) UV _{max} ^{H₂O} nm: 298
	HE	H	H		IR _{max} ^{KBr} (cm ⁻¹): 1750, 1630, 1590, 1460, 1380, 1240, 1090 NMR _δ (D ₂ O): 1.27(3H, d, J=6.3Hz), 3.19(1H, dd, J=2.9 and 9.2Hz), 3.39(1H, dd, J=2.6 and 6.0Hz)

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
40	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm⁻¹): 1780, 1740, 1708, 1640, 1605, 1520, 1345 NMR δ (CDCl₃): 1.50(3H, d, J=6.2Hz), 5.28(4H, s), 8.19(6H, d, J=8.1Hz) UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297
	HE	H	H		IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹): 1760, 1635, 1600, 1450, 1380 NMR δ (D₂O): 1.27(3H, d, J=6.3Hz), 3.19(1H, dd, J=2.9 and 9.1Hz), 3.39(1H, dd, J=2.7 and 6.0Hz), 3.55(2H, d, J=4.0Hz), 3.69(1H, dd, J=2.0 and 4.3Hz)

55 50 45 40 35 30 25 20 15 10 5

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
41	PNZE	PNZ	PNB		IRν_{max}^{CHCl₃} (cm⁻¹): 1780, 1750, 1705, 1635, 1605, 1520, 1345 NMRδ (CDCl₃): 1.49(3H, d, J=6.4Hz), 5.26(4H, s), 8.20(6H, d, J=8.8Hz) UVλ_{max}^{H₂O} nm: 298 IRν_{max}^{KBr} (cm⁻¹): 1755, 1625, 1440, 1380, 1240 NMRδ (D₂O): 1.23(3H, d, J=6.5Hz), 1.25(3H, d, J=6Hz), 1.31(3H, d, J=7Hz)
	HE	H	H		

55 50 45 40 35 30 25 20 15 10 5

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
42	PNZE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm ⁻¹): 1785, 1746, 1705, 1657, 1610, 1525, 1345 NMR δ (CDCl ₃): 1.47(3H, d, J=6.2Hz), 5.25(4H, s), 8.16(6H, d, J=8.6Hz) UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 298
	HE	H	H		IR $\nu_{\text{max}}^{\text{KBr}}$ (cm ⁻¹): 1750, 1655(sh), 1635, 1610(sh), 1380, 1220 NMR δ (D ₂ O): 1.26(3H, d, J=6.3Hz)

Example
No. R_1 R_2 R_3

Y

Spectral Data

43

PNZE

PNZ

PNB

-NHOPNB

IR $\nu_{\max}^{\text{Nujol}}$ (cm^{-1}): 1790, 1750, 1715, 1670, 1602, 1515, 1340

m.p. 149-152°C (dec.)

UV $\lambda_{\max}^{\text{H}_2\text{O}}$ nm: 300IR $\nu_{\max}^{\text{KBr}}$ (cm^{-1}): 1750, 1680, 1600, 1400, 1120IR $\nu_{\max}^{\text{Nujol}}$ (cm^{-1}): 1787, 1745, 1710, 1665, 1605, 1520, 1345

m.p. 188-189.5°C (dec.)

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HE

H

H

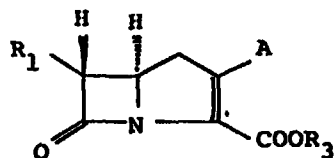
-NHOCH₃UV $\lambda_{\max}^{\text{H}_2\text{O}}$ nm: 299IR $\nu_{\max}^{\text{KBr}}$ (cm^{-1}): 1745, 1680, 1600, 1440, 1390, 1245, 1050NMR δ (D₂O): 3.70(3H, s)

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
45	PNZE	PNZ	PNB		$\text{IR}_{\text{max}}^{\text{neat}} (\text{cm}^{-1}): 1780, 1750, 1710, 1605, 1525, 1350, 1260$ $\text{NMR}_{\delta} (\text{CDCl}_3): 1.49(3\text{H}, \text{d}, J=6.4\text{Hz}), 5.25(4\text{H}, \text{s}), 5.36(2\text{H}, \text{ABq}, J=13.6\text{Hz}), 7.53(4\text{H}, \text{d}, J=8.8\text{Hz}), 7.62(2\text{H}, \text{d}, J=8.8\text{Hz}), 8.21(6\text{H}, \text{d}, J=8.8\text{Hz})$ $\text{UV}\lambda_{\text{max}}^{\text{H}_2\text{O}} \text{ nm}: 300$ $\text{IR}_{\text{max}}^{\text{KBr}} (\text{cm}^{-1}): 1735, 1595, 1396, 1255, 1215, 1043$
	HE	H	H		

65 50 45 40 35 30 25 20 15 10 5

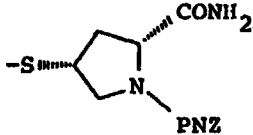
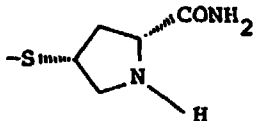
Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
46	PNZE	PNZ	PNB		IR_v^{neat}_{max} (cm⁻¹): 1780, 1745, 1705, 1645, 1520, 1440, 1350, 1262 NMRδ (CDCl₃): 1.49(3H, d, J=6.5Hz), 5.26(4H, s), 5.24 and 5.43(2H, ABq, J=14Hz), 7.44(2H, d, J=9Hz), 7.48(2H, d, J=9Hz), 7.68(2H, d, J=9Hz), 8.19(6H, d, J=9Hz) UVλ_{max}^{H₂O} nm: 298 NMRδ (D₂O): 1.27(3H, d, J=6Hz), 1.83(4H, t, J=7Hz), 1.94-2.09(1H, m), 2.42(4H, t, J=7Hz), 2.77-2.92(1H, m), 3.11-3.42(5H, m), 3.81-3.99(1H, m), 4.14-4.29(2H, m)
	HE	H	H		

55 50 45 40 35 30 25 20 15 10 5



Example No.	R ₁	R ₃	A	Spectral Data
47	PNZE	PNZ		IR_{max}^{neat} (cm⁻¹): 1775, 1745, 1700, 1520, 1345, 1260, 1130 NMR^δ (CDCl₃): 1.48(3H, d, J=6.5Hz), 3.22(2H, br, d, J=9.0Hz), 5.26(4H, s), 5.25 and 5.46(2H, ABq, J=14Hz), 7.50, 7.54 and 7.60(each 2H, d, J=9.0Hz), 8.18(4H, d, J=9.0Hz), 8.21(2H, d, J=9.0Hz) [α]_D²⁹ +37.3° (c=0.244, acetone) UVλ_{max}^{H₂O} nm: 298
	HE	H		

55 50 45 40 35 30 25 20 15 10 5

Example No.	R ₁	R ₃	A	Spectral Data
				IR ν _{max} ^{neat} (cm ⁻¹): 1780, 1745, 1700, 1610, 1520, 1400, 1350, 1260, 1120
48	PNZE	PNZ		NMR δ (CDCl ₃): 1.48(3H, d, J=6Hz), 3.19(2H, d, J=9Hz), 3.44(1H, dd, J=2.5 and 7.5Hz), 5.25(4H, s), 5.23 and 5.42(2H, ABq, J=14Hz), 7.47, 7.52 and 7.60(each 2H, d, J=8.5Hz), 8.16(4H, d, J=8.5Hz), 8.19(2H, d, J=8.5Hz)
	HE	H		[α] _D ³² +57.6° (c=0.279, acetone) UV λ _{max} ^{H₂O} nm: 297

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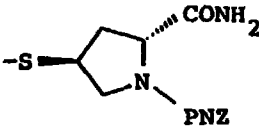
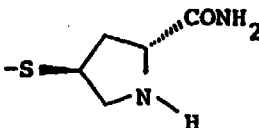
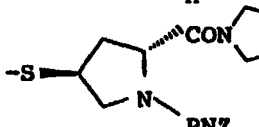
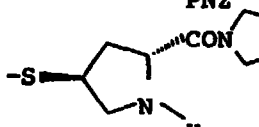
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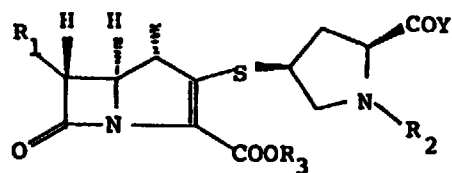
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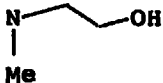
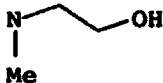
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Example No.	R ₁	R ₃	A	Spectral Data
				IR _v ^{neat} max (cm ⁻¹): 1775, 1750, 1700, 1520, 1345, 1260, 1180
49	PNZE	PNB		NMR _δ (CDCl ₃): 1.48(3H, d, J=6.5Hz), 3.26(2H, br, d, J=9.0Hz), 5.25(4H, s), 5.18 and 5.46(2H, ABq, J=14Hz), 7.49, 7.53 and 7.62(each 2H, d, J=8.5Hz), 8.17(4H, d, J=8.5Hz), 8.19(2H, d, J=8.5Hz) [α] _D ²⁵ +43.7° (c=0.353, acetone)
	HE	H		UVλ ^{H₂O} max nm: 297
50	PNZE	PNB		IR _v ^{CHCl₃} max (cm ⁻¹): 1750, 1705, 1645, 1610, 1525, 1440, 1350, 1265
	HE	H		UVλ ^{H₂O} max nm: 287



Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm ⁻¹): 1775, 1700, 1607, 1520, 1395, 1345, 1105
51	HE	PNZ	PNB	-NH ₂	NMR δ (CDCl ₃): 1.36(3H, d, J=6.0Hz), 1.37(3H, d, J=7.0Hz), 5.24(2H, s), 5.35(2H, ABq, J=13.5Hz), 7.50(2H, d, J=8.8Hz), 7.64(2H, d, J=8.8Hz), 8.22(4H, d, J=8.8Hz)
	HE	H	H	-NH ₂	UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 295 IR $\nu_{\text{max}}^{\text{KBr}}$ (cm ⁻¹): 1750, 1660(sh), 1600, 1380, 1240

55 50 45 40 35 30 25 20 15 10 5

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
52	HE	PNZ	PNB		IR_{max}^{CHCl₃} (cm⁻¹): 1770, 1695, 1650, 1520, 1340 NMR_δ (CDCl₃): 1.34(3H, d, J=6.15Hz), 1.36(3H, d, J=8.0Hz), 3.00(3H, s), 5.20(2H, s), 5.36(2H, ABq, J=14.0Hz), 7.47(2H, d, J=8.8Hz), 7.64(2H, d, J=8.8Hz), 8.20(2H, d, J=8.8Hz) UVλ_{max}^{H₂O} nm: 289 IR_{max}^{KBr} (cm⁻¹): 1750, 1630, 1605, 1375, 1240
	HE	H	H		

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
	HE	PNZ	PNB	NHCH ₂ CONH ₂	IR ν _{max} ^{CHCl₃} (cm ⁻¹): 3380, 1770, 1725(sh), 1700, 1680, 1605, 1520, 1342, 1250, 1102 NMR δ (CDCl ₃): 5.30(2H, s), 5.31(2H, ABq, J=13.8Hz), 7.48(2H, d, J=8.8Hz), 7.64(2H, d, J=8.8Hz), 8.21(4H, d, J=8.8Hz) UV λ _{max} ^{H₂O} nm: 295
53	HE	H	H	NHCH ₂ CONH ₂	IR ν _{max} ^{KBr} (cm ⁻¹): 1750, 1670, 1600, 1390, 1245 NMR δ (D ₂ O): 1.26(3H, d, J=6.5Hz), 1.28(3H, d, J=8Hz), 3.92(2H, s)

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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
54	HE	PNZ	PNB	$\begin{array}{c} \text{NCH}_2\text{CONH}_2 \\ \\ \text{Me} \end{array}$	IR_v^{CHCl₃}_{max} (cm⁻¹): 3480, 3350, 1773, 1678, 1604, 1525, 1345, 1310 NMR_δ (CDCl₃): 1.34(3H, d, J=6.2Hz), 1.37(3H, d, J=7.0Hz), 3.20(3H, s), 5.18(2H, s), 5.36(2H, ABq, J=13.4Hz), 7.46(2H, d, J=8.8Hz), 7.63(2H, d, J=8.8Hz), 8.20(2H, d, J=8.8Hz), 8.21(2H, d, J=8.8Hz) UV_λ^{H₂O}_{max} nm: 292 IR_v^{KBr}_{max} (cm⁻¹): 1752, 1645, 1600, 1385, 1245
	HE	H	H	$\begin{array}{c} \text{NCH}_2\text{CONH}_2 \\ \\ \text{Me} \end{array}$	

55 50 45 40 35 30 25 20 15 10 5

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR _v ^{CHCl₃} (cm ⁻¹): 3420, 1772, 1705, 1660, 1623, 1606, 1526, 1440, 1345
	HE	PNZ	PNB		[α] _D ²⁵ -45° (c=0.11, CHCl ₃)
55					NMRδ (CDCl ₃): 1.33(3H, d, J=6.15Hz), 1.37(3H, d, J=6.8Hz), 4.19(4H, br, s), 5.21(2H, s), 5.36(2H, ABq, J=13.9Hz), 5.84(2H, s), 7.40(2H, d, J=8.6Hz), 7.64(2H, d, J=8.6Hz), 8.14(2H, d, J=8.6Hz), 8.19(2H, d, J=8.6Hz)
					UVλ ^{H₂O} _{max} nm: 293
	HE	H	H		IR _v ^{KBr} (cm ⁻¹): 1750, 1640, 1610, 1460, 1380
					NMRδ (D ₂ O): 1.25(3H, d, J=6Hz), 1.27(3H, d, J=7.5Hz), 5.85(2H, br. s)

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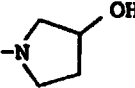
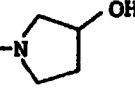
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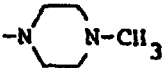
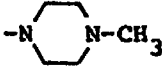
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Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR ν _{max} ^{CHCl₃} (cm ⁻¹): 1770, 1702, 1650, 1520, 1343, 1102
	HE	PNZ	PNB		NMR δ (CDCl ₃): 1.33(3H, d, J=6.15Hz), 1.37(3H, d, J=7.0Hz), 5.21(2H, s), 5.36(2H, ABq, J=13.9Hz), 7.50(2H, d, J=8.6Hz), 7.64(2H, d, J=8.6Hz), 8.20(4H, d, J=8.6Hz)
56					UV λ _{max} ^{H₂O} nm: 293
	HE	H	H		IR ν _{max} ^{KBr} (cm ⁻¹): 1755, 1630(sh), 1610, 1442, 1383, 1240, 1110
					NMR δ (D ₂ O): 1.25(3H, d, J=6.5Hz), 1.28(3H, d, J=7Hz)

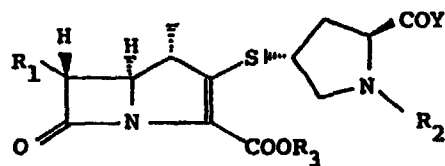
Example No.	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	Y	Spectral Data
57	HE	PNZ	PNB		IR_{max}^{CHCl₃} (cm⁻¹): 3400, 1770, 1705, 1650, 1520, 1432, 1345, 1107 NMR_δ (CDCl₃): 1.35(3H, d, J=6.0Hz), 1.36(3H, d, J=7.0Hz), 5.20(2H, s), 5.36(2H, ABq, J=13.5Hz), 7.46(2H, d, J=8.8Hz), 7.64(2H, d, J=8.8Hz), 8.21(2H, d, J=8.8Hz)
	HE	H	H		UVλ_{max}^{H₂O} nm: 293 IR_{max}^{KBr} (cm⁻¹): 1760, 1615, 1390, 1245, 1100

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
58	HE	PNZ	PNB		$\text{IR}_{\text{max}}^{\text{CHCl}_3} (\text{cm}^{-1}): 1770, 1705, 1656, 1525, 1345, 1112$ $\text{NMR}_{\delta} (\text{CDCl}_3): 1.35(3\text{H}, \text{d}, J=6.15\text{Hz}), 1.36(3\text{H}, \text{d}, J=7.0\text{Hz}), 5.22(2\text{H}, \text{s}), 5.36(2\text{H}, \text{ABq}, J=13.9\text{Hz}), 7.50(2\text{H}, \text{d}, J=8.0\text{Hz}), 7.64(2\text{H}, \text{d}, J=8.0\text{Hz}), 8.20(4\text{H}, \text{d}, J=8.0\text{Hz})$
	HE	H	H		$\text{UV}_{\text{max}}^{\text{H}_2\text{O}} \text{ nm: } 292$ $\text{IR}_{\text{max}}^{\text{KBr}} (\text{cm}^{-1}): 1760, 1630(\text{sh}), 1605, 1448, 1380, 1245, 1110$

55 50 45 40 35 30 25 20 15 10 5

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
59	HE	PNZ	PNB		IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm⁻¹): 1772, 1710, 1650, 1520, 1435, 1400, 1340 NMR δ (CDCl₃): 1.34(3H, d, J=6.0Hz), 1.35(3H, d, J=7.5Hz), 2.25(3H, s), 2.31(4H, s), 5.22(2H, s), 5.36(2H, ABq, J=14.1Hz), 7.49(2H, d, J=8.6Hz), 7.63(2H, d, J=8.6Hz), 8.20(4H, d, J=8.6Hz) UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 291 IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹): 1755, 1620, 1442, 1380, 1250
	HE	H	H		

55 50 45 40 35 30 25 20 15 10 5

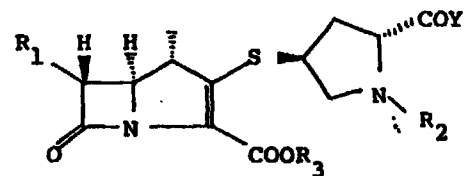


L-trans

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR _{max} ^{CHCl₃} (cm ⁻¹): 3400, 1770, 1708, 1652, 1604, 1523, 1397, 1342
	HE	PNZ	PNB	-N(CH ₃) ₂	[α] _D ²⁵ -33° (c=0.10, CHCl ₃)
60					NMRδ (CDCl ₃): 1.34(3H, d, J=6.15Hz), 1.39(3H, d, J=7.0Hz), 2.97(3H, s), 2.91 and 3.12(3H, s), 5.21(2H, s), 5.35(2H, ABq, J=13.2Hz), 8.20(4H, d, J=8.6Hz)
	HE	H	H	-N(CH ₃) ₂	UVλ _{max} ^{H₂O} nm: 286
					IR _{max} ^{KBr} (cm ⁻¹): 1750, 1630(sh), 1610, 1395, 1250

Example No.	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	Y	Spectral Data	
					IR _v ^{CHCl₃} _{max} (cm ⁻¹):	
61	HE	PNZ	PNB		3400, 1775, 1707, 1642, 1608, 1526, 1445, 1345	
					[α] _D ²⁵ -33° (c=0.11, CHCl ₃)	
					NMRδ (CDCl ₃): 1.33(3H, d, J=6.15Hz), 1.40(3H, d, J=6.8Hz), 5.20(2H, s), 5.35(2H, ABq, J=13.8Hz), 7.47(2H, d, J=8.8Hz), 7.64(2H, d, J=8.8Hz), 8.20(2H, d, J=8.8Hz)	
	HE	H	H		UVλ ^{H₂O} _{max} nm:	288
					IR _v ^{KBr} _{max} (cm ⁻¹): 1760, 1635(sh), 1610, 1450, 1380, 1240	

55 50 45 40 35 30 25 20 15 10 5



D-trans

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					IR ν _{max} ^{CHCl₃} (cm ⁻¹): 3400, 1770, 1700, 1650, 1605, 1520, 1400, 1120
62	HE	PNZ	PNB	-N(CH ₃) ₂	NMR δ (CDCl ₃): 1.33(3H, d, J=6.15Hz), 1.39(3H, d, J=6.8Hz), 2.98(3H, s), 2.92 and 3.12(3H, each s), 5.22(2H, s), 5.36(2H, ABq, J=13.5Hz), 7.50(2H, d, J=8.6Hz), 7.64(2H, d, J=8.6Hz), 8.21(4H, d, J=8.6Hz)
	HE	H	H	-N(CH ₃) ₂	UV λ _{max} ^{H₂O} nm: 291 IR ν _{max} ^{KBr} (cm ⁻¹): 1755, 1630(sh), 1610, 1390, 1250

55 50 45 40 35 30 25 20 15 10 5

Ex mple No.	R ₁	R ₂	R ₃	Y	Spectral Data
63	HE	PNZ	PNB		IR ν _{max} ^{CHCl₃} (cm ⁻¹): 3420, 1775, 1710, 1660, 1621, 1528, 1420, 1405, 1120
	HE	H	H		NMR δ (CDCl ₃): 1.33(3H, d, J=6.15Hz), 1.40(3H, d, J=6.6Hz), 4.20(2H, br, s), 5.23(2H, s), 5.84(2H, s), 7.50(2H, d, J=8.6Hz), 7.65(2H, d, J=8.6Hz), 8.15(2H, d, J=8.6Hz), 8.21(2H, d, J=8.6Hz) UV λ _{max} ^{H₂O} nm: 283 IR ν _{max} ^{KBr} (cm ⁻¹): 1750, 1640, 1610, 1455, 1400, 1250

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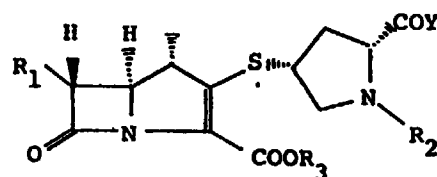
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D-cis

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
64	HE	PNZ	PNB	-N(CH ₃) ₂	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm ⁻¹): 3430, 1775, 1710, 1655, 1525, 1350, 1012 NMR δ (CDCl ₃): 1.34(3H, d, J=6.4Hz), 1.38(3H, d, J=6.8Hz), 2.92, 2.94, 2.98 and 3.08(6H, each s), 5.21(2H, s), 5.36(2H, ABq, J=13.9Hz), 7.50(2H, d, J=8.6Hz), 7.65(2H, d, J=8.6Hz), 8.21(2H, d, J=8.6Hz) UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm: 297 IR $\nu_{\text{max}}^{\text{KBr}}$ (cm ⁻¹): 1755, 1630(sh), 1600, 1380, 1240
	HE	H	H	-N(CH ₃) ₂	

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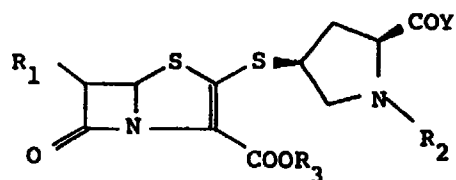
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Example
No.

R₁

R₂

R₃

Y

Spectral Data

$[\alpha]_D^{33} +32^\circ$ (c=0.22, THF)

HE PNZ PNB -NH₂

IR $\nu_{\max}^{\text{Nujol}}$ (cm⁻¹): 1780, 1680, 1608, 1517, 1381, 1350

NMR δ (CDCl₃) : 1.18(3H, d, J=6Hz), 5.22(2H, s),
5.79(1H, s)

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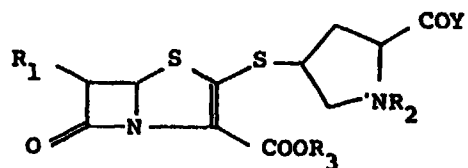
UV $\lambda_{\max}^{\text{H}_2\text{O}}$ nm: 322, 255

HE H H -NH₂

IR $\nu_{\max}^{\text{KBr}}$ (cm⁻¹): 1762, 1655, 1577, 1376

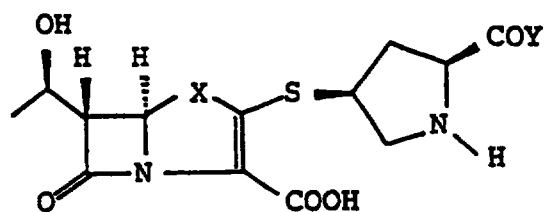
NMR δ (D₂O): 1.29(3H, d, J=6.5Hz), 1.75-1.89(1H, m), 2.62-2.87(1H, m), 3.00-3.09(1H, m), 3.38-3.48(1H, m), 3.65-3.92(2H, m), 3.90(1H, dd, J=1.4Hz and J=6.5Hz), 4.17-4.30(1H, m), 5.68(1H, d, J=1.4Hz)

Example No.	R ₁	R ₂	R ₃	Y	Spectral Data
					$[\alpha]_D^{27} +48^\circ$ (c=0.31, CHCl ₃)
	HE	PNZ	PNB		IR $\nu_{\max}^{\text{CHCl}_3}$ (cm ⁻¹): 1790, 1706, 1653, 1612, 1420, 1356, 1115 NMR δ (CDCl ₃): 1.36(3H, d, J=6Hz), 5.22(2H, s), 5.75(1H, d, J=1.5Hz)
66	HE	H	H		IR $\nu_{\max}^{\text{KBr}}$ (cm ⁻¹): 1765, 1636, 1582, 1365 NMR δ (D ₂ O): 1.29(3H, d, J=6.4Hz), 1.80-2.08(5H, m), 2.88-3.05(1H, m), 3.34-3.61(5H, m), 3.64-3.74(1H, m), 3.93(1H, dd, J=1.4Hz and J=6Hz), 4.04(1H, quin, J=6.6Hz), 4.24(1H, quin, J=6.3Hz), 4.40(1H, t, J=8.2Hz), 5.70(1H, d, J=1.4Hz)



Example No.	R ₁	R ₂	R ₃	Y	Spectral Data	
					IR _{max}	NMR δ (CDCl ₃):
67	H	PNZ	PNB	-NH ₂	Nujol (cm ⁻¹): 1780, 1700, 1675, 1600, 1505	4.40(1H, t, J=7Hz), 5.25(2H, s), 5.37(1H, d, J=13.6Hz), 5.75(1H, dd, J=1.5Hz and J=3.5Hz), 7.47(2H, d, J=9Hz), 7.57(2H, d, J=9Hz), 8.16(4H, d, J=9Hz)

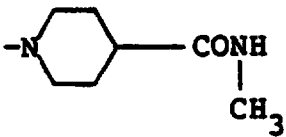
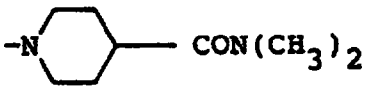
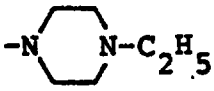
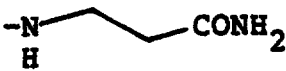
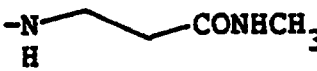
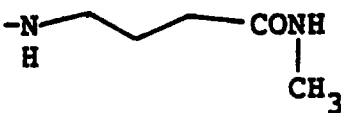
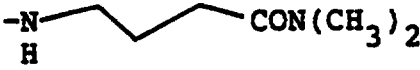
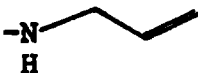
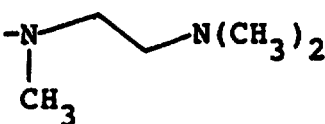
According to the procedures described in preceding Examples, the following compounds can also be prepared. In the following Tables, "Ph" means phenyl group.



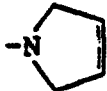
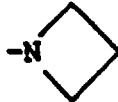
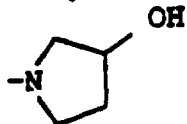
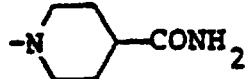
Compound No.	X	Y
1	-CH ₂ -	-NHC ₂ H ₅
2	-CH ₂ -	-NH-nC ₄ H ₉
3	-CH ₂ -	-NH-iC ₄ H ₉
4	-CH ₂ -	-N(nC ₃ H ₇) ₂
5	-CH ₂ -	-N(iC ₃ H ₇) ₂
6	-CH ₂ -	-N(nC ₄ H ₉) ₂
7	-CH ₂ -	-N(iC ₄ H ₉) ₂
8	-CH ₂ -	-N $\begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{C}_2\text{H}_5 \end{array}$
9	-CH ₂ -	-N $\begin{array}{l} \diagup \text{C}_2\text{H}_5 \\ \diagdown \text{nC}_4\text{H}_9 \end{array}$
10	-CH ₂ -	-N $\begin{array}{l} \diagup \text{H} \\ \diagdown \text{Ph} \end{array}$

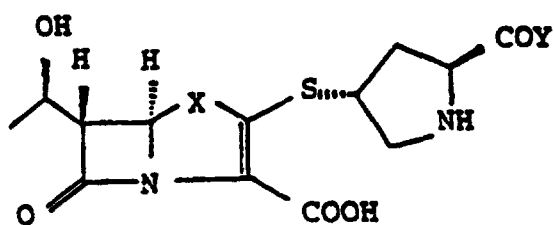
Compound No.	X	Y
11	-CH ₂ -	-N-CH ₂ -CH ₂ -Ph CH ₃
12	-CH ₂ -	-NCH ₂ -Ph C ₂ H ₅
13	-CH ₂ -	-N(CH ₂ -Ph) ₂
14	-CH ₂ -	-N-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ H
15	-CH ₂ -	-N-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ CH ₃
16	-CH ₂ -	-N-CH ₂ -CH ₂ -N(CH ₃) ₂ C ₂ H ₅
17	-CH ₂ -	-N-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ C ₂ H ₅
18	-CH ₂ -	-N-CH ₂ -CH ₂ -CH ₂ -N(CH ₃) ₂ H
19	-CH ₂ -	-N-CH ₂ -CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ H
20	-CH ₂ -	-N-CH ₂ -CH ₂ -CH ₂ -N(CH ₃) ₂ CH ₃
21	-CH ₂ -	-N-CH ₂ -CH ₂ -CH ₂ -N(CH ₃) ₂ C ₂ H ₅
22	-CH ₂ -	-N-CH ₂ -CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ C ₂ H ₅
23	-CH ₂ -	-N-CH ₂ -CH ₂ -CH ₂ -OH CH ₃

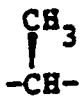
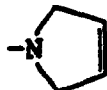
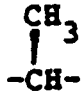
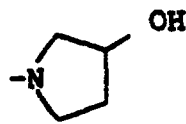
Compound No.	X	Y
24	-CH ₂ -	
25	-CH ₂ -	
26	-CH ₂ -	
27	-CH ₂ -	
28	-CH ₂ -	
29	-CH ₂ -	
30	-CH ₂ -	
31	-CH ₂ -	
32	-CH ₂ -	
33	-CH ₂ -	
34	-CH ₂ -	

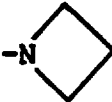
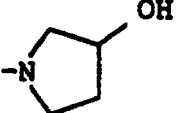
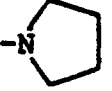
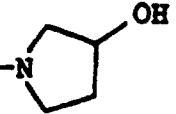
Compound No.	X	Y
35	$-\text{CH}_2-$	
36	$-\text{CH}_2-$	
37	$-\text{CH}_2-$	
38	$-\text{CH}_2-$	
39	$-\text{CH}_2-$	
40	$-\text{CH}_2-$	
41	$-\text{CH}_2-$	
42	$-\text{CH}_2-$	
43	$-\text{CH}_2-$	
44		
45		

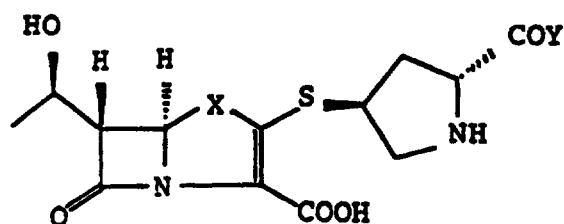
Compound No.	X	Y
46	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}- \end{array}$	$\begin{array}{c} -\text{NCH}_2\text{CONHCH}_3 \\ \\ \text{H} \end{array}$
47	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}- \end{array}$	$\begin{array}{c} -\text{NCH}_2\text{CONHCH}_3 \\ \\ \text{CH}_3 \end{array}$
48	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}- \end{array}$	$\begin{array}{c} \text{CONH}_2 \\ \\ \text{N} \end{array}$
49	-S-	$\begin{array}{c} \text{N} \\ \\ \text{H} \end{array}$
50	-S-	$\begin{array}{c} \text{N} \\ \\ \text{CH}_3 \end{array}$
51	-S-	$\begin{array}{c} \text{N} \\ \\ \text{CH}_3 \end{array}$
52	-S-	$\begin{array}{c} -\text{NCH}_2\text{CONH}_2 \\ \\ \text{H} \end{array}$
53	-S-	$\begin{array}{c} -\text{NCH}_2\text{CONH} \\ \\ \text{H} \end{array}$
54	-S-	$\begin{array}{c} -\text{NCH}_2\text{CONHCH}_3 \\ \\ \text{CH}_3 \end{array}$
55	-S-	$\begin{array}{c} \text{N} \\ \\ \text{O} \end{array}$
56	-S-	$\begin{array}{c} \text{N} \\ \\ \text{N-CH}_3 \end{array}$

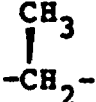
Compound No.	X	Y
57	-S-	
58	-S-	
59	-S-	
60	-S-	

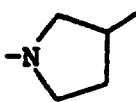
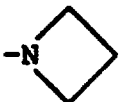
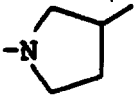
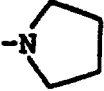
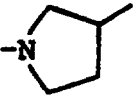
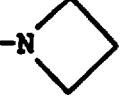


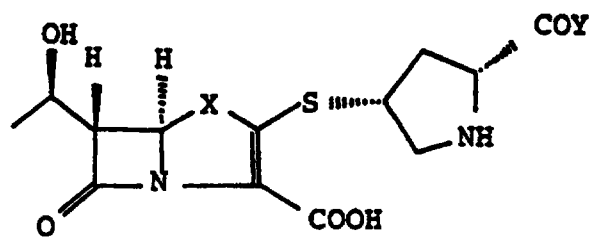
Compound No.	X	Y
61		
62		

Compound No.	X	Y
63	$-\text{CH}_2-$	
64	$-\text{CH}_2-$	
65	$-\text{S}-$	
66	$-\text{S}-$	
67	$-\text{S}-$	
68	$-\text{S}-$	$-\text{N}(\text{CH}_3)_2$

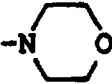
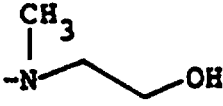
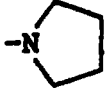
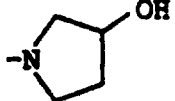


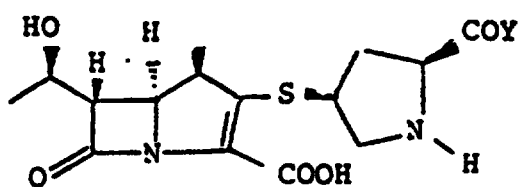
Compound No.	X	Y
69		

	Compound No.	X	Y
5			
	70	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}- \end{array}$	
10			
	71	$-\text{CH}_2-$	
15			
	72	$-\text{CH}_2-$	
20			
	73	$-\text{S}-$	
25			
	74	$-\text{S}-$	
30			
	75	$-\text{S}-$	
	76	$-\text{S}-$	$-\text{N}(\text{CH}_3)_2$



Compound No.	X	Y
77		
78		
79		
80		
81		
82		
83		

Compound No.	X	Y
84	-CH ₂ -	
85	-CH ₂ -	
86	-S-	
87	-S-	
88	-S-	
89	-S-	-N(CH ₃) ₂



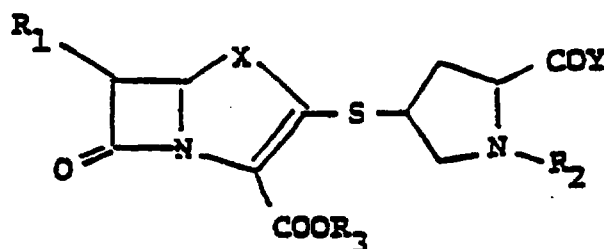
Compounds No.	Y
90	$-\text{NH}_2$
91	$-\text{N}(\text{CH}_3)\text{CH}_2\text{OH}$
92	$-\text{NHCH}_2\text{CONH}_2$
93	$-\text{N}(\text{CH}_3)\text{CH}_2\text{CONH}_2$
94	$-\text{N}$ (cyclopent-1-en-1-yl)
95	$-\text{N}$ (cyclobutyl)
96	$-\text{N}$ (2-hydroxycyclopentyl)
97	$-\text{N}$ (morpholinyl)
98	$-\text{N}$ (N-methylpiperidinyl)



Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A β -lactam compound represented by the formula (I)



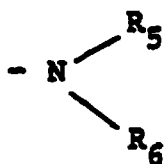
(I).

wherein R_1 represents a 1-hydroxyethyl group or a 1-hydroxyethyl group in which the hydroxy group is protected with a protecting group; R_2 represents a hydrogen atom or a protecting group for an amino group; R_3 represents a hydrogen atom or a protecting group for a carboxyl group; X represents a substituted or unsubstituted methylene group of the formula (1):



(1)

wherein R_4 represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, or X represents a sulfur atom; and Y represents (i) a group of the formula (2):



(2)

wherein R_5 and R_6 , which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a substituted alkyl group having 1 to 5 carbon atoms wherein the substituent is selected from a hydroxy group, a di(C_{1-3})alkylamino group, a carbamoyl group, a mono- or di(C_{1-3})alkylaminocarbonyl group and a protected or unprotected carboxyl group wherein the protecting group is a protecting group for a carboxyl group; or a pyridyl group; or R_5 and R_6 taken together represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_{1-3})alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof wherein the substituent is selected from a (C_{1-3})alkyl group, a carbamoyl group, a carboxyl group, a mono- or di(C_{1-3})alkylaminocarbonyl group and a hydroxy group; or (ii) a group of the formula (4):



wherein R_8 represents a hydrogen atom, a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms; and a pharmaceutically acceptable salt thereof.



2. A compound as claimed in Claim 1, wherein R_1 represents a 1-hydroxyethyl group, R_2 and R_3 each represents a hydrogen atom, and Y is a group represented by the formula (2-a):



wherein R_{5-a} and R_{6-a} each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, an alkyl group having 1 to 5 carbon atoms which is substituted with a hydroxyl group, a di-(C_1 - C_3)alkylamino group, a carbamoyl group, a mono- or di-(C_1 - C_3)alkyl-substituted aminocarbonyl group or a carboxyl group, or a pyridyl group; or R_{5-a} and R_{6-a} jointly represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1 - C_3) alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, an unsubstituted or substituted 3-to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof wherein the substituent is an alkyl group having 1 to 3 carbon atoms, a carbamoyl group, a carboxyl group, a mono- or di-(C_1 - C_3)alkyl-substituted aminocarbonyl group or a hydroxyl group; or a group represented by the formula (4-a):



wherein R_{8-a} represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

3. A compound as claimed in Claim 1, wherein R_1 represents a 1-hydroxyethyl group, R_2 and R_3 each represents a hydrogen atom, and Y is a group represented by the formula (2-b):



wherein R_{5-b} and R_{6-b} each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a substituted alkyl group having 1 to 5 carbon atoms

wherein the substituent is a hydroxyl group, a di-(C_1 - C_3)alkylamino group, a carbamoyl group, a mono- or di-(C_1 - C_3)alkyl-substituted aminocarbonyl group or a carboxyl group, or a pyridyl group, or R_{5-b} and R_{6-b} jointly represents an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1 - C_3)alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, an unsubstituted or substituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof wherein the substituent is an alkyl group having 1 to 3 carbon atoms, a carbamoyl group or a hydroxyl group; or a group represented by the formula (4-a):



wherein R_{8-a} represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

4. A compound as claimed in Claim 1, wherein R_1 represents a 1-hydroxyethyl group, R_2 and R_3 each represents a hydrogen atom, and Y is a group represented by the formula (2-c):

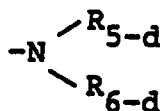


5

wherein R_{5-c} and R_{6-c} have one of the following meanings:

- (1) R_{5-c} represents an alkyl group having 1 to 5 carbon atoms which may be substituted with a carbamoyl group, a mono- or di-($\text{C}_1\text{-C}_3$)alkylaminocarbonyl group or a hydroxyl group, or a pyridyl group, and R_{6-c} represents a hydrogen atom or has the same meaning as defined for R_{5-c} ;
- (2) R_{5-c} and R_{6-c} jointly represent an alkylene chain to form, together with the adjacent nitrogen atom, an unsubstituted or substituted 4- to 6-membered saturated cyclic amino group or an unsubstituted or substituted 5- to 6-membered cyclic amino group having double bond(s) in the ring thereof wherein the substituent on the cyclic amino ring is a carbamoyl group or a hydroxyl group; and
- (3) R_{5-c} and R_{6-c} jointly represent an alkylene chain containing an oxygen atom or a ($\text{C}_1\text{-C}_3$)alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a 6-membered cyclic amino group.

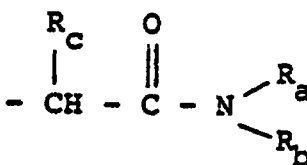
5. A compound as claimed in Claim 3, wherein Y is a group represented by the formula:



25

wherein R_{5-d} represents a hydrogen atom or a methyl group, and R_{6-d} represents a group of the formula:

30

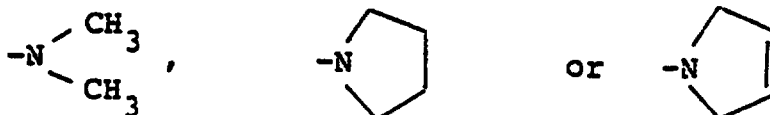


35

wherein R_a , R_b and R_c each represents a hydrogen atom or a methyl group.

40

6. A compound as claimed in Claim 3, wherein Y is represented by the formula:



45

50

7. A compound as claimed in any one of Claims 1 to 6, wherein X represents

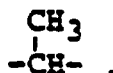


55

wherein R_4 is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.



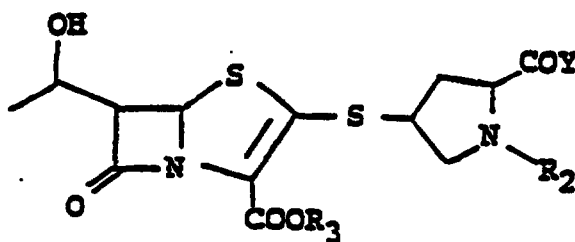
8. A compound as claimed in Claim 7, wherein X represents



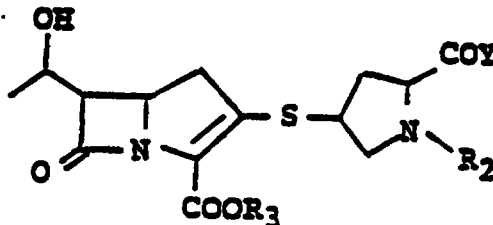
9. A compound as claimed in Claim 7, wherein R_4 is a hydrogen atom.

10. A compound as claimed in any one of Claims 1 to 6, wherein X is a sulfur atom.

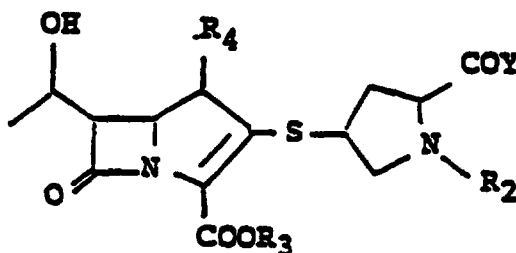
11. A (5R)-compound of the compound as claimed in any one of Claims 1 to 6 and 10, which is represented by the formula:



12. A (5R)-compound of the compound as claimed in any one of Claims 1 to 7 and 9, which is represented by the formula:



13. A (5)-compound of the compound as claimed in any one of the Claims 1 to 8, which is represented by the formula:



wherein R_4 is an alkyl group having 1 to 3 carbon atoms.

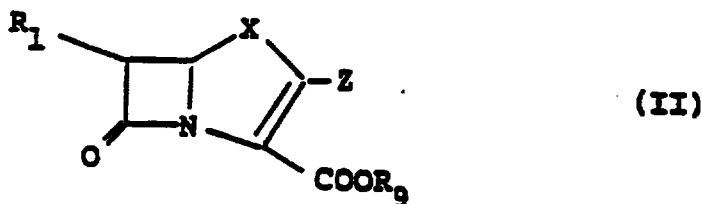
14. (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.



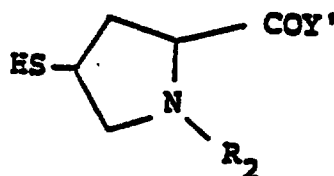
15. (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
16. (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
17. (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
18. (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
19. (5R)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
20. (5R)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
21. (5R)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
22. (5R)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
23. (5R)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
24. (5R)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
25. (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
26. (5R)-3-[2-(4-Pyridylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
27. (5S)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
28. (5S)-3-[2-((1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
29. (5S)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
30. (5S)-3-[2-((1-Azatidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
31. (5S)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
32. (5S)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
33. (5S)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.



34. (5S)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
35. (5S)-3-[2-Carbamoylpyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-carboxylic acid, or a non-toxic pharmaceutically acceptable salt thereof.
36. A (5R,6S,8R)-compound of the compound as claimed in Claim 11.
37. A (5R,6S,8R)-compound of the compound as claimed in Claim 12.
38. A (5S,6S,8R)-compound of the compound as claimed in Claim 13.
39. A (5R,6S,8R)-compound of the compound as claimed in any one of Claims 14 to 26.
40. A (5S,6S,8R)-compound of the compound as claimed in anyone of Claims 27 to 35.
41. A (5R,6S,8R,2'S,4'S)-compound of the compound as claimed in Claim 11.
42. A (5R,6S,8R,2'S,4'S)-compound of the compound as claimed in Claim 12.
43. A (5S,6S,8R,2'S,4'S)-compound of the compound as claimed in Claim 13.
44. A (5R,6S,8R,2'S,4'S)-compound of the compound as claimed in any one of Claims 14 to 26.
45. A (5S,6S,8R,2'S,4'S)-compound of the compound as claimed in any one of Claims 27 to 35.
46. A (4R,5S,6S,8R,2'S,4'S)-compound of the compound as claimed in any one of Claims 3 to 8 and 27 to 35.
47. A pharmaceutical composition which comprises as an active ingredient a pharmaceutically effective amount of at least one of the compounds as claimed in Claim 1 and at least one pharmaceutically acceptable inert carrier or diluent.
48. Use of the compound according to Claim 1 as an antimicrobial agent.
49. A process for preparing a compound as claimed in Claim 1, which comprises reacting a compound of the formula (II):



wherein R_1 and X are as defined in Claim 1, R_9 represents a protecting group for a carboxyl group, Z represents a reactive ester of an alcohol, or a substituted or unsubstituted lower-alkyl sulfinyl group, with a mercaptan derivative of the formula:

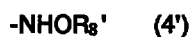




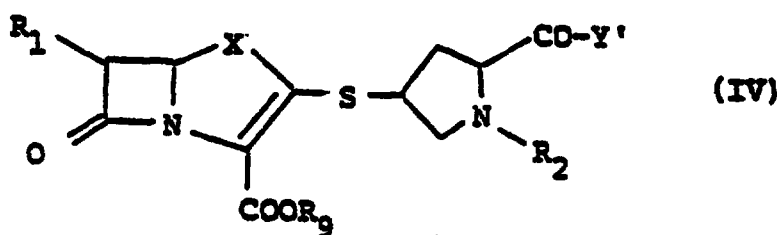
wherein R_2 is as defined in Claim 1, and Y' is a group represented by the formula (2):



wherein R_5 and R_6 are as defined in Claim 1, or a group represented by the formula (4'):

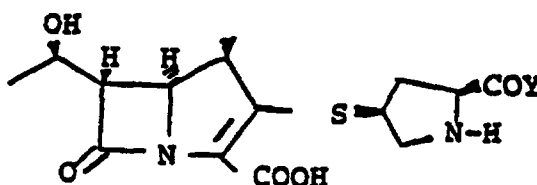


wherein R_8' represents a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms, in the presence of a base in an inert solvent to produce a β -lactam compound represented by the formula (IV):

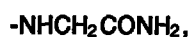
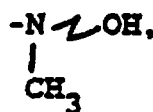


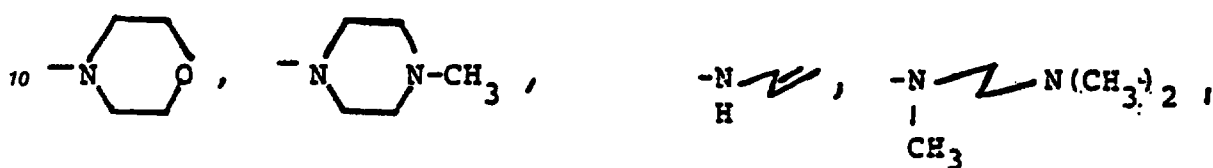
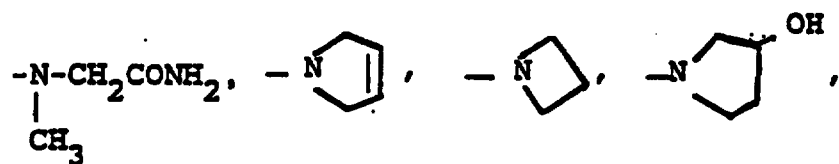
wherein R_1 , R_2 , R_3 , X and Y' are as defined above, and, if desired, subjecting the resulting compound to an appropriate combination of removal of the protecting group for the carboxyl group, the protecting group for the hydroxyl group and/or the protecting group for the amino group, sequentially or simultaneously, to produce the compound of the formula (IV) wherein R_1 is a 1-hydroxyethyl group, R_2 is a hydrogen atom and/or R_3 is a hydrogen atom, or the compound of the formula (IV) wherein the protecting group on the group Y' is removed.

50. A β -lactam compound of the formula:

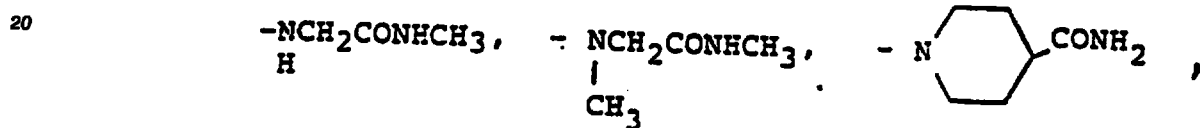


wherein Y is chosen from the group consisting of $-NH_2$,





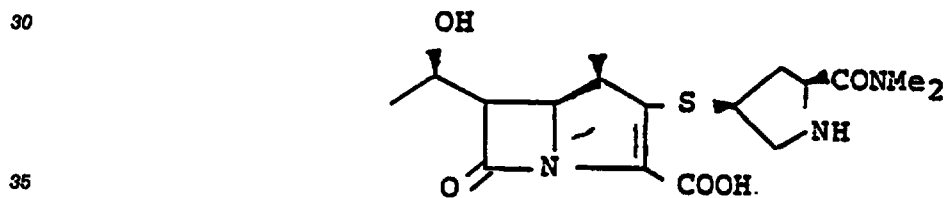
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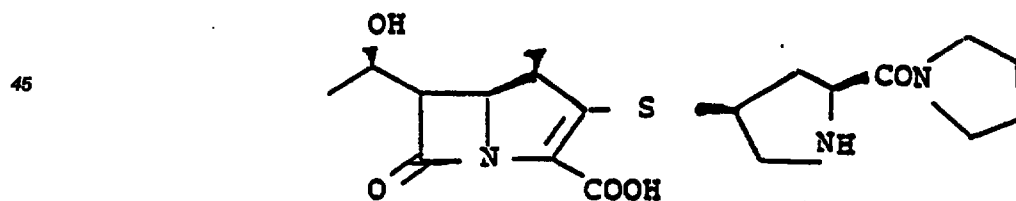
and the pharmaceutically acceptable salts thereof.

51. A β -lactam compound of the formula:



and the pharmaceutically acceptable salts thereof.

40 52. A β -lactam compound of the formula:

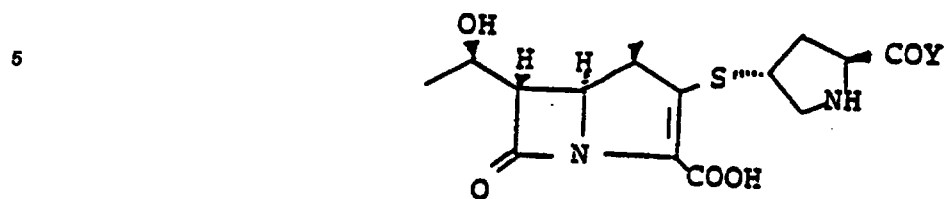


and the pharmaceutically acceptable salts thereof.

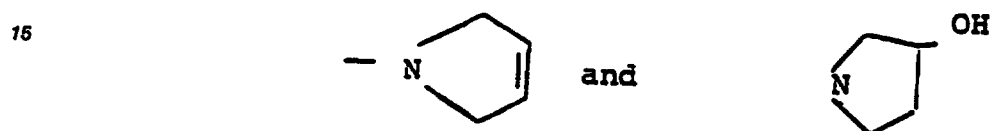
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53. A β -lactam compound of the formula:

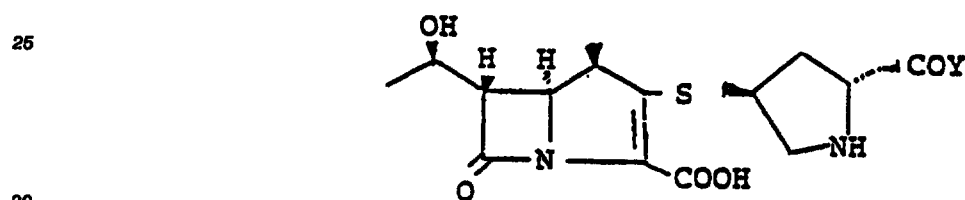


wherein Y is chosen from the group consisting of

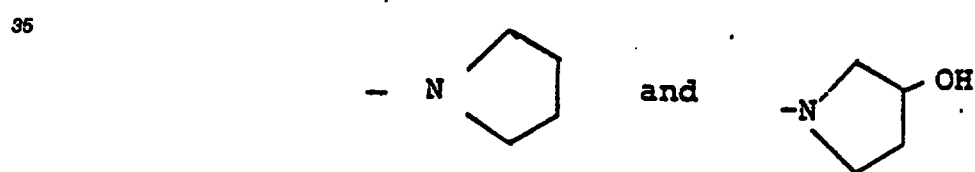


20 and the pharmaceutically acceptable salts thereof.

54. A β -lactam compound of the formula:

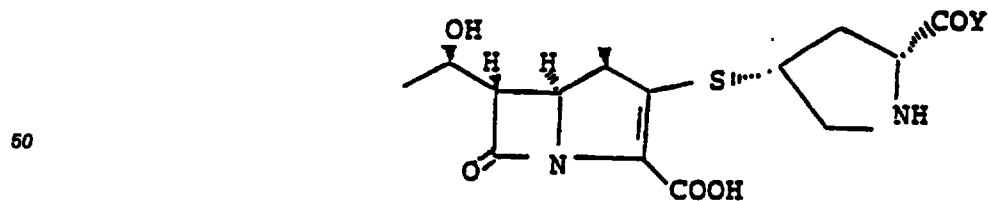


wherein Y is chosen from the group consisting of

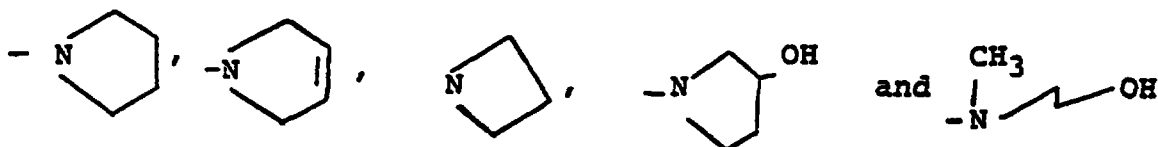


40 and the pharmaceutically acceptable salts thereof.

55. A β -lactam compound of the formula:

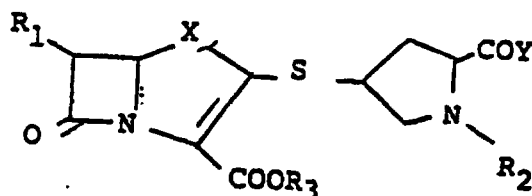


55 wherein Y is selected from the group consisting of



and the pharmaceutically acceptable salts thereof.

10 56. A β -lactam compound represented by the formula:



20 wherein R_1 represents a 1-hydroxyethyl group or a 1-hydroxyethyl group in which the hydroxy group is protected with a protecting group for a hydroxy group; R_2 represents a hydrogen atom or a protecting group for an amino group; R_3 represents a hydrogen atom or a protecting group for a carboxyl group; X represents a sulfur atom; and Y represents a group of the formula (2):



35 wherein R_5 and R_6 , which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a substituted alkyl group having 1 to 5 carbon atoms wherein said substituent is selected from the group consisting of hydroxyl, di-(C_1 - C_3)-alkylamino, carbamoyl, mono- or di-(C_1 - C_3)-alkyl-substituted aminocarbonyl and protected or unprotected carboxyl or a pyridyl group, or R_5 and R_6 taken together represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1 - C_3)-alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof, wherein said substituent is selected from the group consisting of C_1 - C_3 alkyl, carbamoyl, mono- or di-(C_1 - C_3)-alkyl-substituted aminocarbonyl and hydroxyl, or a group of the formula (4):

45 $\text{---NHOR}_8 \quad (4)$

wherein R_8 represents a hydrogen atom, a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms, and a pharmaceutically acceptable salt thereof.

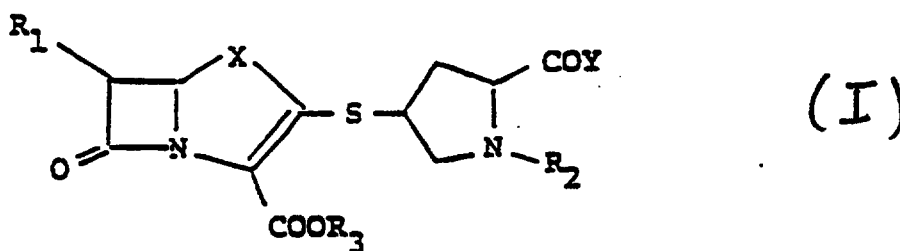
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Claims for the following Contracting State : AT

1. A process for preparing a β -lactam compound represented by the formula (I)



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wherein R_1 represents a 1-hydroxyethyl group or a 1-hydroxyethyl group in which the hydroxy group is protected with a protecting group; R_2 represents a hydrogen atom or a protecting group for an amino group; R_3 represents a hydrogen atom or a protecting group for a carboxyl group; X represents a substituted or unsubstituted methylene group of the formula (1):



wherein R_4 represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, or X represents a sulfur atom; and Y represents (i) a group or the formula (2):



40

wherein R_5 and R_6 , which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a substituted alkyl group having 1 to 5 carbon atoms wherein the substituent is selected from a hydroxy group, a di(C_1 - $_3$)alkylamino group, a carbamoyl group, a mono- or di(C_1 - $_3$)alkylaminocarbonyl group and a protected or unprotected carboxyl group wherein the protecting group is a protecting group for a carboxyl group; or a pyridyl group; or R_5 and R_6 taken together represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C_1 - $_3$)alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof wherein the substituent is selected from a (C_1 - $_3$)alkyl group, a carbamoyl group, a carboxyl group, a mono- or di(C_1 - $_3$)alkylaminocarbonyl group and a hydroxy group;

45

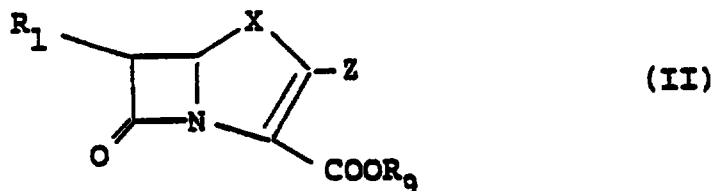
or (ii) a group of the formula (4):

50

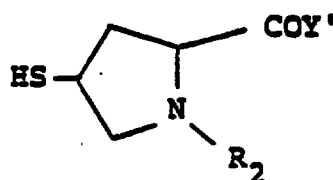


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wherein R_8 represents a hydrogen atom, a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms; or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula (II):



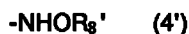
10 wherein R_1 and X are as defined above, R_9 represents a protecting group for a carboxyl group, Z represents a reactive ester of an alcohol, or a substituted or unsubstituted lower-alkyl sulfinyl group, with a mercaptan derivative of the formula:



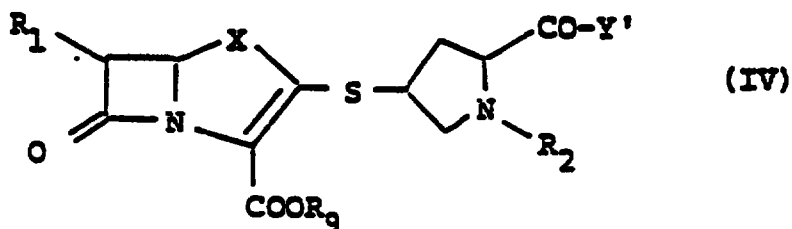
wherein R_2 is as defined above, and Y' is a group represented by the formula (2):



30 wherein R_5 and R_6 are as defined above, or a group represented by the formula (4'):



wherein R_8' represents a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms, in the presence of a base in an inert solvent to produce a β -lactam compound represented by the formula (IV):



50 wherein R_1 , R_2 , R_9 , X and Y' are as defined above, and, if desired, subjecting the resulting compound to an appropriate combination of removal of the protecting group for the carboxyl group, the protecting group for the hydroxyl group and/or the protecting group for the amino group, sequentially or simultaneously, to produce the compound of the formula (IV) wherein R_1 is a 1-hydroxyethyl group, R_2 is a hydrogen atom and/or R_3 is a hydrogen atom, or the compound of the formula (IV) wherein the protecting group on the group Y' is removed, and optionally converting the obtained compound into a pharmaceutically acceptable salt.

55



2. The process as claimed in Claim 1 for producing a compound of formula (I), wherein R₁ represents a 1-hydroxyethyl group, R₂ and R₃ each represents a hydrogen atom, and Y is a group represented by the formula (2-a):



wherein R_{5-a} and R_{6-a} each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, an alkyl group having 1 to 5 carbon atoms which is substituted with a hydroxyl group, a di-(C₁-C₃)alkylamino group, a carbamoyl group, a mono- or di-(C₁-C₃)alkyl-substituted aminocarbonyl group or a carboxyl group, or a pyridyl group; or R_{5-a} and R_{6-a} jointly represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C₁-C₃) alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, an unsubstituted or substituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof wherein the substituent is an alkyl group having 1 to 3 carbon atoms, a carbamoyl group, a carboxyl group, a mono- or di-(C₁-C₃)alkyl-substituted aminocarbonyl group or a hydroxyl group; or a group represented by the formula (4-a):



wherein R_{8-a} represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

3. The process as claimed in Claim 1 for producing a compound of formula (I), wherein R₁ represents a 1-hydroxyethyl group, R₂ and R₃ each represents a hydrogen atom, and Y is a group represented by the formula (2-b):



wherein R_{5-b} and R_{6-b} each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a substituted alkyl group having 1 to 5 carbon atoms wherein the substituent is a hydroxyl group, a di-(C₁-C₃)alkylamino group, a carbamoyl group, a mono- or di-(C₁-C₃)alkyl-substituted aminocarbonyl group or a carboxyl group, or a pyridyl group, or R_{5-b} and R_{6-b} jointly represents an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C₁-C₃)alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, an unsubstituted or substituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof wherein the substituent is an alkyl group having 1 to 3 carbon atoms, a carbamoyl group or a hydroxyl group; or a group represented by the formula (4-a):



wherein R_{8-a} represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

4. The process as claimed in Claim 1 for producing a compound of formula (I), wherein R₁ represents a 1-hydroxyethyl group, R₂ and R₃ each represents a hydrogen atom, and Y is a group represented by the formula (2-c):



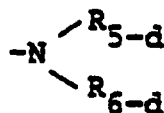
wherein R_{5-c} and R_{6-c} have one of the following meanings:

(1) R_{5-c} represents an alkyl group having 1 to 5 carbon atoms which may be substituted with a carbamoyl group, a mono- or di-(C_1 - C_3)alkylaminocarbonyl group or a hydroxyl group, or a pyridyl group, and R_{6-c} represents a hydrogen atom or has the same meaning as defined for R_{5-c} ;

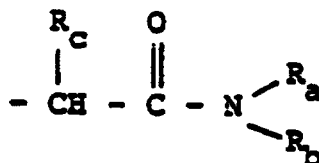
(2) R_{5-c} and R_{6-c} jointly represent an alkylene chain to form, together with the adjacent nitrogen atom, an unsubstituted or substituted 4- to 6-membered saturated cyclic amino group or an unsubstituted or substituted 5- to 6-membered cyclic amino group having double bond(s) in the ring thereof wherein the substituent on the cyclic amino ring is a carbamoyl group or a hydroxyl group; and

(3) R_{5-c} and R_{6-c} jointly represent an alkylene chain containing an oxygen atom or a (C_1 - C_3)alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a 6-membered cyclic amino group.

5. The process as claimed in Claim 3 for producing a compound of formula (I), wherein Y is a group represented by the formula:

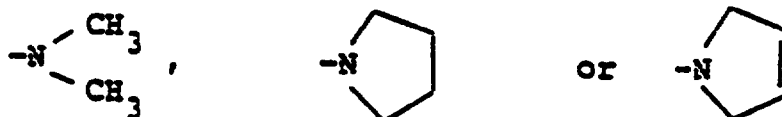


wherein R_{5-d} represents a hydrogen atom or a methyl group, and R_{6-d} represents a group of the formula:



wherein R_a , R_b and R_c each represents a hydrogen atom or a methyl group.

6. The process as claimed in Claim 3 for producing a compound of formula (I), wherein Y is represented by the formula:



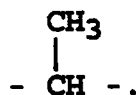
7. The process as claimed in any one of Claims 1 to 6 for producing a compound of formula (I), wherein





X represents wherein R_4 is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

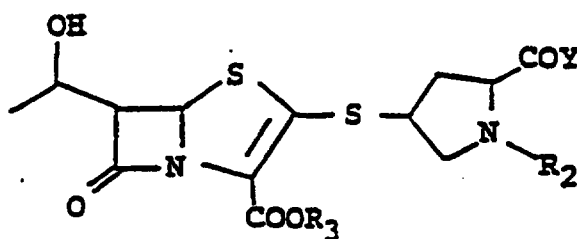
8. The process as claimed in Claim 7 for producing a compound of formula (I), wherein X represents



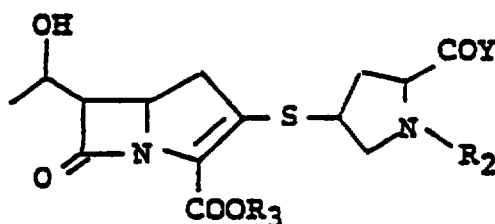
9. The process as claimed in Claim 7 for producing a compound of formula (I), wherein R_4 is a hydrogen atom.

10. The process as claimed in any one of Claims 1 to 6 for producing a compound of formula (I), wherein X is a sulfur atom.

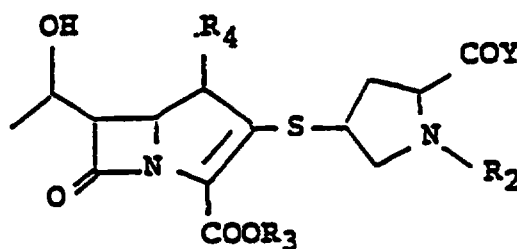
11. The process as claimed in Claim 1 for producing a (5R)-compound of the compound as claimed in any one of Claims 1 to 6 and 10, which is represented by the formula:



12. The process as claimed in Claim 1 for producing a (5R)-compound of the compound as claimed in any one of Claims 1 to 7 and 9, which is represented by the formula:



13. The process as claimed in Claim 1 for producing a (5S)-compound of the compound as claimed in any one of the Claims 1 to 8 which is represented by the formula:



wherein R_4 is an alkyl group having 1 to 3 carbon atoms.



14. The process as claimed in Claim 1 for producing (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 5 15. The process as claimed in Claim 1 for producing (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 10 16. The process as claimed in Claim 1 for producing (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-4-thia-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 15 17. The process as claimed in Claim 1 for producing (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 20 18. The process as claimed in Claim 1 for producing (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 25 19. The process as claimed in Claim 1 for producing (5R)-3-[2-((1-Pyrrolidin-3-yl)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 30 20. The process as claimed in Claim 1 for producing (5R)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 35 21. The process as claimed in Claim 1 for producing (5R)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 40 22. The process as claimed in Claim 1 for producing (5R)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 45 23. The process as claimed in Claim 1 for producing (5R)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 50 24. The process as claimed in Claim 1 for producing (5R)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 55 25. The process as claimed in Claim 1 for producing (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
26. The process as claimed in Claim 1 for producing (5R)-3-[2-(4-Pyridylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
27. The process as claimed in Claim 1 for producing (5S)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
28. The process as claimed in Claim 1 for producing (5S)-3-[2-((1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.

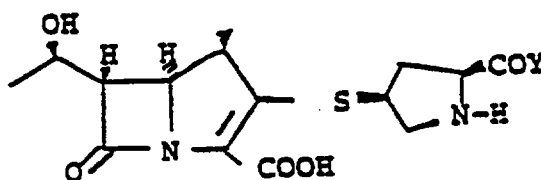


pharmaceutically acceptable salt thereof.

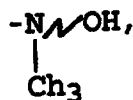
- 5 **29.** The process as claimed in Claim 1 for producing (5S)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 10 **30.** The process as claimed in Claim 1 for producing (5S)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 15 **31.** The process as claimed in Claim 1 for producing (5S)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0] hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 20 **32.** The process as claimed in Claim 1 for producing (5S)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0] hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 25 **33.** The process as claimed in Claim 1 for producing (5S)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 30 **34.** The process as claimed in Claim 1 for producing (5S)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0] hept-2-ene-7-one-2-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 35 **35.** The process as claimed in Claim 1 for producing (5S)-3-[2-Carbamoylpyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-ene-7-one-carboxylic acid or a non-toxic pharmaceutically acceptable salt thereof.
- 40 **36.** The process as claimed in Claim 1 for producing a (5R,6S,8R)-compound of the compound as claimed in Claim 11.
- 45 **37.** The process as claimed in Claim 1 for producing a (5R,6S,8R)-compound of the compound as claimed in Claim 12.
- 50 **38.** The process as claimed in Claim 1 for producing a (5S,6S,8R)-compound of the compound as claimed in Claim 13.
- 55 **39.** The process as claimed in Claim 1 for producing a (5R,6S,8R)-compound of the compound as claimed in any one of Claims 14 to 26.
- 40.** The process as claimed in Claim 1 for producing a (5S,6S,8R)-compound of the compound as claimed in anyone of Claims 27 to 35.
- 41.** The process as claimed in Claim 1 for producing a (5R,6S,8R,2'S,4'S)-compound of the compound as claimed in Claim 11.
- 42.** The process as claimed in Claim 1 for producing a (5R,6S,8R,2'S,4'S)-compound of the compound as claimed in Claim 12.
- 43.** The process as claimed in Claim 1 for producing a (5S,6S,8R,2'S,4'S)-compound of the compound as claimed in Claim 13.
- 44.** The process as claimed in Claim 1 for producing a (5R,6S,8R,2'S,4'S)-compound of the compound as claimed in any one of Claims 14 to 26.



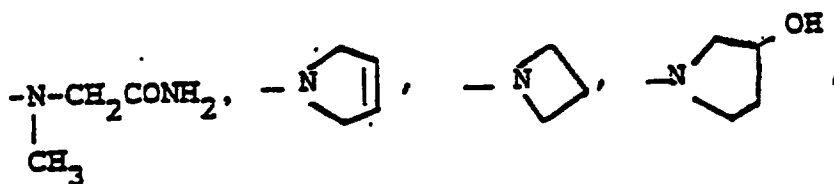
45. The process as claimed in Claim 1 for producing a (5S,6S,8R,2'S,4'S)-compound of the compound as claimed in any one of Claims 27 to 35.
46. The process as claimed in Claim 1 for producing a (4R,5S,6S,8R,2'S,4'S)-compound of the compound as claimed in any one of Claims 3 to 8 and 27 to 35.
47. A process for producing a pharmaceutical composition which comprises combining as an active ingredient a pharmaceutically effective amount of at least one of the compounds as claimed in Claim 1 and at least one pharmaceutically acceptable inert carrier or diluent.
48. Use of the compound according to Claim 1 as an antimicrobial agent.
49. The process as claimed in claim 1 for producing a β -lactam compound of the formula:



wherein Y is chosen from the group consisting of NH_2 ,



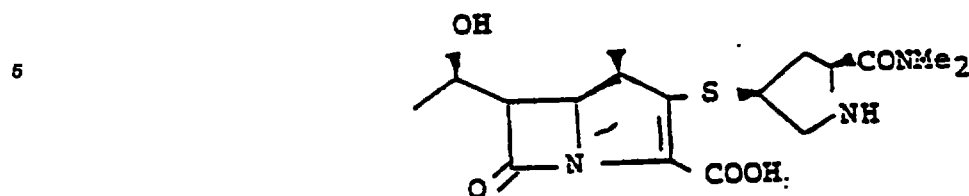
$-\text{NHCH}_2\text{CONH}_2$,



and the pharmaceutically acceptable salts thereof.

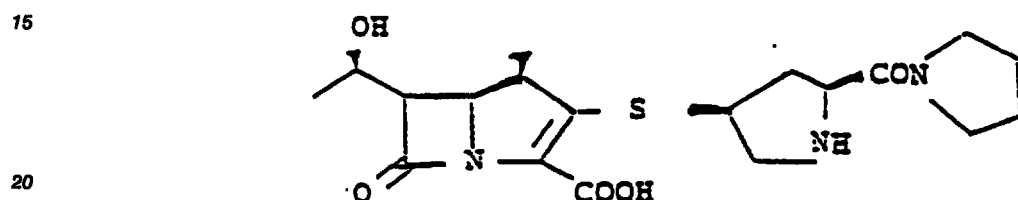


50. The process as claimed in claim 1 for producing a β -lactam compound of the formula:



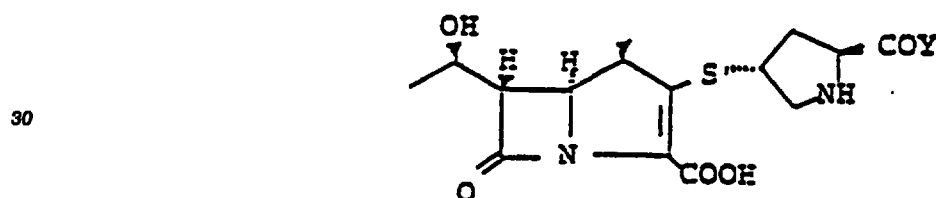
and the pharmaceutically acceptable salts thereof.

51. The process as claimed in Claim 1 for producing a β -lactam compound of the formula:

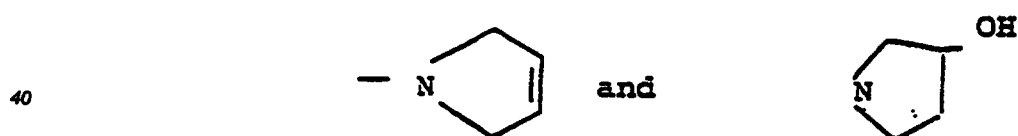


and the pharmaceutically acceptable salts thereof.

25 52. The process as claimed in Claim 1 for producing a β -lactam compound of the formula:

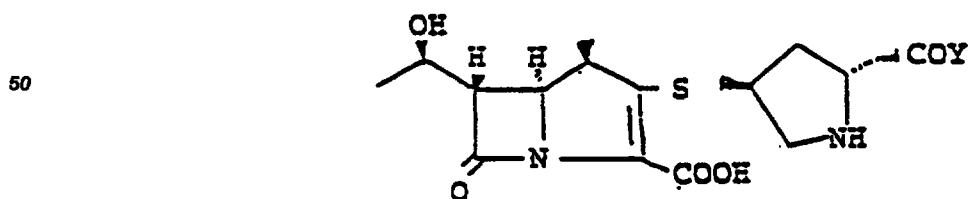


wherein Y is chosen from the group consisting of



and the pharmaceutically acceptable salts thereof.

53. The process as claimed in Claim 1 for producing a β -lactam compound of the formula:

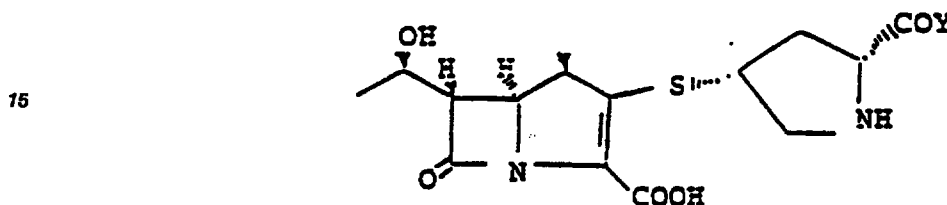


wherein Y is chosen from the group consisting of



and the pharmaceutically acceptable salts thereof.

10 54. The process as claimed in Claim 1 for producing a β -lactam compound of the formula:

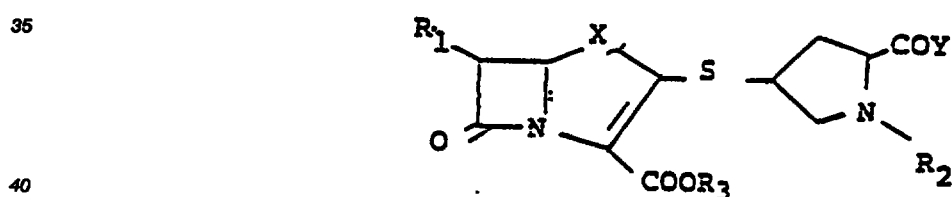


20 wherein Y is selected from the group consisting of



30 and the pharmaceutically acceptable salts thereof.

55. The process as claimed in Claim 1 for producing a β -lactam compound represented by the formula:



45 wherein R₁ represents a 1-hydroxyethyl group or a 1-hydroxyethyl group in which the hydroxy group is protected with a protecting group for a hydroxy group; R₂ represents a hydrogen atom or a protecting group for an amino group; R₃ represents a hydrogen atom or a protecting group for a carboxyl group; X represents a sulfur atom; and Y represents a group of the formula (2):



55 wherein R₅ and R₆, which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 4 carbon atoms, a benzyl group, a phenethyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group or a 4-pyridylmethyl group, a



substituted alkyl group having 1 to 5 carbon atoms wherein said substituent is selected from the group consisting of hydroxyl, di-(C₁-C₃)-alkylamino, carbamoyl, mono- or di-(C₁-C₃)-alkyl-substituted aminocarbonyl and protected or unprotected carboxyl or a pyridyl group, or R₅ and R₆ taken together represent an alkylene chain or an alkylene chain containing an oxygen atom, a sulfur atom or a (C₁-C₃)-alkyl-substituted nitrogen atom to form, together with the adjacent nitrogen atom, a substituted or unsubstituted 3- to 7-membered cyclic amino group which may contain double bond(s) in the ring thereof, wherein said substituent is selected from the group consisting of C₁-C₃ alkyl, carbamoyl, mono- or di-(C₁-C₃)-alkyl-substituted aminocarbonyl and hydroxyl, or a group of the formula (4):

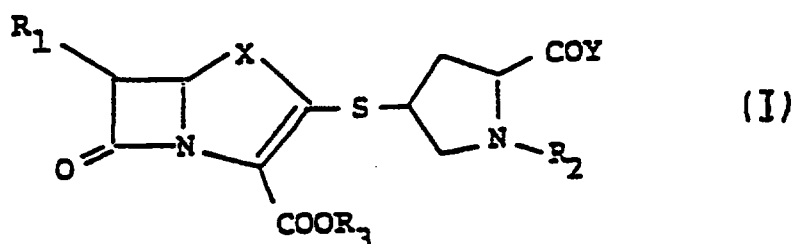


wherein R₈ represents a hydrogen atom, a protecting group for a hydroxyl group or an alkyl group having 1 to 3 carbon atoms, and a pharmaceutically acceptable salt thereof.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE

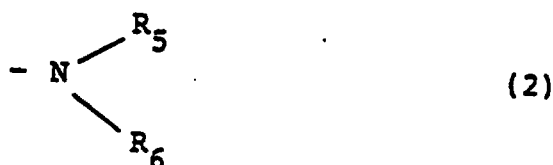
1. β -Lactamverbindung wiedergegeben durch die Formel (I)



in der R₁ eine 1-Hydroxyethylgruppe oder eine 1-Hydroxyethylgruppe, wobei die Hydroxygruppe mit einer Schutzgruppe geschützt ist, bedeutet; R₂ ein Wasserstoffatom oder eine Schutzgruppe für eine Aminogruppe bedeutet; R₃ ein Wasserstoffatom oder eine Schutzgruppe für eine Carboxygruppe bedeutet; X eine substituierte oder unsubstituierte Methylengruppe der Formel (1) bedeutet:



wobei R₄ ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet, oder X ein Schwefelatom bedeutet; und Y (i) einen Rest der Formel (2) bedeutet:



wobei R₅ und R₆, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, Phenethyl-, 2-Pyridylmethyl-, 3-Pyridylmethyl- oder 4-Pyridylmethylgruppe, einen substituierten Alkylrest mit 1 bis 5 Kohlenstoffatomen, wobei der Substituent aus einer Hydroxygruppe, einem Di-(C₁-C₃)-alkylamino-, Carbamoyl-, einem Mono- oder Di-(C₁-C₃)-alkylaminocarbonylrest und einer geschützten



oder ungeschützten Carboxygruppe ausgewählt ist, wobei die Schutzgruppe eine Schutzgruppe für eine Carboxygruppe ist; oder einen Pyridylrest bedeutet; oder R_5 und R_6 zusammen eine Alkylkette oder eine Alkylkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1-C_3) -alkylsubstituiertes Stickstoffatom enthält, bedeuten, wobei zusammen mit dem benachbarten Stickstoffatom ein substituierter oder unsubstituierter 3- bis 7-gliedriger cyclischer Aminorest erzeugt wird, der in dem Ring eine Doppelbindung (Doppelbindungen) enthalten kann, wobei der Substituent aus einem (C_1-C_3) -Alkyl-, einem Carbamoyl-, einem Carboxy-, einem Mono- oder Di- (C_1-C_3) -alkylaminocarbonylrest und einer Hydroxygruppe ausgewählt ist; oder (ii) einen Rest der Formel (4) bedeutet:



wobei R_8 ein Wasserstoffatom, eine Schutzgruppe für die Hydroxygruppe oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet; und ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, wobei R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 und R_3 jeweils ein Wasserstoffatom bedeutet, und Y einen Rest, wiedergegeben durch die Formel (2-a), bedeutet:



wobei R_{5-a} und R_{6-a} jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, eine Phenethyl-, eine 2-Pyridylmethyl-, eine 3-Pyridylmethyl- oder eine 4-Pyridylmethylgruppe, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, der mit einer Hydroxygruppe, einem Di- (C_1-C_3) -alkylamino-, einem Carbamoyl-, einem mono- oder di- (C_1-C_3) -alkylsubstituierten Aminocarbonylrest oder einer Carboxygruppe substituiert ist; oder einen Pyridylrest bedeutet; oder R_{5-a} und R_{6-a} zusammen eine Alkylkette oder eine Alkylkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1-C_3) -alkylsubstituiertes Stickstoffatom enthält, bedeuten, wobei zusammen mit dem benachbarten Stickstoffatom ein unsubstituierter oder substituierter 3- bis 7-gliedriger cyclischer Aminorest erzeugt wird, der in seinem Ring eine Doppelbindung (Doppelbindungen) enthalten kann, wobei der Substituent einen Alkylrest mit 1 bis 3 Kohlenstoffatomen, einen Carbamoyl-, einen Carboxy-, einen mono- oder di- (C_1-C_3) -alkylsubstituierten Aminocarbonylrest oder eine Hydroxygruppe bedeutet; oder einen Rest, wiedergegeben durch die Formel (4-a), bedeutet:



wobei R_{8-a} ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet.

3. Verbindung nach Anspruch 1, wobei R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 und R_3 jeweils ein Wasserstoffatom bedeutet, und Y einen Rest, wiedergegeben durch die Formel (2-b), bedeutet:



wobei R_{5-b} und R_{6-b} jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, eine Phenethyl-, eine 2-Pyridylmethyl-, eine 3-Pyridylmethyl- oder eine 4-Pyridylmethylgruppe, einen substituierten Alkylrest mit 1 bis 5 Kohlenstoffatomen, wobei der Substituent eine Hydroxygruppe, eine Di- (C_1-C_3) -alkylamino-, eine Carbamoyl-, eine mono- oder di- (C_1-C_3) -alkylsubstituierte Aminocarbonyl- oder eine Carboxygruppe ist, oder einen Pyridylrest bedeutet, oder R_{5-b} und R_{6-b} zusammen eine Alkylkette oder eine Alkylkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1-C_3) -alkylsubstituiertes Stickstoffatom enthält, darstellt, wobei zusammen mit dem benachbarten Stickstoffatom ein unsubstituierter oder substituierter 3- bis 7-



gliedriger cyclischer Aminorest erzeugt wird, der in dem Ring eine Doppelbindung (oder Doppelbindungen) enthalten kann, wobei der Substituent einen Alkylrest mit 1 bis 3 Kohlenstoffatomen, eine Carbamoyl- oder eine Hydroxygruppe ist; oder einen Rest, wiedergegeben durch die Formel (4-a), bedeutet:



wobei R_{8-a} ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet.

4. Verbindung nach Anspruch 1, wobei R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 und R_3 jeweils ein Wasserstoffatom bedeutet und Y einen Rest, wiedergegeben durch die Formel (2-c), darstellt:



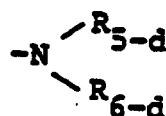
wobei R_{5-c} und R_{6-c} eine der nachstehenden Bedeutungen besitzen:

(1) R_{5-c} bedeutet einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, der mit einer Carbamoyl-, einer Mono- oder Di-(C_1 - C_3)alkylaminocarbonyl- oder einer Hydroxygruppe substituiert ist, oder einen Pyridylrest, und R_{6-c} bedeutet ein Wasserstoffatom oder besitzt die für R_{5-c} angegebenen Bedeutungen;

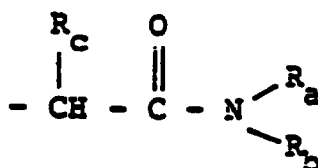
(2) R_{5-c} und R_{6-c} bedeuten zusammen eine Alkylkette, wobei zusammen mit dem benachbarten Stickstoffatom ein unsubstituierter oder substituierter 4- bis 6-gliedriger gesättigter cyclischer Aminorest oder ein unsubstituierter oder substituierter 5- bis 6-gliedriger cyclischer Aminorest mit einer Doppelbindung (oder Doppelbindungen) im Ring erzeugt wird, wobei der Substituent an dem cyclischen Aminoring eine Carbamoyl- oder eine Hydroxygruppe ist; und

(3) R_{5-c} und R_{6-c} bedeuten zusammen eine Alkylkette, die ein Sauerstoffatom oder ein (C_1 - C_3)-alkylsubstituiertes Stickstoffatom enthält, wobei zusammen mit dem benachbarten Stickstoffatom ein 6-gliedriger cyclischer Aminorest erzeugt wird.

5. Verbindung nach Anspruch 3, wobei Y einen Rest, wiedergegeben durch die Formel:



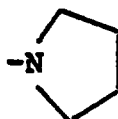
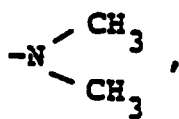
bedeutet, wobei R_{5-d} ein Wasserstoffatom oder eine Methylgruppe bedeutet, und R_{6-d} einen Rest der Formel:



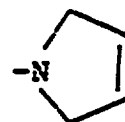
bedeutet, wobei R_a , R_b und R_c jeweils ein Wasserstoffatom oder eine Methylgruppe bedeutet.



6. Verbindung nach Anspruch 3, wobei Y durch die Formeln:



oder



wiedergegeben ist.

7. Verbindung nach einem der Ansprüche 1 bis 6, wobei X



bedeutet, wobei R_4 ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen darstellt.

8. Verbindung nach Anspruch 7, wobei X

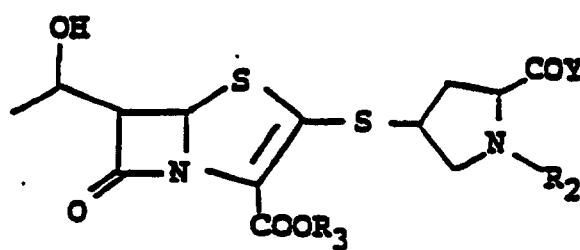


bedeutet.

9. Verbindung nach Anspruch 7, wobei R_4 ein Wasserstoffatom ist.

10. Verbindung nach einem der Ansprüche 1 bis 6, wobei X ein Schwefelatom ist.

11. (5R)-Verbindung der Verbindung nach einem der Ansprüche 1 bis 6 und 10, die durch die Formel:



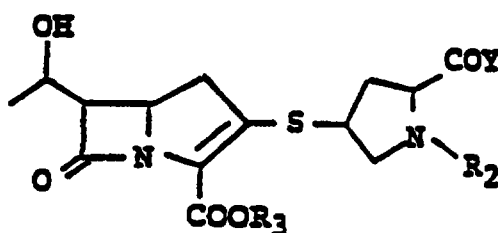
wiedergegeben ist.



12. (5R)-Verbindung der Verbindung nach einem der Ansprüche 1 bis 7 und 9, die durch die Formel:

5

10

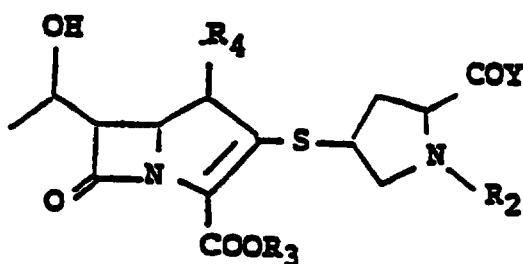


wiedergegeben ist.

13. (5S)-Verbindung der Verbindung nach einem der Ansprüche 1 bis 8, wiedergegeben durch die Formel:

20

25



wobei R₄ einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet.

14. (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-4-thia-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
15. (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-4-thia-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
16. (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-4-thia-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
17. (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
18. (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
19. (5R)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
20. (5R)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
21. (5R)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
22. (5R)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
23. (5R)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.



24. (5R)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
- 5 25. (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
26. (5R)-3-[2-(4-Pyridylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
- 10 27. (5S)-3-[2-Dimethylaminocarbonyl]pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
28. (5S)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
- 15 29. (5S)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
30. (5S)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
- 20 31. (5S)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
- 25 32. (5S)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
- 30 33. (5S)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
34. (5S)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
- 35 35. (5S)-3-[2-Carbamoylpyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-carbonsäure oder ein nicht toxisches pharmazeutisch verträgliches Salz davon.
36. (5R,6S,8R)-Verbindung der Verbindung nach Anspruch 11.
- 40 37. (5R,6S,8R)-Verbindung der Verbindung nach Anspruch 12.
38. (5S,6S,8R)-Verbindung der Verbindung nach Anspruch 13.
- 45 39. (5R,6S,8R)-Verbindung der Verbindung nach einem der Ansprüche 14 bis 26.
40. (5S,6S,8R)-Verbindung der Verbindung nach einem der Ansprüche 27 bis 35.
41. (5R,6S,8R,2'S,4'S)-Verbindung der Verbindung nach Anspruch 11.
- 50 42. (5R,6S,8R,2'S,4'S)-Verbindung der Verbindung nach Anspruch 12.
43. (5S,6S,8R,2'S,4'S)-Verbindung der Verbindung nach Anspruch 13.
- 55 44. (5R,6S,8R,2'S,4'S)-Verbindung der Verbindung nach einem der Ansprüche 14 bis 26.
45. (5S,6S,8R,2'S,4'S)-Verbindung der Verbindung nach einem der Ansprüche 27 bis 35.

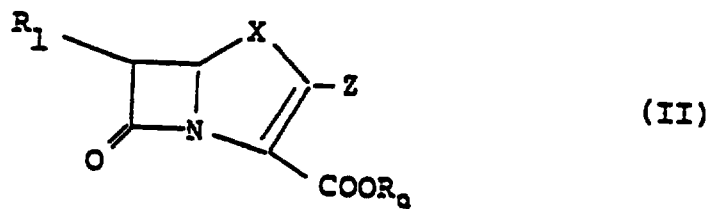


46. (4R,5S,6S,8R,2'S,4'S)-Verbindung der Verbindung nach einem der Ansprüche 3 bis 8 und 27 bis 35.

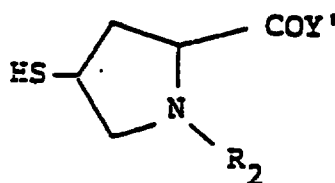
47. Pharmazeutische Zusammensetzung, umfassend eine pharmazeutisch wirksame Menge mindestens einer der Verbindungen nach Anspruch 1 als Wirkstoff und mindestens ein pharmazeutisch verträgliches inertes Träger- oder Verdünnungsmittel.

48. Verwendung der Verbindung nach Anspruch 1 als ein antimikrobielles Mittel.

49. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 umfassend das Umsetzen einer Verbindung der Formel (II):



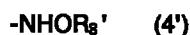
wobei R_1 und X die im Anspruch 1 angegebenen Bedeutungen besitzen, R_9 eine Schutzgruppe für eine Carboxygruppe bedeutet, Z einen reaktiven Ester eines Alkohols, oder einen substituierten oder unsubstituierten niederen Alkylsulfinylrest bedeutet, mit einem Mercaptanderivat der Formel:



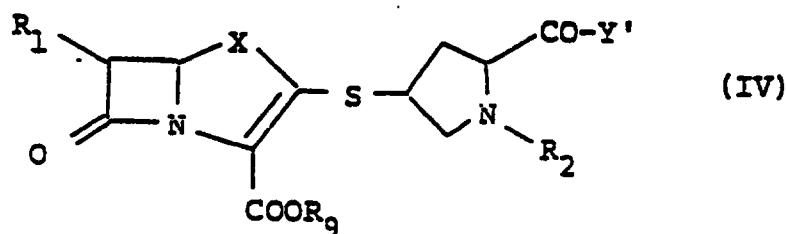
wobei R_2 die im Anspruch 1 angegebene Bedeutung besitzt und Y' einen Rest, wiedergegeben durch die Formel (2), bedeutet:



wobei R_5 und R_6 die in Anspruch 1 angegebenen Bedeutungen besitzen, oder einen Rest, wiedergegeben durch die Formel (4'), bedeutet:



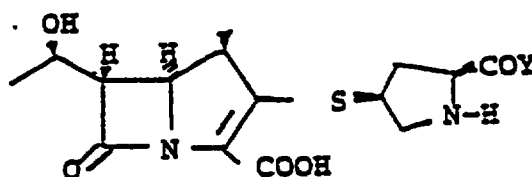
wobei R_8' eine Schutzgruppe für die Hydroxygruppe oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet, in Gegenwart einer Base in einem inerten Lösungsmittel, wobei eine β -Lactamverbindung, wiedergegeben durch die Formel (IV), hergestellt wird:



wobei R_1 , R_2 , R_9 , X und Y' die vorstehend angegebenen Bedeutungen besitzen, und, falls gewünscht, Unterwerfen der erhaltenen Verbindung einer geeigneten Kombination zum aufeinanderfolgenden oder gleichzeitigen Entfernen der Schutzgruppe für die Carboxygruppe, der Schutzgruppe für die Hydroxygruppe und/oder der Schutzgruppe für die Aminogruppe, wobei die Verbindung der Formel (IV), in der R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 ein Wasserstoffatom bedeutet und/oder R_9 ein Wasserstoffatom bedeutet, oder die Verbindung der Formel (IV) hergestellt wird, wobei die Schutzgruppe an dem Rest Y' entfernt wird.

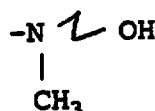
20

50. β -Lactamverbindung der Formel:

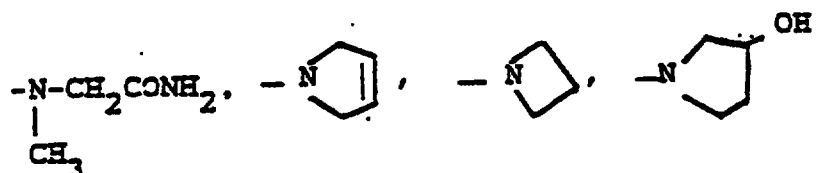


30

wobei Y aus der Gruppe bestehend aus NH_2 ,



- $NHCH_2CONH_2$,



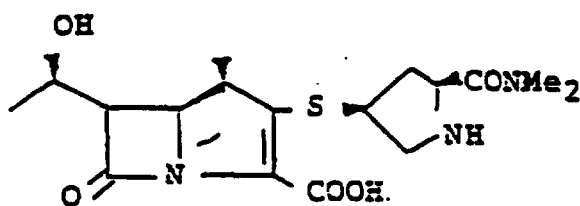


ausgewählt ist und die pharmazeutisch verträglichen Salze davon.

51. β -Lactamverbindung der Formel:

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10

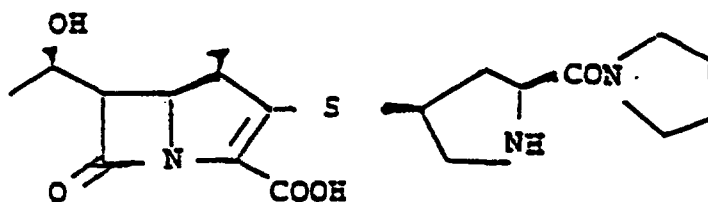


und die pharmazeutisch verträglichen Salze davon.

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52. β -Lactamverbindung der Formel:

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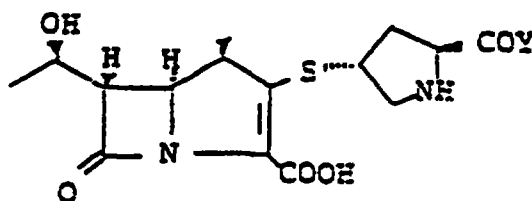
25

und die pharmazeutisch verträglichen Salze davon.

53. β -Lactamverbindung der Formel:

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35



wobei Y aus der Gruppe bestehend aus

40



45

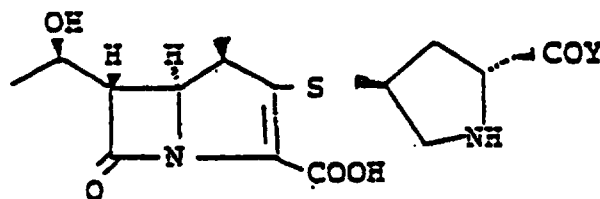
ausgewählt ist und die pharmazeutisch verträglichen Salze davon.

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54. β -Lactamverbindung der Formel:

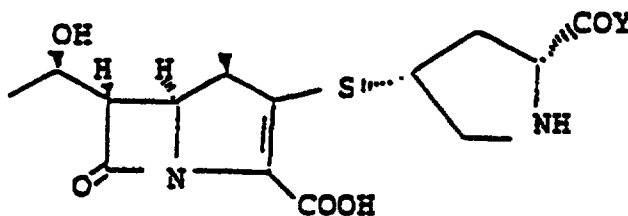


wobei Y aus der Gruppe bestehend aus



ausgewählt ist und die pharmazeutisch verträglichen Salze davon.

55. β -Lactamverbindung der Formel:

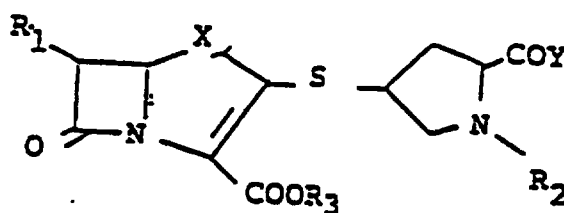


wobei Y aus der Gruppe bestehend aus



ausgewählt ist und die pharmazeutisch verträglichen Salze davon.

56. β -Lactamverbindung wiedergegeben durch die Formel:



in der R_1 eine 1-Hydroxyethylgruppe oder eine 1-Hydroxyethylgruppe, wobei die Hydroxygruppe mit



einer Schutzgruppe für eine Hydroxygruppe geschützt ist, bedeutet; R_2 ein Wasserstoffatom oder eine Schutzgruppe für eine Aminogruppe bedeutet; R_3 ein Wasserstoffatom oder eine Schutzgruppe für eine Carboxygruppe bedeutet; X ein Schwefelatom darstellt; und Y einen Rest der Formel (2) bedeutet:



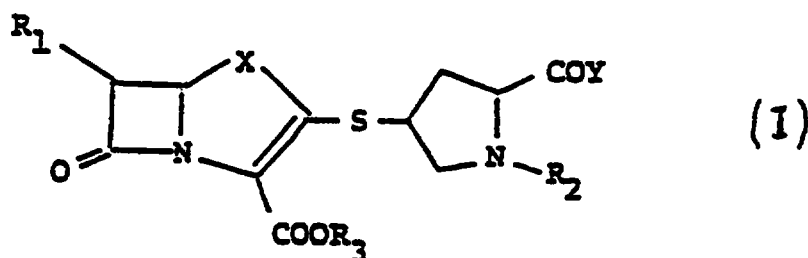
wobei R_5 und R_6 , die gleich oder verschieden sein können, jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, eine Phenethyl-, eine 2-Pyridylmethyl-, eine 3-Pyridylmethyl- oder eine 4-Pyridylmethylgruppe, einen substituierten Alkylrest mit 1 bis 5 Kohlenstoffatomen, wobei der Substituent aus der Gruppe bestehend aus dem Hydroxy-, dem Di-(C_1 - C_3)alkylamino-, Carbamoyl-, einem mono- oder di-(C_1 - C_3)alkylsubstituierten Aminocarbonylrest und einer geschützten oder ungeschützten Carboxygruppe ausgewählt ist, oder einen Pyridylrest bedeutet, oder R_5 und R_6 zusammen eine Alkylenkette oder eine Alkylenkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1 - C_3)alkylsubstituiertes Stickstoffatom enthält, bedeutet, wobei zusammen mit dem benachbarten Stickstoffatom ein substituiertes oder unsubstituierter 3- bis 7-gliedriger cyclischer Aminorest erzeugt wird, der in dem Ring eine Doppelbindung (Doppelbindungen) enthalten kann, wobei der Substituent aus der Gruppe bestehend aus einer C_1 - C_3 -Alkyl-, der Carbamoyl-, einer mono- oder di-(C_1 - C_3)alkylsubstituierten Aminocarbonyl- und Hydroxygruppe ausgewählt ist, oder einen Rest der Formel (4) bedeutet:



wobei R_8 ein Wasserstoffatom, eine Schutzgruppe für eine Hydroxygruppe oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet, und ein pharmazeutisch verträgliches Salz davon.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Herstellung einer β -Lactamverbindung wiedergegeben durch die Formel (I)



in der R_1 eine 1-Hydroxyethylgruppe oder eine 1-Hydroxyethylgruppe, wobei die Hydroxygruppe mit einer Schutzgruppe geschützt ist, bedeutet; R_2 ein Wasserstoffatom oder eine Schutzgruppe für eine Aminogruppe bedeutet; R_3 ein Wasserstoffatom oder eine Schutzgruppe für eine Carboxygruppe bedeutet; X eine substituierte oder unsubstituierte Methylengruppe der Formel (1) bedeutet:





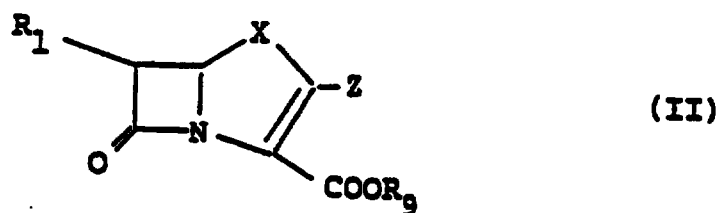
wobei R₄ ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet, oder X ein Schwefelatom bedeutet; und Y (i) einen Rest der Formel (2) bedeutet:



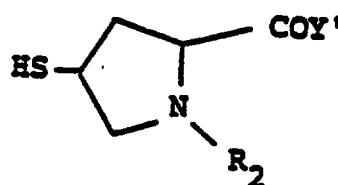
wobei R_5 und R_6 , die gleich oder verschieden sein können, jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, Phenethyl-, 2-Pyridylmethyl-, 3-Pyridylmethyl- oder 4-Pyridylmethylgruppe, einen substituierten Alkylrest mit 1 bis 5 Kohlenstoffatomen, wobei der Substituent aus einer Hydroxygruppe, einem Di-(C_1 - C_3)-alkylamino-, Carbamoyl-, einem Mono- oder Di-(C_1 - C_3)-alkylaminocarbonylrest und einer geschützten oder ungeschützten Carboxygruppe ausgewählt ist, wobei die Schutzgruppe eine Schutzgruppe für eine Carboxygruppe ist; oder einen Pyridylrest bedeutet; oder R_5 und R_6 zusammen eine Alkylenkette oder eine Alkylenkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1 - C_3)-alkylsubstituiertes Stickstoffatom enthält, bedeuten, wobei zusammen mit dem benachbarten Stickstoffatom ein substituierter oder unsubstituierter 3- bis 7-gliedriger cyclischer Aminorest erzeugt wird, der in dem Ring eine Doppelbindung (Doppelbindungen) enthalten kann, wobei der Substituent aus einem (C_1 - C_3)-Alkyl-, einem Carbamoyl-, einem Carboxy-, einem Mono- oder Di-(C_1 - C_3)-alkylaminocarbonylrest und einer Hydroxygruppe ausgewählt ist; oder (ii) einen Rest der Formel (4) bedeutet:



wobei R₈ ein Wasserstoffatom, eine Schutzgruppe für die Hydroxygruppe oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet; oder ein pharmazeutisch verträgliches Salz davon, umfassend das Umsetzen einer Verbindung der Formel (II):



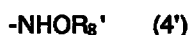
wobei R₁ und X die vorstehenden Bedeutungen besitzen, R₉ eine Schutzgruppe für eine Carboxygruppe bedeutet, Z einen reaktiven Ester eines Alkohols, oder einen substituierten oder unsubstituierten niederen Alkylsulfinylrest bedeutet,
mit einem Mercaptanderivat der Formel:



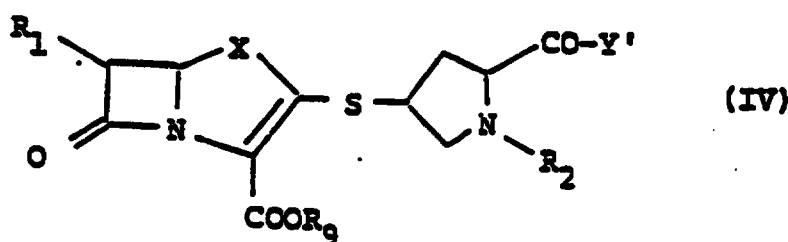
wobei R_2 die vorstehend angegebene Bedeutung besitzt und Y' einen Rest, wiedergegeben durch die Formel (2), bedeutet:



wobei R_5 und R_6 die vorstehend angegebenen Bedeutungen besitzen, oder einen Rest, wiedergegeben durch die Formel (4'), bedeutet:



wobei R_8' eine Schutzgruppe für die Hydroxygruppe oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet, in Gegenwart einer Base in einem inerten Lösungsmittel, wobei eine β -Lactamverbindung, wiedergegeben durch die Formel (IV), hergestellt wird:



wobei R_1 , R_2 , R_9 , X und Y' die vorstehend angegebenen Bedeutungen besitzen, und, falls gewünscht, Unterwerfen der erhaltenen Verbindung einer geeigneten Kombination zum aufeinanderfolgenden oder gleichzeitigen Entfernen der Schutzgruppe für die Carboxygruppe, der Schutzgruppe für die Hydroxygruppe und/oder der Schutzgruppe für die Aminogruppe, wobei die Verbindung der Formel (IV), in der R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 ein Wasserstoffatom bedeutet und/oder R_9 ein Wasserstoffatom bedeutet, oder die Verbindung der Formel (IV) hergestellt wird, wobei die Schutzgruppe an dem Rest Y' entfernt wird, und gegebenenfalls Umwandlung der erhaltenen Verbindung in ein pharmazeutisch verträgliches Salz.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I), wobei R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 und R_3 jeweils ein Wasserstoffatom bedeutet, und Y einen Rest, wiedergegeben durch die Formel (2-a), bedeutet:



wobei R_{5-a} und R_{6-a} jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, eine Phenethyl-, eine 2-Pyridylmethyl-, eine 3-Pyridylmethyl- oder eine 4-Pyridylmethylgruppe, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, der mit einer Hydroxygruppe, einem Di-(C_1 - C_3)alkylamino-, einem Carbamoyl-, einem mono- oder di-(C_1 - C_3)-alkylsubstituierten Aminocarbonylrest oder einer Carboxygruppe substituiert ist; oder einen Pyridylrest bedeutet; oder R_{5-a} und R_{6-a} zusammen eine Alkylkette oder eine Alkylkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1 - C_3)alkylsubstituiertes Stickstoffatom enthält, bedeuten, wobei zusammen mit dem benachbarten Stickstoffatom ein unsubstituierter oder substituierter 3- bis 7-gliedriger cyclischer Aminorest erzeugt wird, der in seinem Ring eine Doppelbindung (Doppelbindungen) enthalten kann, wobei der Substituent einen Alkylrest mit 1 bis 3 Kohlenstoffatomen, einen Carbamoyl-, einen Carboxy-, einen mono- oder di-(C_1 - C_3)alkylsubstituierten Aminocarbonylrest oder eine Hydroxygruppe bedeutet; oder einen Rest, wiedergegeben durch die Formel (4-a), bedeutet:



wobei R_{8-a} ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I), wobei R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 und R_3 jeweils ein Wasserstoffatom bedeutet, und Y einen Rest, wiedergegeben durch die Formel (2-b), bedeutet:



wobei R_{5-b} und R_{6-b} jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, eine Phenethyl-, eine 2-Pyridylmethyl-, eine 3-Pyridylmethyl- oder eine 4-Pyridylmethylgruppe, einen substituierten Alkylrest mit 1 bis 5 Kohlenstoffatomen, wobei der Substituent eine Hydroxygruppe, eine Di-(C_1-C_3)alkylamino-, eine Carbamoyl-, eine mono- oder di-(C_1-C_3)alkylsubstituierte Aminocarbamoyl- oder eine Carboxygruppe ist, oder einen Pyridylrest bedeutet, oder R_{5-b} und R_{6-b} zusammen eine Alkylenkette oder eine Alkylenkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1-C_3)alkylsubstituiertes Stickstoffatom enthält, darstellt, wobei zusammen mit dem benachbarten Stickstoffatom ein unsubstituierter oder substituierter 3- bis 7-gliedriger cyclischer Aminorest erzeugt wird, der in dem Ring eine Doppelbindung (oder Doppelbindungen) enthalten kann, wobei der Substituent einen Alkylrest mit 1 bis 3 Kohlenstoffatomen, eine Carbamoyl- oder eine Hydroxygruppe ist; oder einen Rest, wiedergegeben durch die Formel (4-a), bedeutet:



wobei R_{8-a} ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet.

4. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I), wobei R_1 eine 1-Hydroxyethylgruppe bedeutet, R_2 und R_3 jeweils ein Wasserstoffatom bedeutet und Y einen Rest, wiedergegeben durch die Formel (2-c), darstellt:



wobei R_{5-c} und R_{6-c} eine der nachstehenden Bedeutungen besitzen:

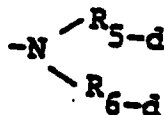
(1) R_{5-c} bedeutet einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, der mit einer Carbamoyl-, einer Mono- oder Di-(C_1-C_3)alkylaminocarbonyl- oder einer Hydroxygruppe substituiert ist, oder einen Pyridylrest, und R_{6-c} bedeutet ein Wasserstoffatom oder besitzt die für R_{5-c} angegebenen Bedeutungen;

(2) R_{5-c} und R_{6-c} bedeuten zusammen eine Alkylenkette, wobei zusammen mit dem benachbarten Stickstoffatom ein unsubstituierter oder substituierter 4- bis 6-gliedriger gesättigter cyclischer Aminorest oder ein unsubstituierter oder substituierter 5- bis 6-gliedriger cyclischer Aminorest mit einer Doppelbindung (oder Doppelbindungen) im Ring erzeugt wird, wobei der Substituent an dem cyclischen Aminoring eine Carbamoyl- oder eine Hydroxygruppe ist; und

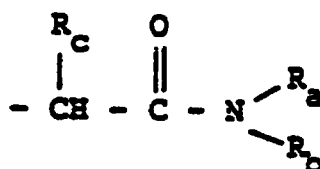
(3) R_{5-c} und R_{6-c} bedeuten zusammen eine Alkylenkette, die ein Sauerstoffatom oder ein (C_1-C_3)-alkylsubstituiertes Stickstoffatom enthält, wobei zusammen mit dem benachbarten Stickstoffatom ein 6-gliedriger cyclischer Aminorest erzeugt wird.



5. Verfahren nach Anspruch 3 zur Herstellung einer Verbindung der Formel (I), wobei Y einen Rest, wiedergegeben durch die Formel:

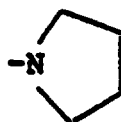
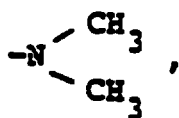


- bedeutet, wobei $\text{R}_5\text{-d}$ ein Wasserstoffatom oder eine Methylgruppe bedeutet, und $\text{R}_6\text{-d}$ einen Rest der Formel:

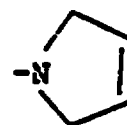


- bedeutet, wobei R_a , R_b und R_c jeweils ein Wasserstoffatom oder eine Methylgruppe bedeutet.

6. Verfahren nach Anspruch 3 zur Herstellung einer Verbindung der Formel (I), wobei Y durch die Formeln:



oder



wiedergegeben ist.

7. Verfahren nach einem der Ansprüche 1 bis 6 zur Herstellung einer Verbindung der Formel (I), in der X



bedeutet, wobei R_4 ein Wasserstoffatom oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen darstellt.

8. Verfahren nach Anspruch 7 zur Herstellung einer Verbindung der Formel (I), in der X



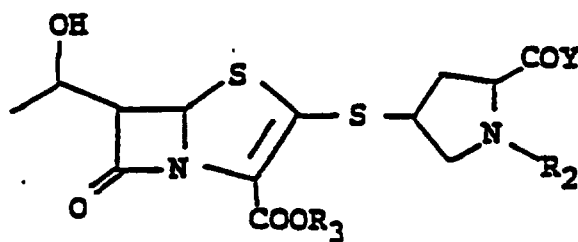
bedeutet.

9. Verfahren nach Anspruch 7 zur Herstellung einer Verbindung der Formel (I), in der R_4 ein Wasserstoffatom ist.

10. Verfahren nach einem der Ansprüche 1 bis 6 zur Herstellung einer Verbindung der Formel (I), in der X ein Schwefelatom ist.

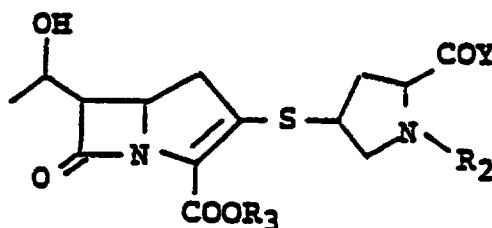


11. Verfahren nach Anspruch 1 zur Herstellung einer (5R)-Verbindung der Verbindung nach einem der Ansprüche 1 bis 6 und 10, die durch die Formel:



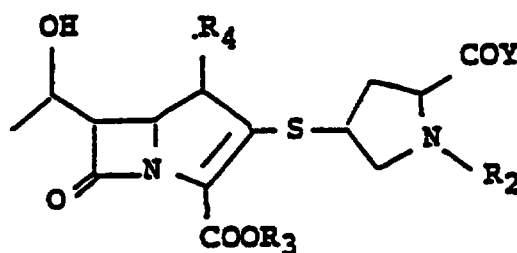
wiedergegeben ist.

12. Verfahren nach Anspruch 1 zur Herstellung einer (5R)-Verbindung der Verbindung nach einem der Ansprüche 1 bis 7 und 9, die durch die Formel:



wiedergegeben ist.

13. Verfahren nach Anspruch 1 zur Herstellung einer (5S)-Verbindung der Verbindung nach einem der Ansprüche 1 bis 8, wiedergegeben durch die Formel:



wobei R₄ einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet.

14. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-4-thia-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.

15. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-4-thia-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.

16. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-4-thia-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.



17. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-(Dimethylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 5 18. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 10 19. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 15 20. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 20 21. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 25 22. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 30 23. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 35 24. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 40 25. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-Carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 45 26. Verfahren nach Anspruch 1 zur Herstellung von (5R)-3-[2-(4-Pyridylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 50 27. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-Dimethylaminocarbonyl]pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
- 55 28. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-((1-Pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
29. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-((1-Pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
30. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-((1-Azetidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.
31. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-((3-Hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht



toxischen pharmazeutisch verträglichen Salzes davon.

5 32. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-((2-Hydroxyethyl)methylaminocarbonyl)-pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.

10 33. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-(1-Morpholinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.

34. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-(1-N-Methylpiperazinocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-2-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.

15 35. Verfahren nach Anspruch 1 zur Herstellung von (5S)-3-[2-Carbamoylpyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-on-carbonsäure oder eines nicht toxischen pharmazeutisch verträglichen Salzes davon.

20 36. Verfahren nach Anspruch 1 zur Herstellung einer (5R,6S,8R)-Verbindung der Verbindung nach Anspruch 11.

37. Verfahren nach Anspruch 1 zur Herstellung einer (5R,6S,8R)-Verbindung der Verbindung nach Anspruch 12.

25 38. Verfahren nach Anspruch 1 zur Herstellung einer (5S,6S,8R)-Verbindung der Verbindung nach Anspruch 13.

30 39. Verfahren nach Anspruch 1 zur Herstellung einer (5R,6S,8R)-Verbindung der Verbindung nach einem der Ansprüche 14 bis 26.

40. Verfahren nach Anspruch 1 zur Herstellung einer (5S,6S,8R)-Verbindung der Verbindung nach einem der Ansprüche 27 bis 35.

35 41. Verfahren nach Anspruch 1 zur Herstellung einer (5R,6S,8R,2'S,4'S)-Verbindung der Verbindung nach Anspruch 11.

42. Verfahren nach Anspruch 1 zur Herstellung einer (5R,6S,8R,2'S,4'S)-Verbindung der Verbindung nach Anspruch 12.

40 43. Verfahren nach Anspruch 1 zur Herstellung einer (5S,6S,8R,2'S,4'S)-Verbindung der Verbindung nach Anspruch 13.

44. Verfahren nach Anspruch 1 zur Herstellung einer (5R,6S,8R,2'S,4'S)-Verbindung der Verbindung nach einem der Ansprüche 14 bis 26.

45 45. Verfahren nach Anspruch 1 zur Herstellung einer (5S,6S,8R,2'S,4'S)-Verbindung der Verbindung nach einem der Ansprüche 27 bis 35.

50 46. Verfahren nach Anspruch 1 zur Herstellung einer (4R,5S,6S,8R,2'S,4'S)-Verbindung der Verbindung nach einem der Ansprüche 3 bis 8 und 27 bis 35.

55 47. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Vermischen einer pharmazeutisch wirksamen Menge mindestens einer der Verbindungen nach Anspruch 1 als Wirkstoff und mindestens eines pharmazeutisch verträglichen inerten Träger- oder Verdünnungsmittels.

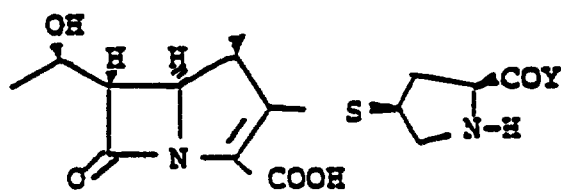
48. Verwendung der Verbindung gemäß Anspruch 1 als ein antimikrobielles Mittel.



49. Verfahren nach Anspruch 1 zur Herstellung einer β -Lactamverbindung der Formel:

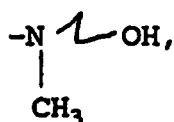
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wobei Y aus der Gruppe bestehend aus NH_2 ,

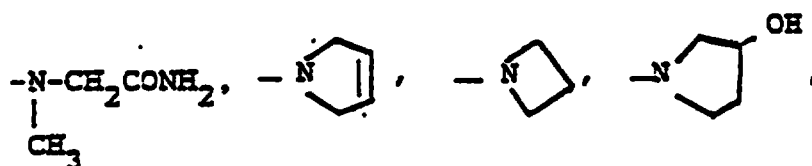
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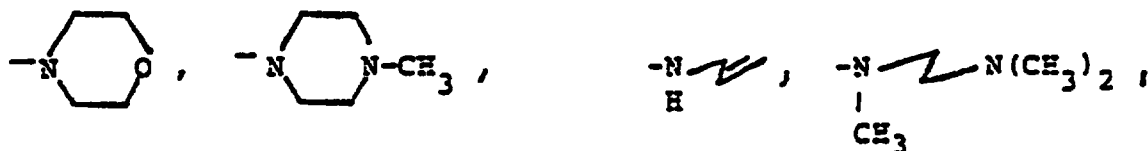
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$-\text{NHCH}_2\text{CONH}_2$,

25



30



35



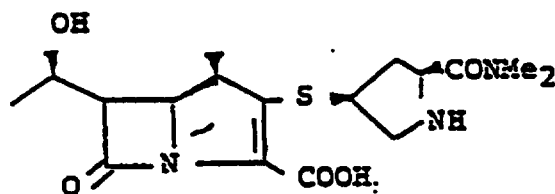
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ausgewählt ist und der pharmazeutisch verträglichen Salze davon.

50. Verfahren nach Anspruch 1 zur Herstellung einer β -Lactamverbindung der Formel:

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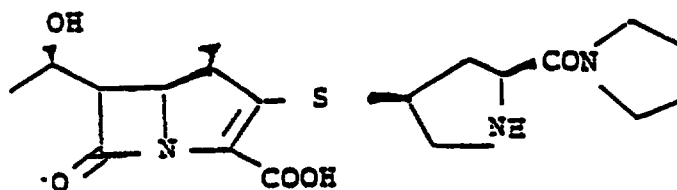


und der pharmazeutisch verträglichen Salze davon.

55

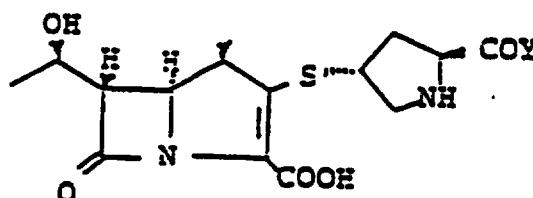


51. Verfahren nach Anspruch 1 zur Herstellung einer β -Lactamverbindung der Formel:



und der pharmazeutisch verträglichen Salze davon.

52. Verfahren nach Anspruch 1 zur Herstellung einer β -Lactamverbindung der Formel:

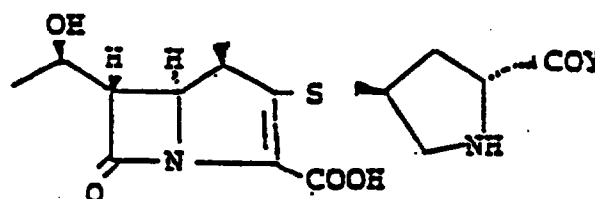


wobei Y aus der Gruppe bestehend aus



ausgewählt ist und der pharmazeutisch verträglichen Salze davon.

53. Verfahren nach Anspruch 1 zur Herstellung einer β -Lactamverbindung der Formel:



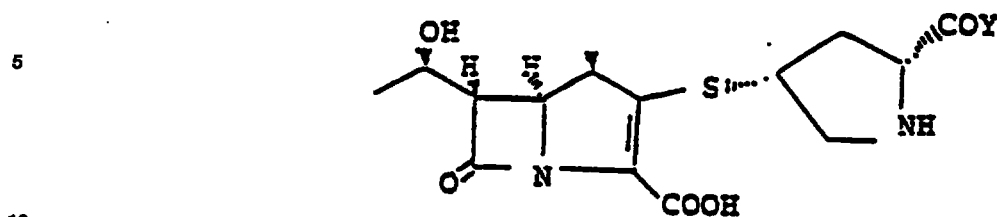
wobei Y aus der Gruppe bestehend aus



ausgewählt ist und der pharmazeutisch verträglichen Salze davon.



54. Verfahren nach Anspruch 1 zur Herstellung einer β -Lactamverbindung der Formel:

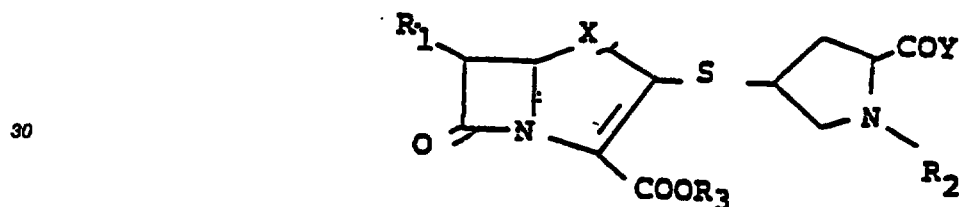


wobei Y aus der Gruppe bestehend aus

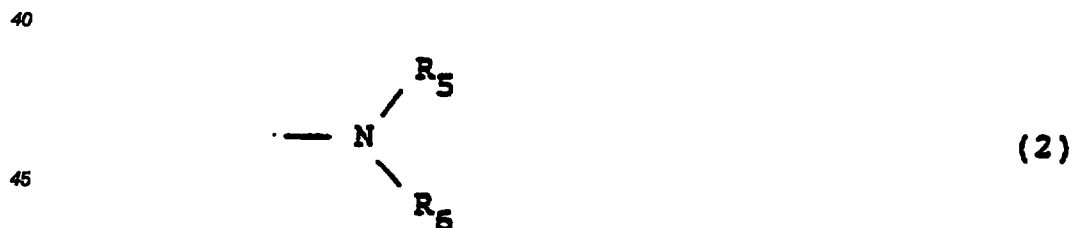


ausgewählt ist und der pharmazeutisch verträglichen Salze davon.

55. Verfahren nach Anspruch 1 zur Herstellung einer β -Lactamverbindung wiedergegeben durch die Formel:



35 in der R_1 eine 1-Hydroxyethylgruppe oder eine 1-Hydroxyethylgruppe, wobei die Hydroxygruppe mit einer Schutzgruppe für eine Hydroxygruppe geschützt ist, bedeutet; R_2 ein Wasserstoffatom oder eine Schutzgruppe für eine Aminogruppe bedeutet; R_3 ein Wasserstoffatom oder eine Schutzgruppe für eine Carboxygruppe bedeutet; X ein Schwefelatom darstellt; und Y einen Rest der Formel (2) bedeutet:



50 wobei R_5 und R_6 , die gleich oder verschieden sein können, jeweils ein Wasserstoffatom, einen Alkylrest mit 1 bis 5 Kohlenstoffatomen, einen Alkenylrest mit 3 bis 4 Kohlenstoffatomen, eine Benzyl-, eine Phenethyl-, eine 2-Pyridylmethyl-, eine 3-Pyridylmethyl- oder eine 4-Pyridylmethylgruppe, einen substituierten Alkylrest mit 1 bis 5 Kohlenstoffatomen, wobei der Substituent aus der Gruppe bestehend aus dem Hydroxy-, dem Di-(C_1 - C_3)alkylamino-, Carbamoyl-, einem mono- oder di-(C_1 - C_3)-alkylsubstituierten Aminocarbonylrest und einer geschützten oder ungeschützten Carboxygruppe ausgewählt ist, oder einen Pyridylrest bedeutet, oder R_5 und R_6 zusammen eine Alkylkette oder eine Alkylkette, die ein Sauerstoffatom, ein Schwefelatom oder ein (C_1 - C_3)alkylsubstituiertes Stickstoffatom enthält, bedeutet, wobei zusammen mit dem benachbarten Stickstoffatom ein substituiertes oder unsubstituierter 3- bis 7-gliedriger cyclischer Aminorest erzeugt wird, der in dem Ring eine Doppelbin-



dung (Doppelbindungen) enthalten kann, wobei der Substituent aus der Gruppe bestehend aus einer C₁-C₃-Alkyl-, der Carbamoyl-, einer mono- oder di-(C₁-C₃)alkylsubstituierten Aminocarbonyl- und Hydroxygruppe ausgewählt ist, oder einen Rest der Formel (4) bedeutet:



wobei R₈ ein Wasserstoffatom, eine Schutzgruppe für eine Hydroxygruppe oder einen Alkylrest mit 1 bis 3 Kohlenstoffatomen bedeutet, und ein pharmazeutisch verträgliches Salz davon.

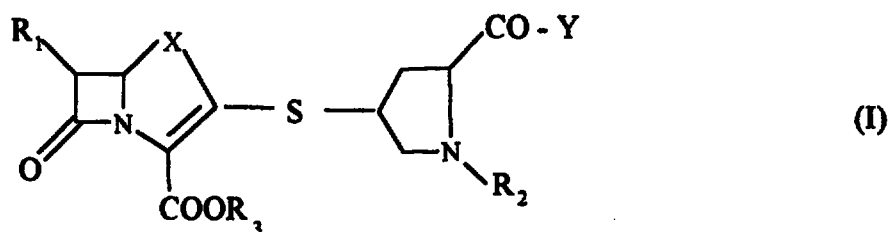
10 **Revendications**

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Composé β -lactame représenté par la formule (I):

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dans laquelle R₁ représente un groupe 1-hydroxyéthyle ou un groupe 1-hydroxyéthyle dans lequel le groupe hydroxy est protégé par un groupement protecteur ; R₂ représente un atome d'hydrogène ou un groupement protecteur pour un groupe amino ; R₃ représente un atome d'hydrogène ou un groupement protecteur pour un groupe carboxyle ; X représente un groupe méthylène substitué ou non substitué de formule (1) :

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dans laquelle R₄ représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone, ou X représente un atome de soufre ; et Y représente (i) un groupe de formule (2) :

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dans laquelle R₅ et R₆, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridylméthyle, un groupe alkyle substitué ayant 1 à 5 atomes de carbone dans lequel le substituant est choisi parmi un groupe hydroxyle, un groupe di(C₁-C₃)-alkylamino, un groupe carbamoyle, un groupe mono- ou di(C₁-C₃)-alkylaminocarbonyle et un groupe carboxyle protégé ou non protégé dans lequel le groupe protecteur est un groupe protecteur pour un groupe carboxyle : ou un groupe pyridyle ; ou R₅ et R₆ forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone, de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué, dont le cycle peut contenir une ou des

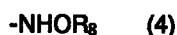
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doubles liaisons, le substituant étant choisi parmi un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, un groupe carboxyle, un groupe mono- ou di(C₁-C₃)-alkylaminocarbonyle et un groupe hydroxyle ;

ou (ii) un groupe de formule (4) :



dans laquelle R₈ représente un atome d'hydrogène, un groupement protecteur pour un groupe hydroxyle ou un groupe alkyle ayant 1 à 3 atomes de carbone, et ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel R₁ représente un groupe 1-hydroxyéthyle, R₂ et R₃ représentent tous deux des atomes d'hydrogène, et Y est un groupe représenté par la formule (2-a) :



dans laquelle R_{5-a} et R_{6-a} représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridylméthyle, un groupe alkyle ayant 1 à 5 atomes de carbone substitué par un groupe hydroxyle, un groupe di(C₁-C₃)-alkylamino, un groupe carbamoyle, un groupe aminocarbonyle mono- ou di(C₁-C₃)-alkyl-substitué ou un groupe carboxyle, ou un groupe pyridyle, ou R_{5-a} et R_{6-a} forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone, de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué, dont le cycle peut contenir une ou des doubles liaisons, le substituant étant un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, un groupe carboxylique, a groupe aminocarbonyle mono- ou di(C₁-C₃)-alkyl-substitué ou un groupe hydroxyle ; ou un groupe représenté par la formule (4-a) :



dans laquelle R_{8-a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone.

3. Composé selon la revendication 1, dans lequel R₁ représente un groupe 1-hydroxyéthyle ; R₂ et R₃ représentent tous deux des atomes d'hydrogène et Y est un groupe représenté par la formule (2-b) :



dans laquelle R_{5-b} et R_{6-b} représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridylméthyle, un groupe alkyle substitué ayant 1 à 5 atomes de carbone, le substituant étant un groupe hydroxyle, un groupe di(C₁-C₃)-alkylamino, un groupe carbamoyle, un groupe aminocarbonyle mono- ou di(C₁-C₃)-alkyl-substitué ou un groupe carboxyle, ou un groupe pyridyle, ou R_{5-b} et R_{6-b} forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone, de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué,

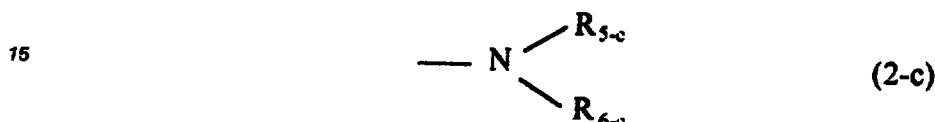


dont le cycle peut contenir une ou des doubles liaisons, le substituant étant un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, ou un groupe hydroxyle : ou un groupe représenté par la formule (4-a) :

5 -NHOR_{8-a} (4-a)

dans laquelle R_{8-a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone.

10 4. Composé selon la revendication 1, dans lequel R₁ représente un groupe 1-hydroxyéthyle ; R₂ et R₃ représentent tous deux des atomes d'hydrogène ; et Y est un groupe représenté la formule (2-c) :



20 dans laquelle R_{5-c} et R_{6-c} ont une des significations suivantes :

(1) R_{5-c} représente un groupe alkyle ayant 1 à 5 atomes de carbone qui peut être substitué par un groupe carbamoyle, un groupe mono- ou di-(C₁-C₃)-alkylaminocarbonyle ou un groupe hydroxy, ou un groupe pyridyle, et R_{6-c} représente un atome d'hydrogène ou a la même définition que celle donnée pour R_{5-c} ;

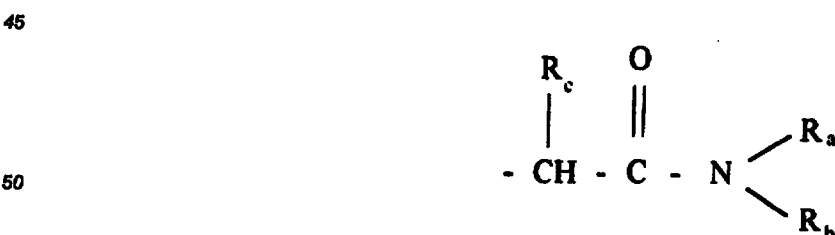
25 (2) R_{5-c} et R_{6-c} forment ensemble une chaîne alkylène de façon à constituer, avec l'atome d'azote adjacent, un groupe amino cyclique saturé à 4 à 6 côtés, non substitué ou substitué, ou un groupe amino cyclique à 5 ou 6 côtés, non substitué ou substitué, dont le cycle contient une ou des doubles liaisons, le substituant du cycle amino cyclique étant un groupe carbamoyle ou un groupe hydroxyle, et

30 (3) R_{5-c} et R_{6-c} forment ensemble une chaîne alkylène contenant un atome d'oxygène ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone de façon à constituer, avec l'atome d'azote adjacent, un groupe amino cyclique à 6 côtés.

5. Composé selon la revendication 3, dans lequel Y est un groupe représenté par la formule :



dans laquelle R_{5-d} représente un atome d'hydrogène ou un groupe méthyle et R_{6-d} représente un groupe de formule :

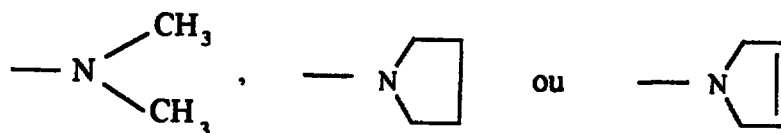


dans laquelle R_a, R_b et R_c représentent chacun un atome d'hydrogène ou un groupe méthyle.

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6. Composé selon la revendication 3, dans lequel Y est représenté par la formule :



7. Composé selon une quelconque des revendications 1 à 6, dans lesquelles X représente



R_4 étant un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone.

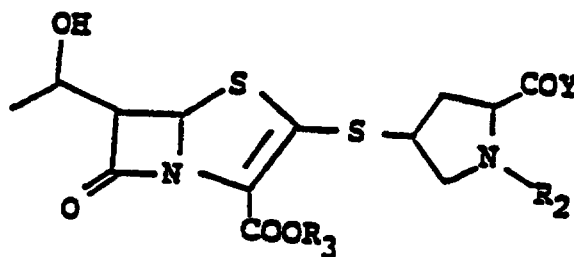
8. Composé selon la revendication 7, dans lequel X représente



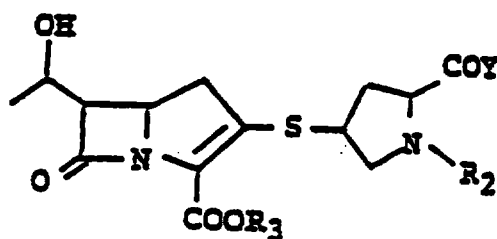
9. Composé selon la revendication 7, dans lequel R_4 est un atome d'hydrogène.

10. Composé selon une quelconque des revendications 1 à 6, dans lequel X est un atome de soufre.

11. Composé (5R) du composé selon une quelconque des revendications 1 à 6 et 10, représenté par la formule :

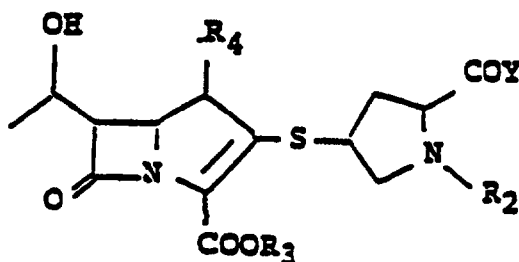


12. Composé (5R) du composé selon une quelconque des revendications 1 à 7 et 9, représenté par la formule :





13. Composé (5S) du composé selon une quelconque des revendications 1 à 8, représenté par la formule :



dans laquelle R₄ est un groupe alkyle ayant 1 à 3 atomes de carbone.

14. Acide (5R)-3-[2-(diméthylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-4-thia-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

15. Acide (5R)-3-[2-((1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-4-thia-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

16. Acide (5R)-3-[2-carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-4-thia-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

17. Acide (5R)-3-[2-(diméthylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

18. Acide (5R)-3-[2-((1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

19. Acide (5R)-3-[2-((1-pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

20. Acide (5R)-3-[2-((1-azétidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

21. Acide (5R)-3-[2-((3-hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

22. Acide (5R)-3-[2-((2-hydroxyéthyl)méthylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-3-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

23. Acide (5R)-3-[2-(1-morpholinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

24. Acide (5R)-3-[2-(1-N-méthylpipérazinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

25. Acide (5R)-3-[2-carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.

26. Acide (5R)-3-[2-(4-pyridylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.



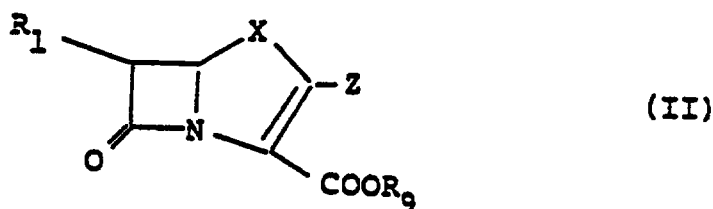
27. Acide (5S)-3-[2-(diméthylaminocarbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
- 5 28. Acide (5S)-3-[2-((1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
- 10 29. Acide (5S)-3-[2-((1-pyrrolin-3-yl)carbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
- 15 30. Acide (5S)-3-[2-((1-azétidino)carbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
- 20 31. Acide (5S)-3-[2-((3-hydroxy-1-pyrrolidino)carbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
- 25 32. Acide (5S)-3-[2-((2-hydroxyéthyl)méthylaminocarbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
- 30 33. Acide (5S)-3-[2-(1-morpholinocarbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
- 35 34. Acide (5S)-3-[2-(1-N-méthylpipérazinocarbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou un de ses sels pharmaceutiquement acceptables non toxiques.
36. Composé (5R, 6S, 8R) du composé selon la revendication 11.
37. Composé (5R, 6S, 8R) du composé selon la revendication 12.
- 40 38. Composé (5S, 6S, 8R) du composé selon la revendication 13.
39. Composé (5R, 6S, 8R) d'un composé selon une quelconque des revendications 14 à 26.
40. Composé (5S, 6S, 8R) d'un composé selon une quelconque des revendications 27 à 35.
- 45 41. Composé (5R, 6S, 8R, 2'S, 4'S) du composé selon la revendication 11
42. Composé (5R, 6S, 8R, 2'S, 4'S) du composé selon la revendication 12
- 50 43. Composé (5S, 6S, 8R, 2'S, 4'S) du composé selon la revendication 13.
44. Composé (5R, 6S, 8R, 2'S, 4'S) d'un composé selon une quelconque des revendications 14 à 26.
45. Composé (5S, 6S, 8R, 2'S, 4'S) d'un composé selon une quelconque des revendications 27 à 35.
- 55 46. Composé (4R, 5S, 6S, 8R, 2'S, 4'S) du composé selon une quelconque des revendications 3 à 8 et 27 à 35.



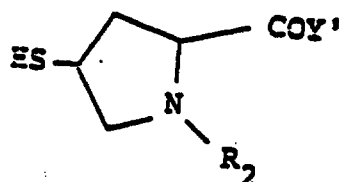
47. Composition pharmaceutique qui comprend en tant que principe actif une quantité pharmaceutiquement efficace d'au moins un des composés selon la revendication 1 et au moins un support inerte ou un diluant pharmaceutiquement acceptable.

5 48. Utilisation du composé selon la revendication 1 en tant qu'agent antimicrobien.

49. Procédé pour la préparation d'un composé selon la revendication 1, qui comprend la réaction d'un composé de formule (II) :



20 dans laquelle R_1 et X sont tels que définis dans la revendication 1, R_9 représente un groupe protecteur pour un groupe carboxyle, Z représente un ester réactif d'un alcool, ou un groupe alkyle-inférieur sulfinyle substitué ou non substitué, avec un dérivé de mercaptan de formule :



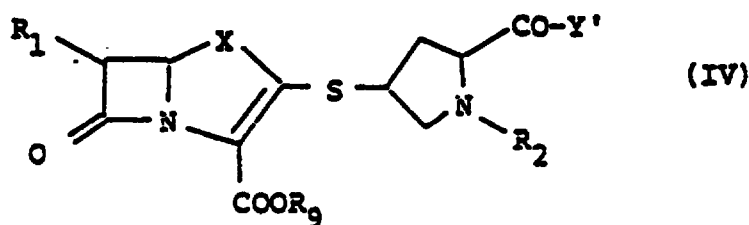
35 dans laquelle R_2 est tel que défini dans la revendication 1, et Y' est un groupe représenté par la formule (2) :



45 dans laquelle R_5 et R_6 sont tels que définis dans la revendication 1, ou un groupe représenté par la formule (4') :

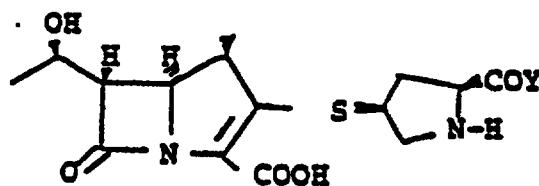


50 dans laquelle R_8 représente un groupe protecteur pour un groupe hydroxyle ou un groupe alkyle ayant 1 à 3 atomes de carbone, en présence d'une base dans un solvant inerte pour produire un composé β -lactame représenté par la formule (IV) :

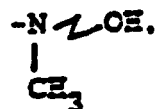


dans laquelle R_1 , R_2 , R_3 , X et Y' sont tels que définis ci-dessus, et, si on le souhaite, le traitement du composé résultat par une combinaison appropriée d'élimination du groupe protecteur du groupe carboxyle, du groupe protecteur du groupe hydroxyle et/ou du groupe protecteur du groupe amino, de façon séquentielle ou simultanée, pour produire le composé de formule (IV) dans laquelle R_1 est un groupe 1-hydroxyéthyle, R_2 est un atome d'hydrogène et/ou R_3 est un atome d'hydrogène ou le composé de formule (IV) dans lequel le groupe protecteur sur le groupe Y' est éliminé.

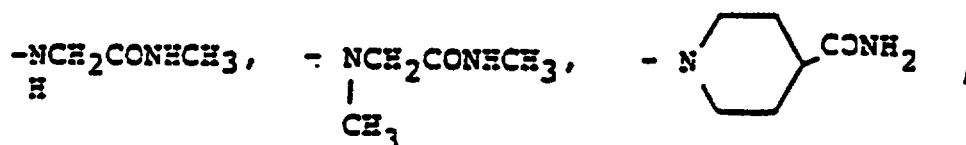
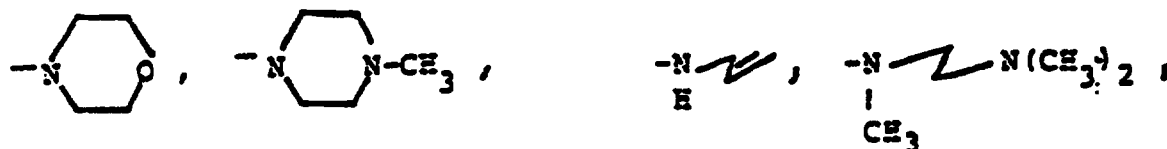
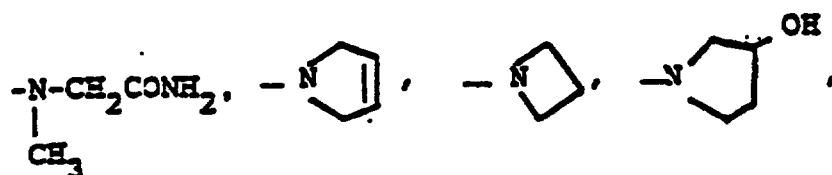
50. Composé β -lactame de formule :



dans laquelle Y est choisi dans le groupe comprenant $-NH_2$,



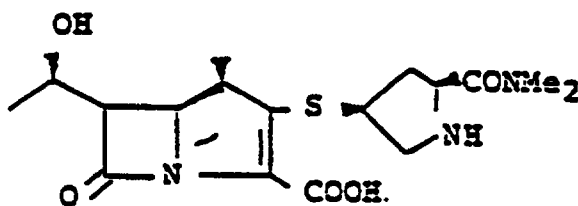
$-NHCH_2CONH_2$,





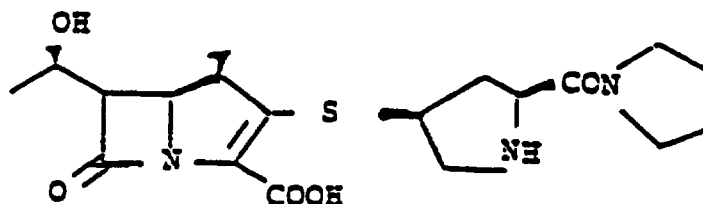
et ses sels pharmaceutiquement acceptables.

51. Composé β -lactame de formule :



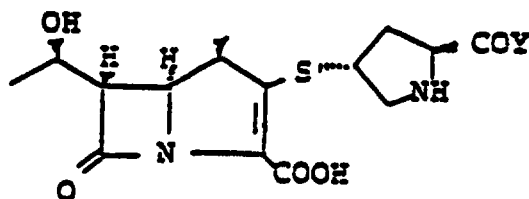
et ses sels pharmaceutiquement acceptables.

52. Composé β -lactame de formule :

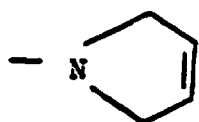


et ses sels pharmaceutiquement acceptables.

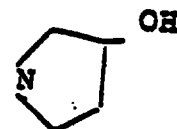
53. Composé β -lactame de formule :



dans laquelle Y est choisi dans le groupe comprenant



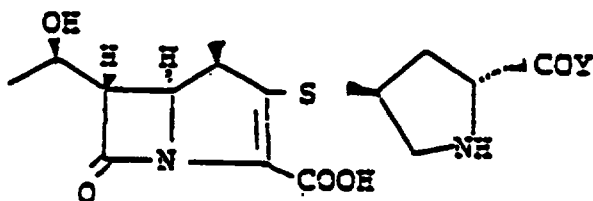
et



et ses sels pharmaceutiquement acceptables.



54. Composé β -lactame de formule :

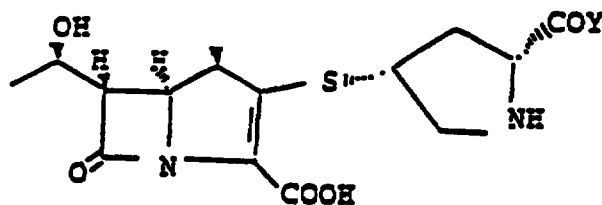


dans laquelle Y est choisi dans le groupe comprenant



et ses sels pharmaceutiquement acceptables.

55. Composé β -lactame de formule :

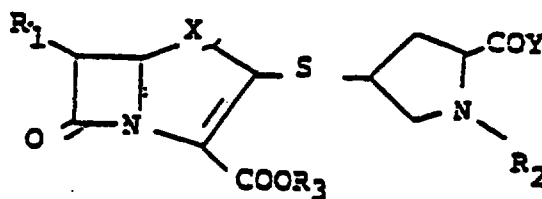


dans laquelle Y est choisi dans le groupe comprenant



et ses sels pharmaceutiquement acceptables.

56. Composé β -lactame représenté par la formule :





dans laquelle R_1 représente un groupe 1-hydroxyéthyle ou un groupe 1-hydroxyéthyle dans lequel le groupe hydroxy est protégé par un groupement protecteur pour un groupe hydroxy ; R_2 représente un atome d'hydrogène ou un groupement protecteur pour un groupe amino ; R_3 représente un atome d'hydrogène ou un groupement protecteur pour un groupe carboxyle ; X représente un atome de soufre et Y représente un groupe de formule (2) :



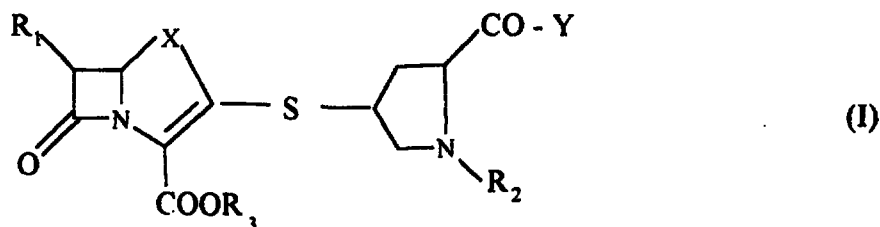
dans laquelle R_5 et R_6 , qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridylméthyle, un groupe alkyle substitué ayant 1 à 5 atomes de carbone dans lequel le substituant est choisi dans le groupe constitué par un groupe hydroxyle, un groupe di(C_1 - C_3)-alkylamino, un groupe carbamoyle, un groupe aminocarbonyle mono- ou di(C_1 - C_3)-alkyl-substitué et un groupe carboxyle protégé ou non protégé ou un groupe pyridyle; ou R_5 et R_6 forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone, de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué, dont le cycle peut contenir une ou des doubles liaisons, le substituant étant choisi parmi un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, un groupe aminocarbonyle mono- ou di(C_1 - C_3)-alkyl-substitué et un groupe hydroxyle ou un groupe de formule (4) :



dans laquelle R_8 représente un atome d'hydrogène, un groupement protecteur pour un groupe hydroxyle ou un groupe alkyle ayant 1 à 3 atomes de carbone, et ses sels pharmaceutiquement acceptables.

Revendications pour l'Etat contractant suivant : AT

1. Procédé pour la préparation d'un composé β -lactame représenté par la formule (I) :



dans laquelle R_1 représente un groupe 1-hydroxyéthyle ou un groupe 1-hydroxyéthyle dans lequel le groupe hydroxy est protégé par un groupement protecteur ; R_2 représente un atome d'hydrogène ou un groupement protecteur pour un groupe amino ; R_3 représente un atome d'hydrogène ou un groupement protecteur pour un groupe carboxyle ; X représente un groupe méthylène substitué ou non substitué de formule (1) :



dans laquelle R_4 représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone, ou X représente un atome de soufre ; et Y représente (i) un groupe de formule (2) :

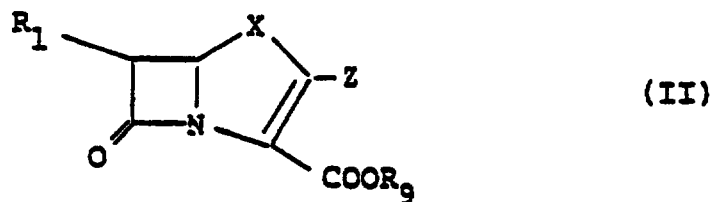


dans laquelle R_5 et R_6 , qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridylméthyle, un groupe alkyle substitué ayant 1 à 5 atomes de carbone dans lequel le substituant est choisi parmi un groupe hydroxyle, un groupe di(C_1-C_3)-alkylamino, un groupe carbamoyle, un groupe mono- ou di(C_1-C_3)-alkylaminocarbonyle et un groupe carboxyle protégé ou non protégé dans lequel le groupe protecteur est un groupe protecteur pour un groupe carboxyle ; ou un groupe pyridyle ; ou R_5 et R_6 forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué, dont le cycle peut contenir une ou des doubles liaisons, le substituant étant choisi parmi un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, un groupe carboxyle, un groupe mono- ou di(C_1-C_3)-alkylaminocarbonyle et un groupe hydroxyle ;

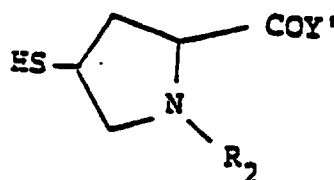
ou (ii) un groupe de formule (4) :



dans laquelle R_8 représente un atome d'hydrogène, un groupement protecteur pour un groupe hydroxyle ou un groupe alkyle ayant 1 à 3 atomes de carbone, ou d'un de ses sels pharmaceutiquement acceptables, qui comprend la réaction d'un composé de formule (II) :



dans laquelle R_1 et X sont tels que définis ci-dessus, R_9 représente un groupe protecteur pour un groupe carboxyle, Z représente un ester réactif d'un alcool, ou un groupe alkyle-inférieur sulfinyle substitué ou non substitué, avec un dérivé mercaptan de formule :



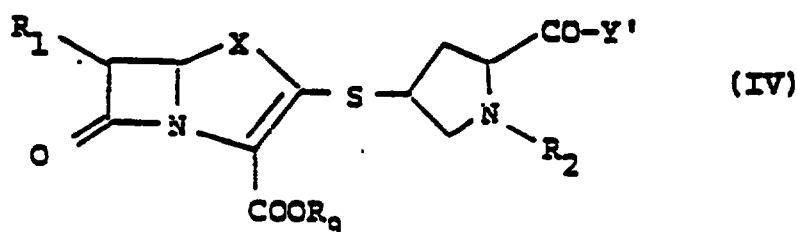
dans laquelle R_2 est tel que défini ci-dessus, et Y' est un groupe représenté par la formule (2) :



dans laquelle R_5 et R_6 sont tels que définis ci-dessus, ou un groupe représenté par la formule (4') :



dans laquelle R_8 représente un groupe protecteur pour un groupe hydroxyle ou un groupe alkyle ayant 1 à 3 atomes de carbone, en présence d'une base dans un solvant inerte pour produire un composé β -lactame représenté par la formule (IV) :



dans laquelle R_1 , R_2 , R_9 , X et Y' sont tels que définis ci-dessus, et, si on le souhaite, le traitement du composé résultant par une combinaison appropriée d'élimination du groupe protecteur du groupe carboxyle, du groupe protecteur du groupe hydroxyle et/ou du groupe protecteur du groupe amino, de façon séquentielle ou simultanée, pour produire le composé de formule (IV) dans laquelle R_1 est un groupe 1-hydroxyéthyle, R_2 est un atome d'hydrogène et/ou R_3 est un atome d'hydrogène ou le composé de formule (IV) dans lequel le groupe protecteur sur le groupe Y' est éliminé, et éventuellement la conversion du composé obtenu en un sel pharmaceutiquement acceptable.

2. Procédé selon la revendication 1 pour la production d'un composé de formule (I) dans laquelle R_1 représente un groupe 1-hydroxyéthyle, R_2 et R_3 représentent tous deux des atomes d'hydrogène, et Y est un groupe représenté par la formule (2-a) :



dans laquelle R_{5-a} et R_{6-a} représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridyl-



méthyle, un groupe alkyle ayant 1 à 5 atomes de carbone substitué par un groupe hydroxyle, un groupe di(C₁-C₃)-alkylamino, un groupe carbamoyle, un groupe aminocarbonyl mono- ou di(C₁-C₃)-alkyl-substitué ou un groupe carboxyle, ou un groupe pyridyle, ou R_{5-a} et R_{6-a} forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone, de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué, dont le cycle peut contenir une ou des doubles liaisons, le substituant étant un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, un groupe carboxylique, un groupe aminocarbonyl mono- ou di(C₁-C₃)-alkyl-substitué ou un groupe hydroxyle ; ou un groupe représenté par la formule (4-a) :



dans laquelle R_{8-a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone.

3. Procédé selon la revendication 1 pour la production d'un composé de formule (I) dans laquelle R₁ représente un groupe 1-hydroxyéthyle ; R₂ et R₃ représentent tous deux des atomes d'hydrogène et Y est un groupe représenté par la formule (2-b) :

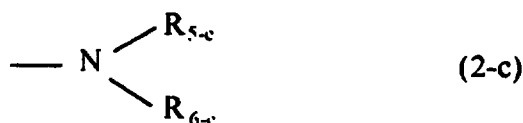


dans laquelle R_{5-b} et R_{6-b} représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridylméthyle, un groupe alkyle substitué ayant 1 à 5 atomes de carbone, le substituant étant un groupe hydroxyle, un groupe di(C₁-C₃)-alkylamino, un groupe carbamoyle, un groupe aminocarbamoyle mono- ou di(C₁-C₃)-alkyl-substitué ou un groupe carboxyle, ou un groupe pyridyle, ou R_{5-b} et R_{6-b} forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone, de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué, dont le cycle peut contenir une ou des doubles liaisons, le substituant étant un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, ou un groupe hydroxyle ; ou un groupe représenté par la formule (4-a) :



dans laquelle R_{8-a} représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone.

4. Procédé selon la revendication 1 pour la production d'un composé de formule (I), dans laquelle R₁ représente un groupe 1-hydroxyéthyle ; R₂ et R₃ représentent tous deux des atomes d'hydrogène ; et Y est un groupe représenté la formule (2-c) :



dans laquelle R_{5-c} et R_{6-c} ont une des significations suivantes :

(1) R_{5-c} représente un groupe alkyle ayant 1 à 5 atomes de carbone qui peut être substitué par un groupe carbamoyle, un groupe mono- ou di-(C₁-C₃)-alkylaminocarbonyl ou un groupe hydroxy, ou un groupe pyridyle, et R_{6-c} représente un atome d'hydrogène ou a la même définition que celle

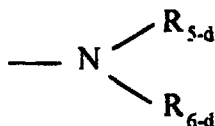


donnée pour R_{5-c} ;

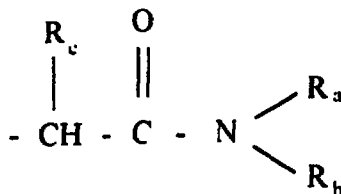
(2) R_{5-c} et R_{6-c} forment ensemble une chaîne alkylène de façon à constituer, avec l'atome d'azote adjacent, un groupe amino cyclique saturé à 4 à 6 côtés, non substitué ou substitué, ou un groupe amino cyclique à 5 ou 6 côtés, non substitué ou substitué, dont le cycle contient une ou des doubles liaisons, le substituant du cycle amino cyclique étant un groupe carbamoyle ou un groupe hydroxyle, et

(3) R_{5-c} et R_{6-c} forment ensemble une chaîne alkylène contenant un atome d'oxygène ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone de façon à constituer, avec l'atome d'azote adjacent, un groupe amino cyclique à 6 côtés.

5. Procédé selon la revendication 3 pour la production d'un composé de formule (I), dans laquelle Y est un groupe représenté par la formule :

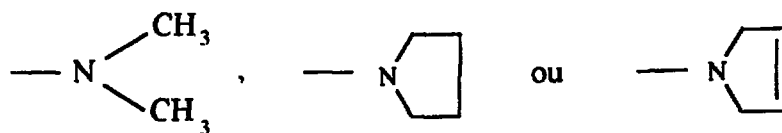


dans laquelle R_{5-d} représente un atome d'hydrogène ou un groupe méthyle et R_{6-d} représente un groupe de formule :



dans laquelle R_a , R_b et R_c représentent chacun un atome d'hydrogène ou un groupe méthyle.

6. Procédé selon la revendication 3 pour la production d'un composé de formule (I), dans laquelle Y est représenté par la formule :



7. Procédé selon une quelconque des revendications 1 à 6 pour la production d'un composé de formule (I), dans laquelle X représente

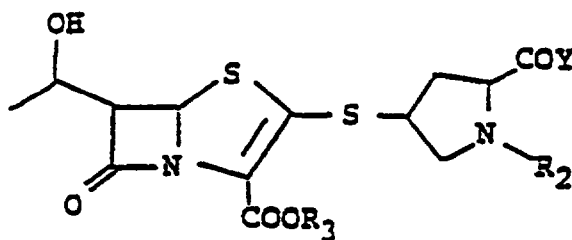


R_4 étant un atome d'hydrogène ou un groupe alkyle ayant 1 à 3 atomes de carbone.

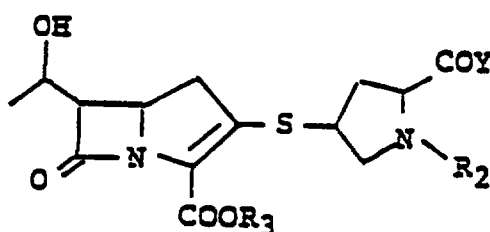
8. Procédé selon la revendication 7 pour la production d'un composé de formule (I), dans laquelle X représente



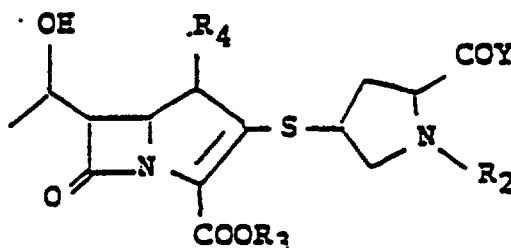
9. Procédé selon la revendication 7 pour la production d'un composé de formule (I), dans laquelle R_4 est un atome d'hydrogène.
10. Composé selon une quelconque des revendications 1 à 6 pour la production d'un composé de formule (I), dans laquelle X est un atome de soufre.
11. Procédé selon la revendication 1 pour la production du composé (5R) du composé selon une quelconque des revendications 1 à 6 et 10, représenté par la formule :



12. Procédé selon la revendication 1 pour la production du composé (5R) du composé selon une quelconque des revendications 1 à 7 et 9, représenté par la formule :



13. Procédé selon la revendication 1 pour la production du composé (5S) du composé selon une quelconque des revendications 1 à 8, représenté par la formule :



dans laquelle R_4 est un groupe alkyle ayant 1 à 3 atomes de carbone.

14. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-(diméthylaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-4-thia-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.



15. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-((1-pyrrolidino)carbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-4-thia-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 5 16. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-4-thia-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 10 17. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-(diméthylaminocarbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 15 18. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-((1-pyrrolidino)carbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 20 19. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-((1-pyrrolin-3-yl)carbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 25 20. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-((1-azétidino)carbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 30 21. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-((3-hydroxy-1-pyrrolidino)carbonyl) pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 35 22. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-((2-hydroxyéthyl)-méthylaminocarbonyl) pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-3-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 40 23. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-(1-morpholinocarbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 45 24. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-(1-N-méthylpipérazinocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 50 25. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-carbamoylpyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 55 26. Procédé selon la revendication 1 pour la production de l'acide (5R)-3-[2-(4-pyridylaminocarbonyl)-pyrrolidin-4-ylthio]-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
27. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-(diméthylaminocarbonyl)-pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
28. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-((1-pyrrolidino)carbonyl)-pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
29. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-((1-pyrrolin-3-yl)carbonyl)-pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou



d'un de ses sels pharmaceutiquement acceptables non toxiques.

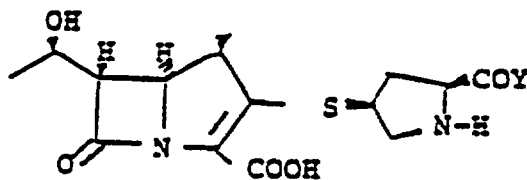
- 5 30. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-((1-azétidino)carbonyl)-pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 10 31. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-((3-hydroxy-1-pyrrolidino)-carbonyl) pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 15 32. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-((2-hydroxyéthyl)-méthylaminocarbonyl) pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 20 33. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-(1-morpholinocarbonyl)-pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 25 34. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-(1-N-méthylpipérazinocarbonyl)pyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 30 35. Procédé selon la revendication 1 pour la production de l'acide (5S)-3-[2-carbamoylpyrrolidin-4-ylthio]-4-méthyl-6-(1-hydroxyéthyl)-1-azabicyclo[3.2.0]hept-2-ène-7-one-2-carboxylique, ou d'un de ses sels pharmaceutiquement acceptables non toxiques.
- 35 36. Procédé selon la revendication 1 pour la production du composé (5R,6S,8R) du composé selon la revendication 11.
- 40 37. Procédé selon la revendication 1 pour la production du composé (5R,6S,8R) du composé selon la revendication 12.
38. Procédé selon la revendication 1 pour la production du composé (5S,6S,8R) du composé selon la revendication 13.
- 45 39. Procédé selon la revendication 1 pour la production du composé (5R,6S,8R) d'un composé selon une quelconque des revendications 14 à 26.
- 40 40. Procédé selon la revendication 1 pour la production du composé (5S,6S,8R) d'un composé selon une quelconque des revendications 27 à 35.
41. Procédé selon la revendication 1 pour la production du composé (5R, 6S, 8R, 2'S, 4'S) du composé selon la revendication 11
- 50 42. Procédé selon la revendication 1 pour la production du composé (5R, 6S, 8R, 2'S, 4'S) du composé selon la revendication 12
43. Procédé selon la revendication 1 pour la production du composé (5S, 6S, 8R, 2'S, 4'S) du composé selon la revendication 13.
- 55 44. Procédé selon la revendication 1 pour la production du composé (5R, 6S, 8R, 2'S, 4'S) d'un composé selon une quelconque des revendications 14 à 26.
45. Procédé selon la revendication 1 pour la production du composé (5S, 6S, 8R, 2'S, 4'S) d'un composé selon une quelconque des revendications 27 à 35.
46. Procédé selon la revendication 1 pour la production du composé (4R, 5S, 6S, 8R, 2'S, 4'S) d'un composé selon une quelconque des revendications 3 à 8 et 27 à 35.



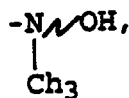
47. Procédé pour la production d'une composition pharmaceutique qui comprend la combinaison en tant que principe actif d'une quantité pharmaceutiquement efficace d'au moins un des composés selon la revendication 1 et d'au moins un support inerte ou un diluant pharmaceutiquement acceptable.

48. Utilisation du composé selon la revendication 1 en tant qu'agent antimicrobien.

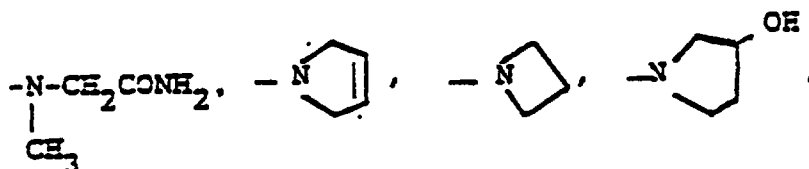
49. Procédé selon la revendication 1 pour la préparation d'un composé de β -lactame de formule :



dans laquelle Y est choisi dans le groupe comprenant NH_2 ,



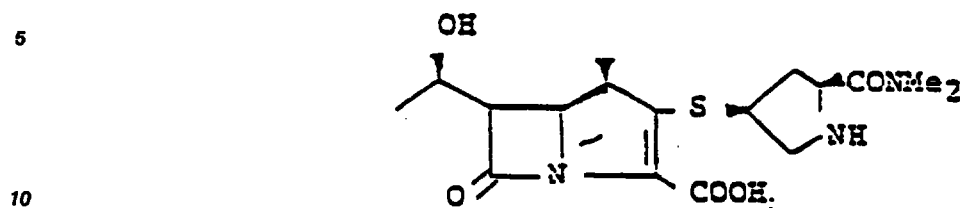
$-\text{NHCH}_2\text{CONH}_2$,



et de ses sels pharmaceutiquement acceptables.

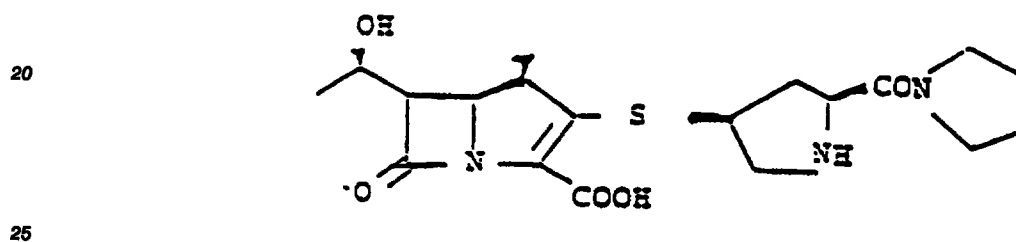


50. Procédé selon la revendication 1 pour la production d'un composé β -lactame de formule :



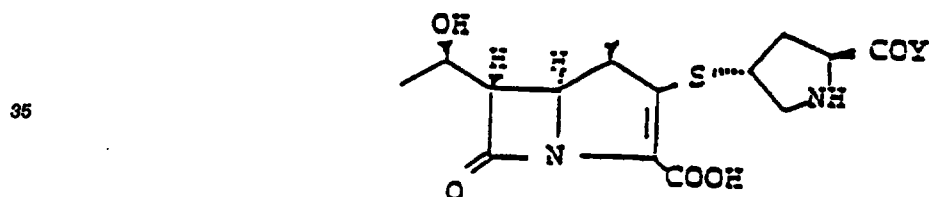
et de ses sels pharmaceutiquement acceptables.

15 51. Procédé selon la revendication 1 pour la production d'un composé β -lactame de formule :

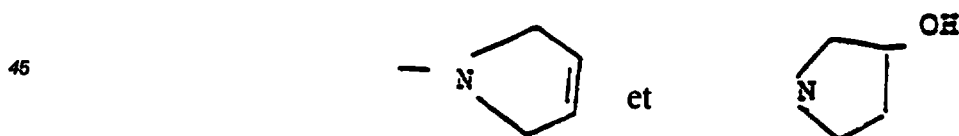


et de ses sels pharmaceutiquement acceptables.

30 52. Procédé selon la revendication 1 pour la production d'un composé β -lactame de formule :



40 dans laquelle Y est choisi dans le groupe comprenant

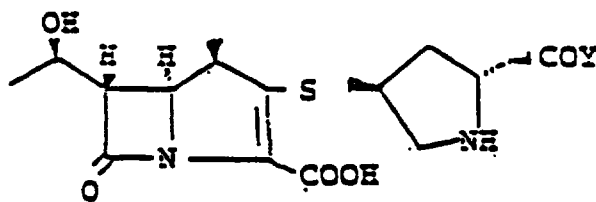


50 et de ses sels pharmaceutiquement acceptables.

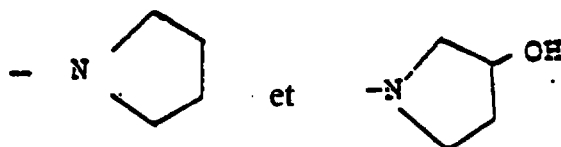
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53. Procédé selon la revendication 1 pour la production d'un composé β -lactame de formule :

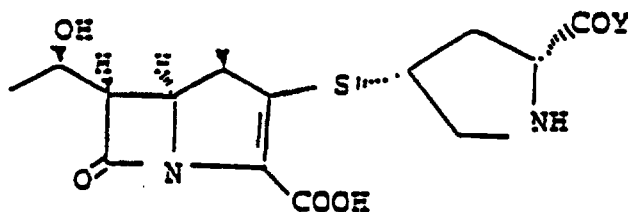


dans laquelle Y est choisi dans le groupe comprenant



et de ses sels pharmaceutiquement acceptables.

54. Procédé selon la revendication 1 pour la production d'un composé β -lactame de formule :

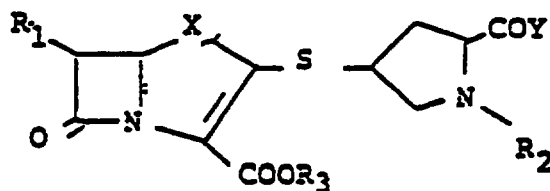


dans laquelle Y est choisi dans le groupe comprenant



et de ses sels pharmaceutiquement acceptables.

55. Procédé selon la revendication 1 pour la production d'un composé β -lactame représenté par la formule :





dans laquelle R_1 représente un groupe 1-hydroxyéthyle ou un groupe 1-hydroxyéthyle dans lequel le groupe hydroxy est protégé par un groupement protecteur pour un groupe hydroxy ; R_2 représente un atome d'hydrogène ou un groupement protecteur pour un groupe amino ; R_3 représente un atome d'hydrogène ou un groupement protecteur pour un groupe carboxyle ; X représente un atome de soufre et Y représente un groupe de formule (2) :



dans laquelle R_5 et R_6 , qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 5 atomes de carbone, un groupe alcényle ayant 3 ou 4 atomes de carbone, un groupe benzyle, un groupe phénéthyle, un groupe 2-pyridylméthyle, un groupe 3-pyridylméthyle ou un groupe 4-pyridylméthyle, un groupe alkyle substitué ayant 1 à 5 atomes de carbone dans lequel le substituant est choisi dans le groupe constitué par un groupe hydroxyle, un groupe di(C_1 - C_3)-alkylamino, un groupe carbamoyle, un groupe mono- ou di(C_1 - C_3)-alkylaminocarbonyle et un groupe carboxyle protégé ou non protégé ou un groupe pyridyle ; ou R_5 et R_6 forment ensemble une chaîne alkylène ou une chaîne alkylène contenant un atome d'oxygène, un atome de soufre ou un atome d'azote substitué par un alkyle ayant 1 à 3 atomes de carbone, de façon à former, avec l'atome d'azote adjacent, un groupe amino cyclique tri- à heptagonal non substitué ou substitué, dont le cycle peut contenir une ou des doubles liaisons, le substituant étant choisi parmi un groupe alkyle ayant 1 à 3 atomes de carbone, un groupe carbamoyle, un groupe mono- ou di(C_1 - C_3)-alkylaminocarbonyle et un groupe hydroxyle,

ou un groupe de formule (4) :



dans laquelle R_8 représente un atome d'hydrogène, un groupement protecteur pour un groupe hydroxyle ou un groupe alkyle ayant 1 à 3 atomes de carbone, et de ses sels pharmaceutiquement acceptables.