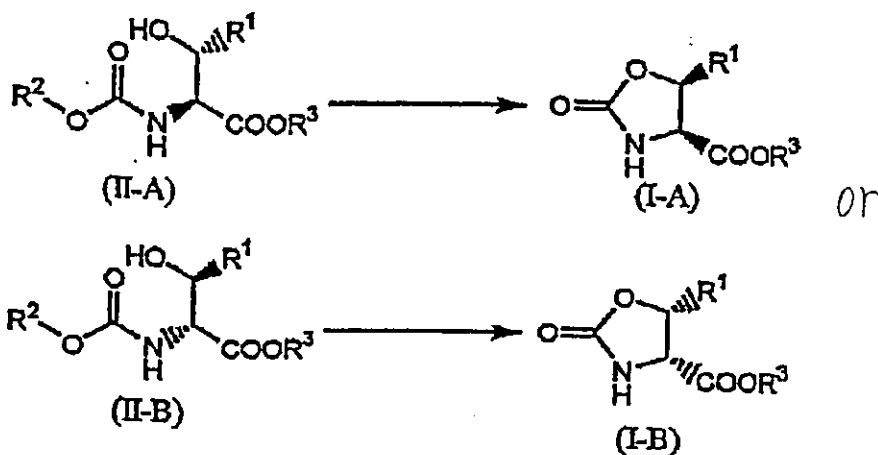


TITLE: "PROCESSES FOR THE PREPARATION OF OXO-OXAZOLINE OR
ALLOAMINO ACID DERIVATIVES"

[Claims]

[Claim 1] A method for production of a compound represented by the general formula (I-A) or the general formula (I-B), comprising the step of treating a compound represented by the general formula (II-A) or the general formula (II-B) with thionyl chloride as follows:

[Chemical Formula 1]

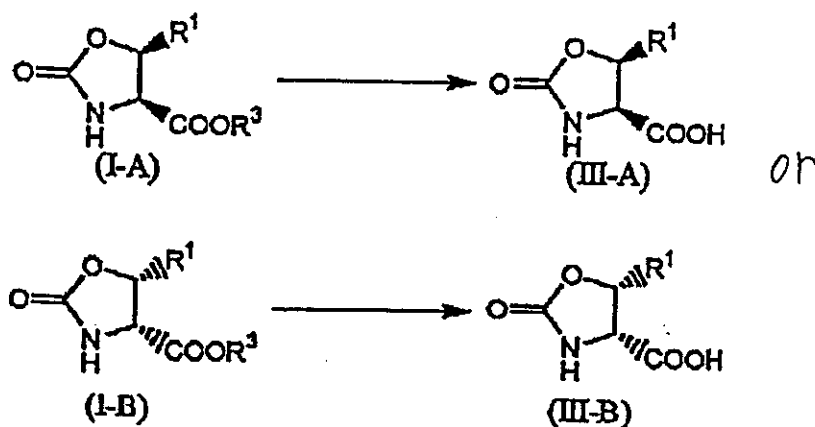


wherein R¹ is an optionally substituted lower alkyl, an optionally substituted aryl, an alkynyl, or an optionally substituted heteroaryl; R² is a lower alkyl, an optionally substituted aralkyl, or an optionally substituted heteroarylalkyl; and R³ is a lower alkyl.

[Claim 2] A method for production of a compound

represented by the general formula (III-A) or the general formula (III-B), comprising the step of subjecting a compound represented by the general formula (I-A) or the general formula (I-B) obtained by a method according to claim 1 to a hydrolysis as follows:

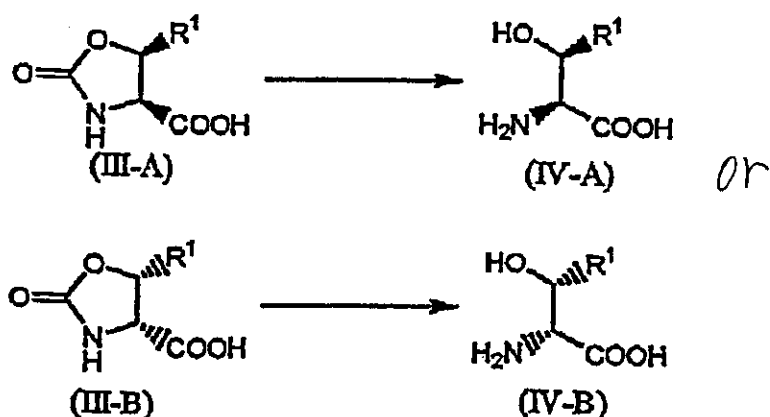
[Chemical Formula 2]



wherein R¹ and R³ are as described above.

[Claim 3] A method for production of a compound represented by the general formula (IV-A) or the general formula (IV-B), comprising the step of subjecting a compound represented by the general formula (III-A) or the general formula (III-B) obtained by a method according to claim 2 to a hydrolysis as follows:

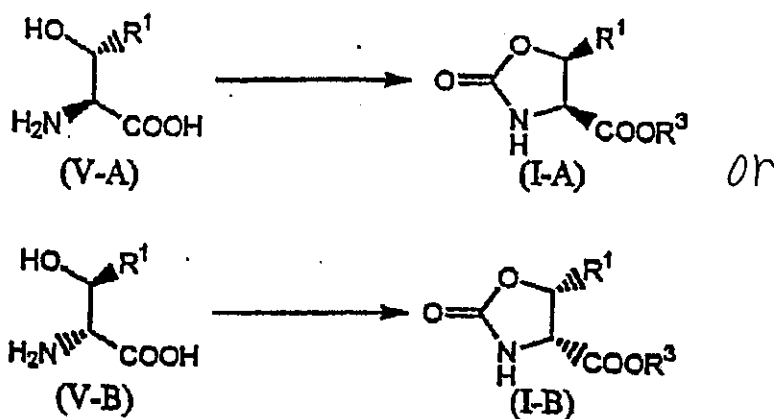
[Chemical Formula 3]



wherein R^1 is as described above.

[Claim 4] A method for production of a compound represented by the general formula (I-A) or the general formula (I-B), comprising the step of protecting the amino group of a compound represented by the general formula (V-A) or the general formula (V-B) with $R^2OC(=O)-$, wherein R^2 is as described above, esterifying the carboxyl group thereof, and treating with thionyl chloride as follows:

[Chemical Formula 4]



[Claim 5] A method for production of a compound represented by the general formula (VI):

O=C1NC(=O)C(R1)C1=O.C#CN2C=CC=C2.CC3(CCC3)N(C)C(=O)C4CC4>>O=C1NC(=O)C(R1)C1=O.CC3(CCC3)N(C)C(=O)C4CC4.C#CN2C=CC=C2

[Claim 6] A method for production according to claim 2, wherein R¹ is phenyl, 5-imidazolyl, methyl, isopropyl, ethynyl, or 1-propynyl.

[Claim 8] A method for production according to claim 2, wherein R² is an aralkyl.

[Claim 9] A method for production according to claim 2, wherein R¹ is methyl and R² is benzyl.

[Claim 10] A method for production according to any of claims 1-9, wherein the compound represented by the general formula (II-A) or the general formula (II-B) is allowed to react with 1.0 to 5.0 equivalents of thionyl chloride in a solvent of toluene, ethyl acetate, cyclohexane, or acetonitrile at 30°C to reflux temperature.

[Claim 11] A method for production according to any of claims 1-9, wherein the compound represented by the general formula (II-A) or the general formula (II-B) is allowed to react with 1.0 to 3.0 equivalents of thionyl chloride in a solvent of toluene, ethyl acetate, cyclohexane, or acetonitrile at 60°C to 80°C.

[Detailed Description of the Invention]

[0001]

[Field of the Invention]

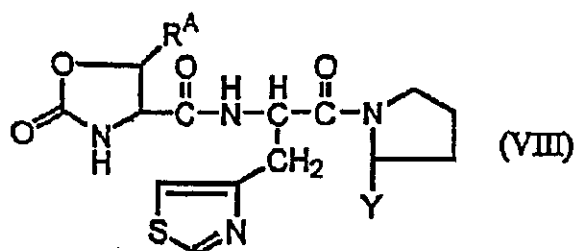
The present invention relates to a method for producing oxo-oxazoline derivatives using a simple and inexpensive method.

[0002]

[Prior Art]

Oxo-oxazoline derivatives are critical intermediates for compounds (WO98/08867) which are TRH (thyrotropin releasing hormone) derivatives represented by the following general formula (VIII):

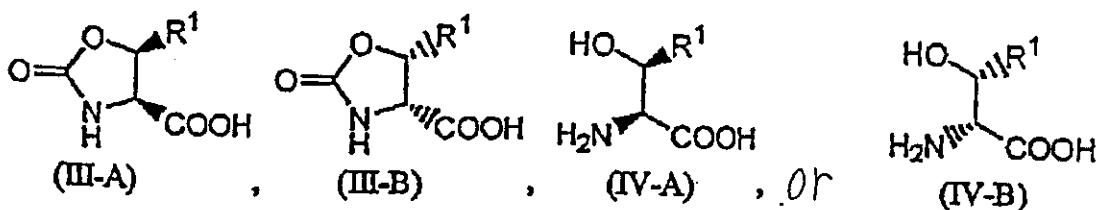
[Chemical Formula 6]



wherein R^A is a hydrogen atom or optionally substituted lower alkyl; Y is an optionally substituted alkyl.

Further, compounds represented by the following general formulas (III-A), (III-B), (IV-A), or (IV-B):

[Chemical Formula 7]



wherein R^1 is an optionally substituted lower alkyl, an optionally substituted aryl, an alkynyl, or an optionally substituted heteroaryl, and derivatives thereof, are useful as tools for combinatorial chemistry.

Conventionally, as a method for producing oxo-oxazoline derivatives having a lower alkyloxycarbonyl group or a carboxyl group, a method of cyclizing a starting material while retaining its stereochemistry, and a method using cyclization reaction

without reference to stereoselectivity are known.

An example of the method of cyclizing a starting material while retaining its stereochemistry is the following:

[Chemical Formula 8]



(Tetrahedron, 48, 2507, 1992). In this reaction, L-allo-threonine used as a starting material is allowed to react with phosgene and potassium hydroxide in toluene solvent at 0°C for one hour, thereby obtaining a cyclized product which retains its stereochemistry. This method has a problem for industrialization since it employs L-allo-threonine which is more expensive than its natural type, and phosgene which is toxic to a human body.

An example of the cyclization method without reference to stereoselectivity is the following:

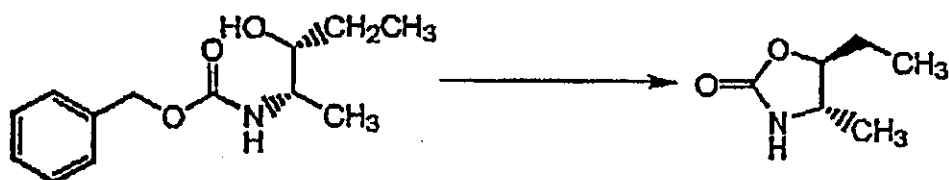
[Chemical Formula 9]



(Japanese Laid-Open Publication No. 60-34955). In this reaction, a starting material is allowed to react with potassium carbonate in water at 60°C for 1.5 hours to obtain a cyclized product. It is believed that the stereochemistry of the material is maintained in view of the mechanism of this method. Therefore, it is considered that allo-threonine needs to be used as a starting material in order to obtain a cis-form cyclized product.

Although a resultant cyclized product is an oxo-oxazoline derivative which does not have a lower alkyloxycarbonyl group or a carboxyl group, the following method is known:

[Chemical Formula 10]



(Bull. Chem. Soc. Japan., 44, 2515, 1971). In this reaction, a starting material is allowed to react in thionyl chloride at 60°C for 24 hours without using solvent, thereby obtaining a cyclized product at a yield of 65%. In this method, similar to the method of the present invention, the position of an ethyl group is inverted after the reaction. However, the starting material is not an amino acid derivative, and the relationship between the amino group and the hydroxyl group is different from that of a starting material used in the method of the present invention. Moreover, since the reaction is conducted in

4 February 2004

thionyl chloride, the yield is as low as 65%.

[0003]

[Problems to be Solved by the Invention]

The objective of the present invention is to provide a method for simply and inexpensively producing oxo-oxazoline derivatives in a stereoselective manner. The oxo-oxazoline derivatives are useful as intermediates for pharmaceuticals and tools for combinatorial chemistry. Moreover, the oxo-oxazoline derivatives in an open-circular form are also useful as tools for combinatorial chemistry.

[0004]

[Means for Solving the Problems]

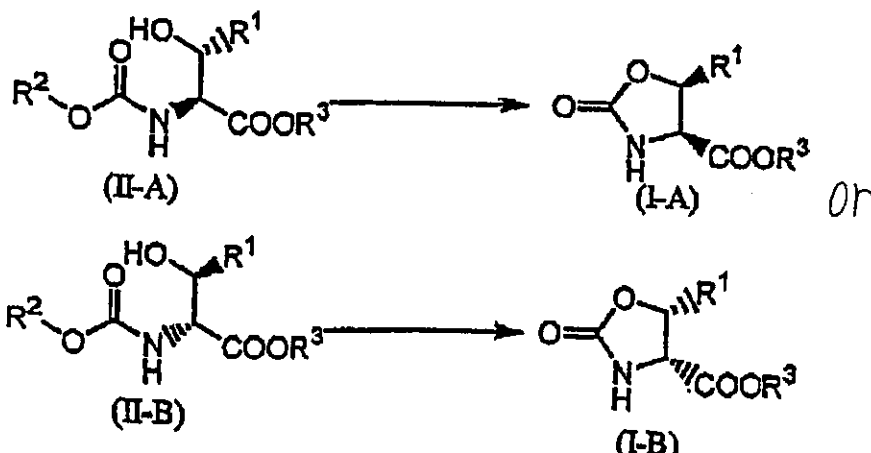
The inventors found a method for producing oxo-oxazoline derivatives in a stereoselective manner, which is suitable for large-scale synthesis.

[0005]

That is, the present invention relates to

I) a method for the production of a compound represented by a general formula (I-A) or a general formula (I-B), comprising the step of treating a compound represented by a general formula (II-A) or a general formula (II-B) with thionyl chloride as follows:

[Chemical Formula 11]



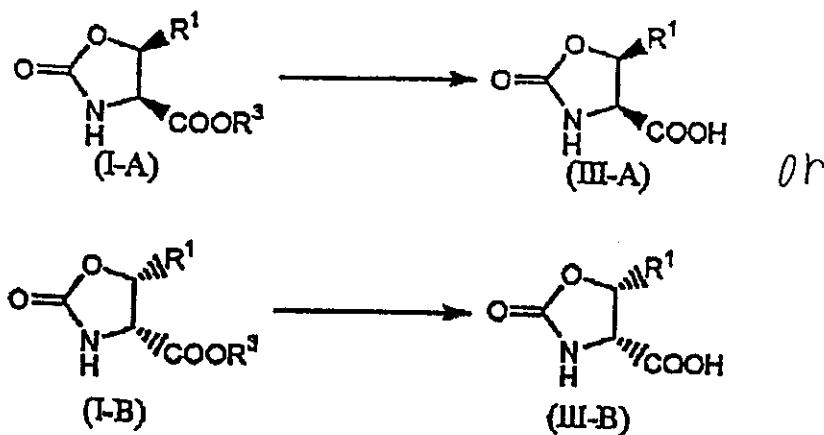
wherein R^1 is an optionally substituted lower alkyl, an optionally substituted aryl, an alkynyl, or an optionally substituted heteroaryl; R^2 is a lower alkyl, an optionally substituted aralkyl, or an optionally substituted heteroarylalkyl; and R^3 is a lower alkyl.

[0006]

Moreover, the present invention relates to the following methods II) to XI).

II) A method for producing the compound represented by a general formula (III-A) or a general formula (III-B), comprising the step of subjecting a compound represented by a general formula (I-A) or a general formula (I-B) obtained by a method according to I) to a hydrolysis reaction as follows:

[Chemical Formula 12]



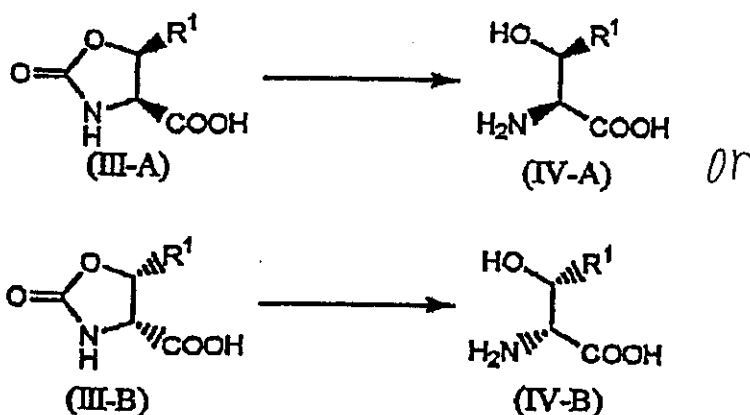
wherein R^1 and R^3 are as described above.

[0007]

III) A method for producing the compound represented by a general formula (IV-A) or a general formula (IV-B), comprising the step

of subjecting a compound represented by the general formula (III-A) or the general formula (III-B) obtained by a method according to II) to a hydrolysis reaction as follows:

[Chemical Formula 13]

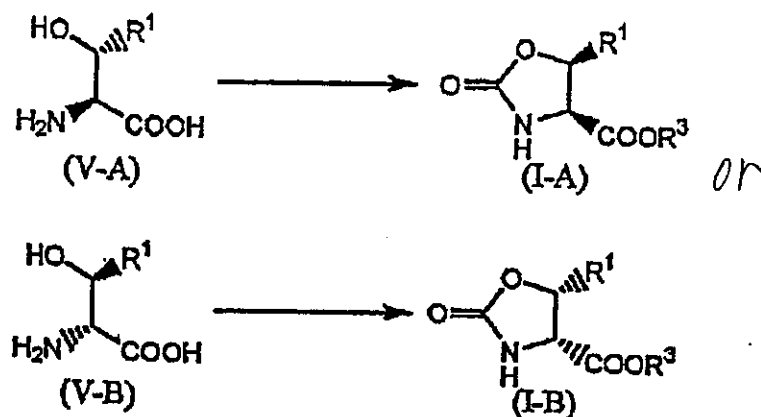


wherein R¹ is as described above.

[0008]

IV) A method for the production of a compound represented by the general formula (I-A) or the general formula (I-B), comprising the step of protecting the amino group of a compound represented by a general formula (V-A) or a general formula (V-B) with R²OC(=O)-, wherein R² is as described above, esterifying the carboxyl group thereof, and treating with thionyl chloride as follows:

[Chemical Formula 14]

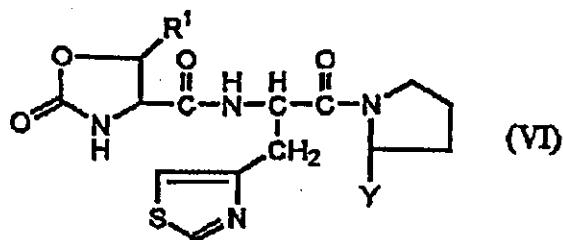


wherein R¹ and R³ are as described above.

[0009]

V) A method for production of a compound, comprising the step of subjecting a compound represented by the general formula (III-A) or the general formula (III-B) obtained by a method according to II) to a peptide bond formation as follows:

[Chemical Formula 15]



wherein R¹ is as described above, and Y is an optionally substituted alkyl.

[0010]

VI) A method for the production according to II), wherein R¹

is phenyl, 5-imidazolyl, methyl, isopropyl, ethynyl, or 1-propynyl.

VII) A method for the production according to II), wherein R^2 is a lower alkyl, an aralkyl, or a heteroarylalkyl.

VIII) A method for the production according to II), wherein R^2 is an aralkyl.

IX) A method for the production according to II), wherein R^1 is methyl and R^2 is benzyl.

X) A method according to any of the methods I) to IX), wherein a compound represented by the general formula (II-A) or the general formula (II-B) is caused to react with 1.0 equivalent to 5.0 equivalents of thionyl chloride at 30°C to reflux temperature in a solvent such as toluene, ethyl acetate, cyclohexane, or acetonitrile.

XI) A method according to any of the methods I) to IX), wherein a compound represented by the general formula (II-A) or the general formula (II-B) is caused to react with 1.0 equivalent to 3.0 equivalents of thionyl chloride at 60°C to 80°C in a solvent such as toluene, ethyl acetate, cyclohexane, or acetonitrile.

In the method V), it is preferable to perform the peptide bond formation two times.

[0011]

"Halogen" as used herein refers to fluorine, chlorine, bromine, and iodine. Chlorine and bromine are preferable.

The term "lower alkyl" as herein used alone or in combination with other words comprises C_1 - C_6 straight chained or branched alkyl. Examples of the lower alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and t-butyl, and the like. Methyl and ethyl are preferable.

[0012]

"Alkynyl" as used herein comprises C_2 - C_8 straight or branched chain monovalent hydrocarbon group having one or two or more triple bonds. The alkynyl may have a double bond. Examples of the alkynyl include ethynyl, 1-propynyl, 2-propynyl, 6-heptynyl, 7-octynyl, and 8-nonyl, and the like. Ethynyl and 1-propynyl are preferable.

The term "aryl" as herein used alone or in combination with other words comprises a monocyclic or condensed ring aromatic hydrocarbon. Examples of the aryl include phenyl, 1-naphthyl, 2-naphthyl, anthryl, and the like.

"Aralkyl" as used herein comprises the above-described "lower alkyl" substituted with the above-described "aryl", where the substitution may be carried out at any possible position. Examples of the aralkyl include benzyl, phenylethyl (e.g., 2-phenylethyl, and the like), phenylpropyl (e.g., 3-phenylpropyl, and the like), naphthylmethyl (e.g., 1-naphthylmethyl, 2-naphthylmethyl, and the like), and anthrylmethyl (e.g., 9-anthrylmethyl, and the like), and the like. Benzyl, and the like are preferable.

[0013]

"Heteroaryl" as used herein comprises a 5 to 6-membered aromatic ring including one or more atoms arbitrarily selected from oxygen atom, sulfur atom or nitrogen atom within the ring.

Heteroaryl may be fused with cycloalkyl, aryl, or other heteroaryl at any possible position. Regardless whether the heteroaryl is monocyclic or fused cyclic, the heteroaryl can bind at any possible position. Examples of the heteroaryl include pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), imidazolyl (e.g., 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), oxazolyl (e.g., 2-oxazolyl), thiazolyl (e.g., 2-thiazolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrazinyl (e.g., 2-pyrazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl), tetrazolyl (e.g., 1H-tetrazolyl), oxadiazolyl (e.g., 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), indolizinyll (e.g., 2-indolizinyll, 6-indolizinyll), isoindolyl (e.g., 2-isoindolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), indazolyl (e.g., 3-indazolyl), purinyl (e.g., 8-purinyl), quinolizinyll (e.g., 2-quinolizinyll), isoquinolyl (e.g., 3-isoquinolyl), quinolyl (e.g., 2-quinolyl, 5-quinolyl), phthalazinyl (e.g., 1-phthalazinyl), naphthyridinyl (e.g., 2-naphthyridinyl), quinolanyl (e.g., 2-quinolanyl), quinazolinyl (e.g., 2-quinazolinyl), cinnolinyl (e.g., 3-cinnolinyl), pteridinyl (e.g., 2-pteridinyl), carbazolyl (e.g., 2-carbazolyl, 4-carbazolyl), phenanthridinyl (e.g., 2-phenanthridinyl, 3-phenanthridinyl), acridinyl (e.g., 1-acridinyl, 2-acridinyl), dibenzofuranyl (e.g., 1-dibenzofuranyl, 2-dibenzofuranyl), benzimidazolyl (e.g., 2-benzimidazolyl), benzisoxazolyl (e.g., 3-benzisoxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzoxadiazolyl (e.g., 4-benzoxadiazolyl), benzisothiazolyl (e.g., 3-benzisothiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzofuryl (e.g., 3-benzofuryl), and benzothienyl (e.g.,

2-benzothienyl). As "heteroaryl" of R¹, imidazolyl and the like are preferable.

"Heteroarylalkyl" as used herein comprises the above-described "lower alkyl" substituted with the above-described "heteroaryl", where such a substitution may be carried out at any possible position.

[0014]

"Optionally substituted lower alkyl" at R¹ as used herein comprises the above-described "lower alkyl" which may have one or more substituents at any possible positions, such as hydroxy, alkyloxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), halogen (e.g., fluorine, chlorine, bromine, and iodine), alkyloxycarbonyl (e.g., methyloxycarbonyl and ethyloxycarbonyl), aryloxycarbonyl (e.g., phenyloxycarbonyl), nitro, cyano, aryloxy, acyloxy, acyloxycarbonyl, alkylcarbonyl, and the like. Preferable examples of the substituent include lower alkyloxy, halogen, and the like. Examples of the "optionally substituted lower alkyl" include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and trifluoromethyl, and the like. An unsubstituted lower alkyl is preferable.

"Optionally substituted alkyl" at Y as used herein comprises the above-described "alkyl" which may have one or more substituents at any possible positions, such as hydroxy, alkyloxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), halogen (e.g., fluorine, chlorine, bromine, and iodine), carboxy, carbamoyl, alkyloxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl),

aryloxycarbonyl (e.g., phenyloxycarbonyl), nitro, cyano, SO_pR^A (p is an integer of 1 to 3, R^A is hydrogen or alkyl), $\text{PO}(\text{OH})_2$ or $\text{P}(\text{O})\text{OH}$ which may be substituted with alkyl, substituted or unsubstituted amino (e.g., methyl amino, dimethyl amino, and carbamoyl amino), optionally substituted aryl (e.g., phenyl and tolyl), optionally substituted heteroaryl, optionally substituted nonaromatic heterocyclic group, aryloxy, acyloxy, acyloxycarbonyl, alkylcarbonyl, nonaromatic heterocyclic carbonyl, heterocyclic imino, hydrazino, hydroxyamino, alkyloxyamino, formyl, and the like. Examples of the "optionally substituted alkyl" include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, hydroxymethyl, tert-butylcarbonyloxymethyl, morpholinomethyl, piperidinomethyl, N-methyl-1-piperazinylmethyl, ethylcarbonylmethyl, morpholinocarbonylmethyl, acetyloxymethyl, and the like. An unsubstituted alkyl is preferable, particularly methyl.

[0015]

"Optionally substituted aryl" as used herein comprises the above-described "aryl" which may have one or more substituents at any possible positions, such as hydroxy, alkyloxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), halogen (e.g., fluorine, chlorine, bromine, and iodine), alkyloxycarbonyl (e.g., methyloxycarbonyl and ethyloxycarbonyl), aryloxycarbonyl (e.g., phenyloxycarbonyl), nitro, cyano, aryloxy, acyloxy, acyloxycarbonyl, alkylcarbonyl, and the like. Preferable examples of the substituent include lower alkyloxy, halogen, and the like. Examples of the "optionally substituted aryl" include phenyl, 2-chlorophenyl, 3-chlorophenyl,

4-chlorophenyl, and the like. An unsubstituted aryl is preferable.

[0016]

"Optionally substituted heteroaryl" as used herein comprises the above-described "heteroaryl" which may have one or more substituents at any possible positions, such as hydroxy, alkyloxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), halogen (e.g., fluorine, chlorine, bromine, and iodine), alkyloxycarbonyl (e.g., methyloxycarbonyl and ethyloxycarbonyl), aryloxycarbonyl (e.g., phenyloxycarbonyl), nitro, cyano, aryloxy, acyloxy, acyloxycarbonyl, alkylcarbonyl, and the like. Preferable examples of the substituents include lower alkyloxy, halogen, and the like. Examples of the "optionally substituted heteroaryl" include 2-chloroimidazole-5-yl, 4-chloroimidazole-5-yl, and the like. An unsubstituted heteroaryl is preferable.

[0017]

"Optionally substituted aralkyl" as used herein comprises the above-described "aralkyl" which may have one or more substituents at any possible positions, such as hydroxy, alkyloxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), halogen (e.g., fluorine, chlorine, bromine, and iodine), alkyloxycarbonyl (e.g., methyloxycarbonyl and ethyloxycarbonyl), aryloxycarbonyl (e.g., phenyloxycarbonyl), nitro, cyano, aryloxy, acyloxy, acyloxycarbonyl, alkylcarbonyl, and the like. Preferable examples of the substituents include lower alkyloxy, halogen, and the like. Examples of the "optionally substituted aralkyl"

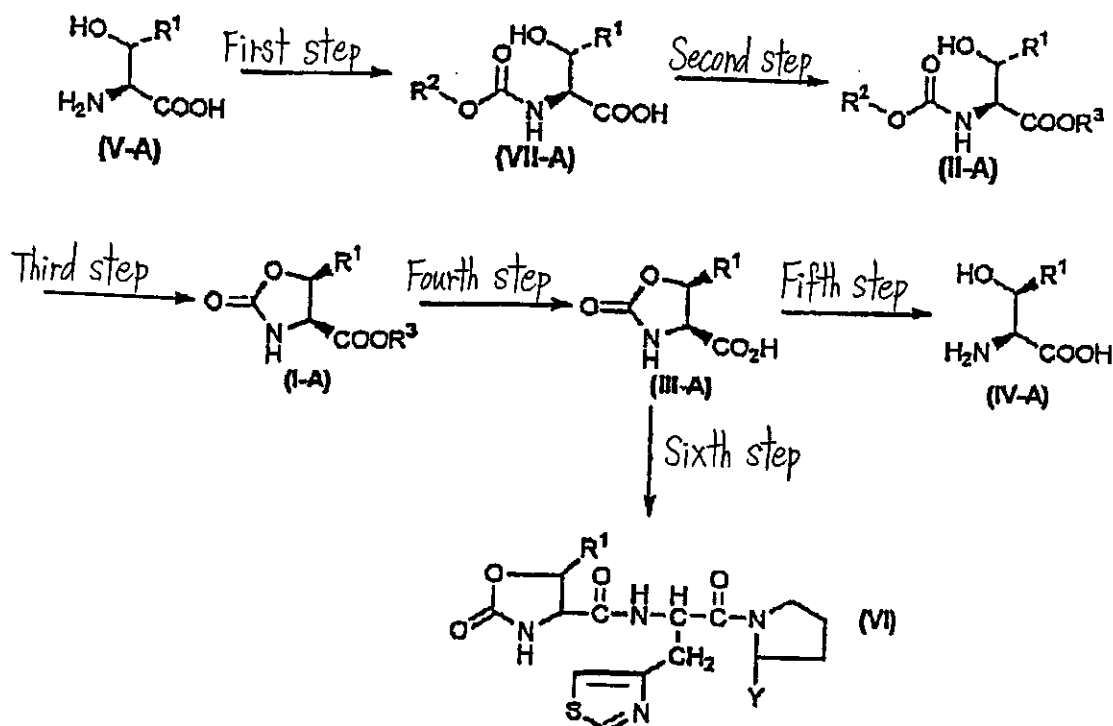
include furyl, thienyl, pyridyl, 5-chlorofuryl, 5-thienyl, 3-chloropyridyl, and the like. An unsubstituted aralkyl is preferable.

[0018]

[Embodiments of the Invention]

The production method of the present invention will be described in detail in which a starting material is one optically active substance. When the other material is used, similar reactions can be carried out. When a starting material has a substituent which is an obstacle to a reaction in first to sixth steps shown below, the starting material may be protected in advance in accordance with a method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons), and the like, and deprotected in an appropriate stage.

[Chemical Formula 16]



wherein R^1 , R^2 , R^3 , and Y are as described above.

[0019]

(First step)

In the first step, $R^2OC(=O)-Hal$, wherein Hal is halogen, $[R^2OC(=O)]_2O$, and the like are caused to react with a compound represented by the general formula (V-A) to obtain a compound (VII-A) in which an amino group is protected by $R^2OC(=O)-$. This step can be carried out in accordance with a method described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons), and the like.

For example, a compound represented by the general formula (V-A) is caused to react with 1.0 equivalent to 3.0 equivalents, preferably 1.0 equivalent to 1.5 equivalents, of $R^2OC(=O)-Hal$, wherein Hal is halogen, and 2.0 equivalents to 6.0 equivalents, preferably 2.0 equivalents to 3.0 equivalents, of an organic base (e.g., triethylamine, and the like) or an inorganic base (e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like), in a mixed solvent, such as water-toluene, water-dioxane, water-acetone, and the like, or a solvent, such as water, dioxane, and the like at $-20^\circ C$ to $50^\circ C$, preferably $0^\circ C$ to $20^\circ C$ for 0.5 to 3 hours to obtain a compound represented by the general formula (VII-A).

In the above-described IV), "step of protecting an amino group with $R^2OC(=O)-$ " refers to this first step.

[0020]

(Second step)

In the second step, the carboxyl group of a compound

represented by a general formula (VII-A) is esterified to obtain a compound represented by a general formula (II-A). This step can be carried out by a commonly used esterification.

For example, a compound represented by the general formula (VII-A) is dissolved in a solvent, such as methanol, ethanol, isopropyl alcohol, and the like, and allowed to react with 1 equivalent to 5 equivalents, preferably 1 equivalent to 2 equivalents, of a halogenating agent, such as thionyl chloride, hydrochloric acid, phosphorus oxychloride, and the like, at -20°C to 50°C, preferably 0°C to 25°C, for one hour to 24 hours, preferably one hour to 3 hours, to obtain a compound represented by the general formula (II-A).

In the above-described IV), "step of esterifying a carboxyl group" refers to this second step.

[0021]

(Third step)

The third step is a cyclization reaction in which the stereochemistry of R¹ is reversed.

For example, a compound represented by a general formula (I-A) can be obtained in accordance with 1) to 3) described below. 1) a compound represented by the general formula (II-A) is dissolved in a solvent, such as toluene, ethyl acetate, cyclohexane, acetonitrile, and the like, preferably toluene. The amount of the solvent is preferably 1 V to 50 V, particularly 1 V to 10 V, where use of 1 ml of a solvent with respect to 1 g of a starting material is referred to as 1 V. 2) 1.0 equivalent to 20 equivalents, preferably 1.0 equivalent to 2.0 equivalents, of thionyl chloride are added at 25°C to 80°C, preferably 25°C to 50°C. Thionyl chloride

also can be used as a solvent. 3) The reaction solution is stirred at 25°C to 80°C, preferably 60°C to 80°C, for 5 hours to 48 hours, preferably 6 hours to 12 hours.

In this reaction, the closer the equivalent value of thionyl chloride is to 1.0 and the higher the "V" value of the amount of the solvent, the proportion of the cis-form of the intended compound was increased (the proportion of the trans-form was decreased).

The yield of the total compounds of cis-form and trans-form is not substantially affected by the equivalent value of thionyl chloride and the amount of the solvent.

In the above-described IV), "step of treating with thionyl chloride" refers to this third step.

[0022]

(Fourth step)

In the fourth step, an ester compound represented by the general formula (I-A) is hydrolyzed to carboxylic acid. This step can be carried out by a commonly used hydrolysis.

For example, a compound represented by the general formula (I-A) is dissolved in a solvent, such as water, and the like, and 0.1 equivalent to 10 equivalents, preferably 1 equivalent to 5 equivalents, of acid (e.g., hydrochloric acid, sulfuric acid, and the like) are added to the solution at 0°C to 100°C, preferably 25°C to 80°C. The resultant solution is allowed to react at 25°C to 100°C, preferably 50°C to 80°C for 1 hour to 5 hours to obtain a compound represented by the general formula (III-A). This step also can be carried out under basic conditions.

[0023]

(Fifth step)

In the fifth step, a compound represented by the general formula (III-A) is hydrolyzed to obtain allo-amino acid derivatives represented by a general formula (IV-A).

For example, a compound represented by the general formula (III-A) is dissolved in a solvent, such as water, and 0.1 equivalent to 20 equivalents, preferably 1 equivalent to 10 equivalents, of acid (e.g., hydrochloric acid, sulfuric acid, and the like) are added to the solution at 0°C to 100°C, preferably 25°C to 80°C. The resultant solution is allowed to react at 25°C to 100°C, preferably 80°C to 100°C for 1 hour to 48 hours to obtain a compound represented by the general formula (IV-A).

[0024]

(Sixth step) (peptide bond formation)

Three amino acid derivatives can be subjected to two peptide bond formations to synthesize a compound (VI) (WO98/08867). A compound represented by the general formula (I-A) obtained by the above-described method is used to synthesize the compound (VI) in the following two methods (method A and method B).

[Chemical Formula 17]

First step

Second step

[0026]

Method A - First step

The carboxyl group of 3-(4-thiazole)alanine synthesized in accordance with a method described in Synth. Commun., 20, 22, 3507 (1990) and Chem. Pharm. Bull., 38, 1, 103 (1990), is protected as an ester, such as methyl ester, benzylester, t-butylester, diphenylmethylester, and the like, resulting in a compound represented by a general formula (VIII). This compound and a compound represented by the general formula (III-A) are subjected to a peptide bond formation.

When the carboxyl group is protected as diphenylmethylester, the protecting reaction can be carried out as follows. 3-(4-thiazole)alanine is dissolved in a mixed solvent of an alcohol solvent, such as methanol, ethanol, and the like and a solvent, such as tetrahydrofuran, dioxane, and the like. 1 to 3 equivalents, preferably 1 to 2 equivalents, of diphenyl diazomethane are added to the solution at 0 to 50°C, preferably 20 to 40°C for 10 minutes to 1 hour, preferably 20 to 40 minutes. The resultant solution is allowed to react at the same temperature for 30 minutes to 3 hours, preferably 1 to 2 hours while being stirred.

The peptide bond formation is described in "Peptido Gosei [Peptide Synthesis]" (Nobuo Izumiya, Maruzen), and the like, and can be carried out by such a commonly used peptide bond formation method.

As commonly used peptide bond formation methods, a method employing a condensing agent, such as N,N-dicyclohexylcarbodiimide (DCC), and the like, an azide method, an acid chloride method, an acid anhydride method, an active ester method, and the like. When a starting material has a substituent (amino, carboxy, hydroxyl, and the like) which is an obstacle to the peptide formation, the substituent can

be protected in advance in accordance with a method described in Protective Groups in Organic Synthesis, Theodora W. Green (John Wiley & Sons), and the like, and the protecting group is removed at a desired stage.

A compound represented by the general formula (VIII) and a compound represented by the general formula (III-A) are dissolved in a solvent, such as N,N-dimethylformamide, tetrahydrofuran, acetonitrile, and the like. An N,N-dimethylformamide solution of a base, such as triethylamine, and the like, and dicyclohexylcarbodiimide (DCC), is added to that solution at -10 to 10°C, preferably in ice bath. 1-hydroxybenzotriazole may be added. The resultant solution is stirred at 10 to 50°C, preferably 20 to 30°C, for one hour to one day, preferably 5 to 10 hours, followed by typical subsequent processes. Thus, a compound represented by a general formula (IX) can be obtained.

[0027]

Method A - Second step

A deprotecting reaction can be carried out by a commonly used deprotecting reaction (Protective Groups in Organic Synthesis, Theodora W. Green (John Wiley & Sons)). For example, when R⁴ is diphenylmethyl, a compound represented by a general formula (IX) can be added to anisole and trifluoro acetic acid at -10 to 10°C, preferably in ice bath. The mixture is stirred at the same temperature for 5 to 30 minutes, preferably 10 to 20 minutes. After the mixture is warmed to 20 to 40°C, the mixture can be stirred for 1 to 4 hours, preferably 2 to 3 hours.

The resultant deprotected substance can be reacted with a pyrrolidine derivative synthesized by a method described in Tetrahedron, 27, 2599 (1971) through a peptide bond formation

similar to method A - first step, thereby obtaining a compound represented by the general formula (VI).

[0028]

Method B - First step

The amino group of 3-(4-thiazole)alanine synthesized in accordance with a method described in Synth. Commun., 20, 22, 3507 (1990) and Chem. Pharm. Bull., 38, 1, 103 (1990), is protected by a protecting group for an amino group, such as t-butyloxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, phthaloyl, trifluoroacetyl, and the like to obtain a compound represented by a general formula (X). This compound and a pyrrolidine derivative synthesized by a method described in Tetrahedron, 27, 2599 (1971) are subjected to a peptide bond formation.

When t-butyloxycarbonyl is used for the protection, the protecting reaction can be carried out as follows. 3-(4-thiazole)alanine is dissolved in a solvent, such as dioxane, tetrahydrofuran, acetonitrile, and the like. Boc_2O is added to the solution at 0 to 50°C, preferably 10 to 30°C, and stirred for 1 to 5 hours, preferably 2 to 4 hours.

A peptide bond formation can be carried out in a manner similar to that of the above-described method A - First step.

[0029]

Method B - Second step

A deprotecting reaction for an amino group can be carried out as follows. When the protecting group is t-butyloxycarbonyl, a compound represented by a general formula (XI) is dissolved in a solvent, such as ethyl acetate, and the like. 1 to 4 N hydrochloric acid-ethyl acetate solution is

added to that solution at -10 to 30°C, preferably in ice. The resultant mixture is stirred at the same temperature for 1 to 5 hours, preferably 2 to 3 hours.

The resultant deprotected substance can be subjected to a peptide bond formation similar to that of method A - First step, thereby obtaining a compound represented by the general formula (VI).

In the production method, a compound represented by the general formula (V-A) or (V-B) is preferably L-threonine or D-threonine (R^1 = methyl). Further, compounds represented by the general formulas (VII-A), (VII-B), (II-A), (II-B), (I-A), (I-B), (III-A), (III-B), (IV-A), (IV-B), and (VI) are also preferably compounds derived from L-threonine or D-threonine.

As R^2 , benzyl is preferable. As R^3 and Y, methyl is preferable.

In Examples, the following abbreviations are used.

Me:methyl

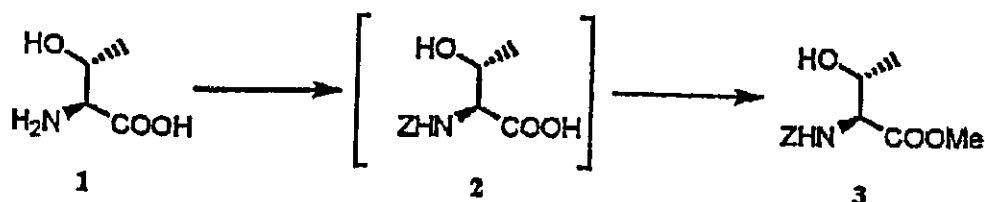
Z:benzyloxycarbonyl

[0030]

[Examples]

Example 1

[Chemical Formula 18]



[0031]

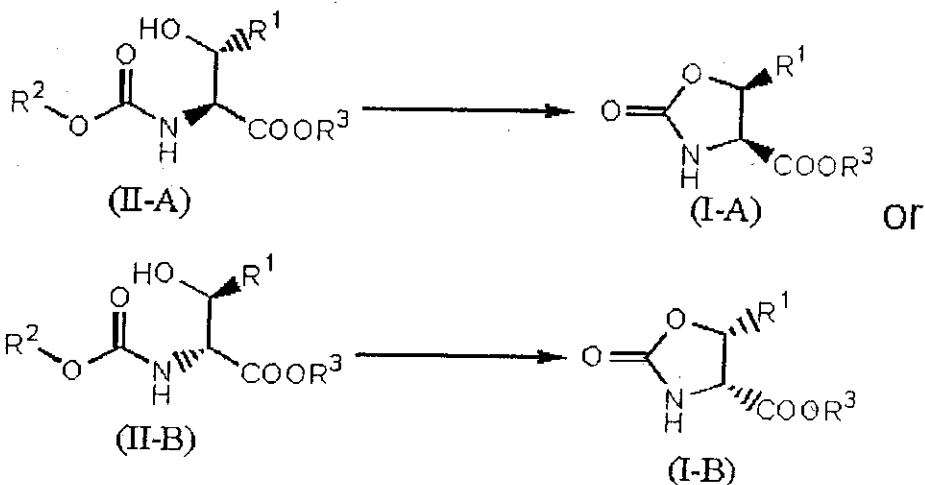
Potassium hydroxide (54.77 g) and a compound (1) (L-threonine) (100.0 g) were dissolved in water (1000 ml). To the solution was added potassium carbonate (139.23 g). The resultant solution was cooled below 10°C. Toluene (180 ml) solution of Z-Cl (157.5 g) was dropped into the solution at 10±5°C for about one hour while the solution was vigorously stirred. The stirring was further continued for about 1.5 hours at the same temperature. Thereafter, the resulting reaction mixture was extracted with toluene (120 ml). The aqueous layer was washed with toluene (200 ml). Each toluene layer was extracted with water (50 ml) again. The aqueous layers were combined. To the resultant aqueous layer was added 25% hydrochloric acid (about 294 g) to adjust the pH to 2.0±0.5, followed by extraction with ethyl acetate (800 ml). The organic layer was washed with 10% brine (400 ml). Each aqueous layer was extracted with ethyl acetate (200 ml) again. Thereafter, the organic layers were combined. The organic layer was evaporated. Adding ethyl acetate (1000 ml) to the residue and condensing were repeated twice. Further, methanol (500 ml) was added, followed by evaporation. Thereafter methanol was added to adjust the volume to about 440 ml. To the resultant methanol solution of compound (2) was dropped thionyl chloride (109.9 g) at 10±10°C, followed by stirring at 20±10°C for 2.5 hours. The reaction solution was dropped into a slurry of sodium hydrogencarbonate (211.6 g) in water (1320 ml) over about 30 minutes. The resultant slurry was stirred at 5°C for one hour. Thereafter, crystals were collected by filtration and dried, to obtain 206.3 g of compound (3) (yield 92%).

Melting point: 91°C

¹H NMR (CD₃OD) δ 1.19 (d, J=6.38, 3H), 3.73(s, 3H), 4.21-4.31

AMENDED CLAIMS

1. A method for production of a compound represented by the general formula (I-A) or the general formula (I-B), comprising the step of treating a compound represented by the general formula (II-A) or the general formula (II-B) with thionyl chloride as follows:



wherein R¹ is an optionally substituted lower alkyl, an optionally substituted aryl, an alkynyl, or an optionally substituted heteroaryl; R² is a lower alkyl, an optionally substituted aralkyl, or an optionally substituted heteroarylalkyl; and R³ is a lower alkyl.

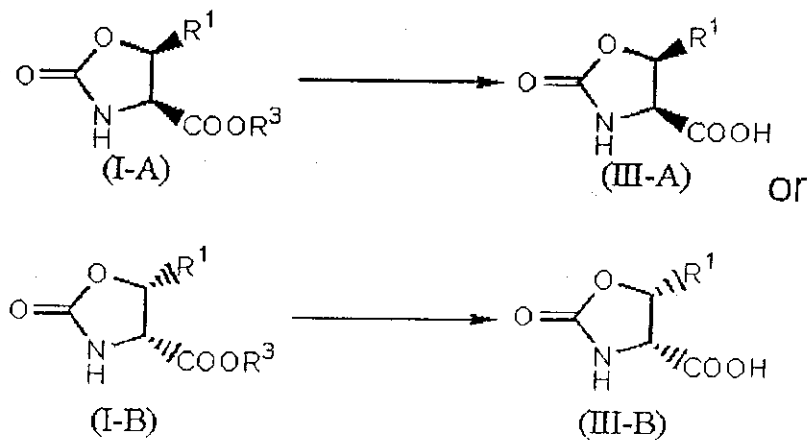
2. A method for production according to claim 1, wherein the compound represented by the general formula (II-A) or the general formula (II-B) is allowed to react with 1.0 to 5.0 equivalents of thionyl chloride in a solvent of toluene, ethylacetate, cyclohexane, or acetonitrile at 30°C to reflux.

3. A method for production according to claim 1, wherein the compound represented by the general formula (II-A) or the general formula (II-B) is allowed to react with 1.0 to 3.0 equivalents of thionyl chloride in a solvent of toluene,

4 February 2004

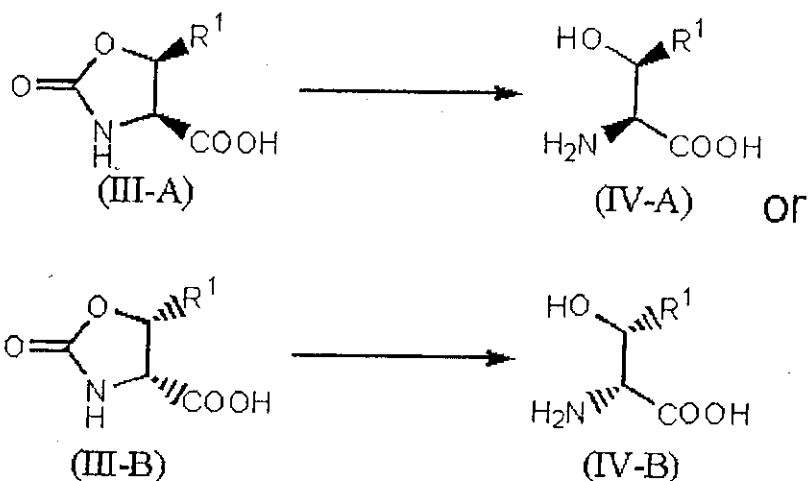
ethyl acetate, cyclohexane, or acetonitrile at 60°C to 80°C.

4(amended). A method for production of a compound represented by the general formula (III-A) or the general formula (III-B), comprising the step of obtaining a compound represented by the general formula (I-A) or the general formula (I-B) by a method according to any of claims 1-3 and subjecting the obtained compound represented by the general formula (I-A) or the general formula (I-B) to a hydrolysis as follows:



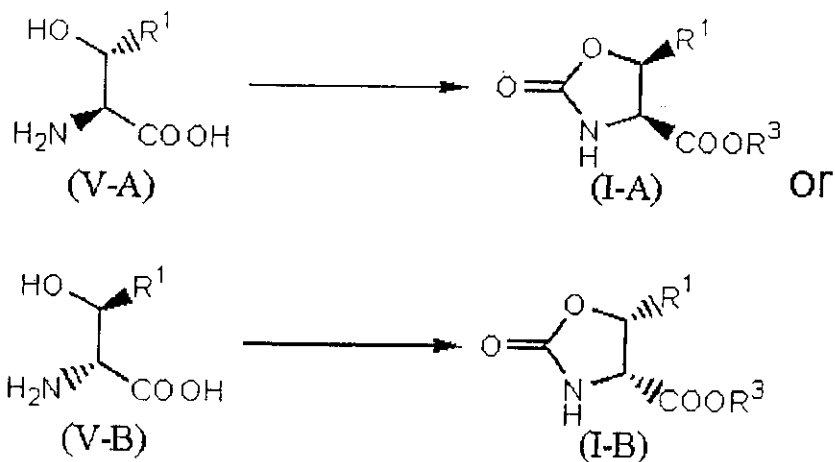
wherein R¹ and R³ are as described above.

5(amended). A method for production of a compound represented by the general formula (IV-A) or the general formula (IV-B), comprising the step of obtaining a compound represented by the general formula (III-A) or the general formula (III-B) by a method according to claim 4 and subjecting the obtained compound represented by the general formula (III-A) or the general formula (III-B) to a hydrolysis as follows:



wherein R^1 is as described above.

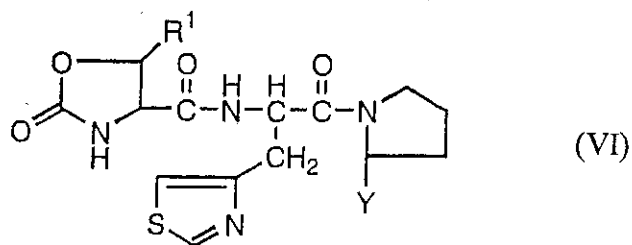
6. A method for production of a compound represented by the
 5 general formula (I-A) or the general formula (I-B),
 comprising the step of protecting the amino group of a compound
 represented by the general formula (V-A) or the general
 formula (V-B) with $R^2OC(=O)-$, wherein R^2 is as described above,
 esterifying the carboxyl group thereof, and treating with
 10 thionyl chloride as follows:



wherein R^1 and R^3 are as described above.

7(amended). A method for production of a compound represented
 15 by the general formula (VI):

4 February 2004

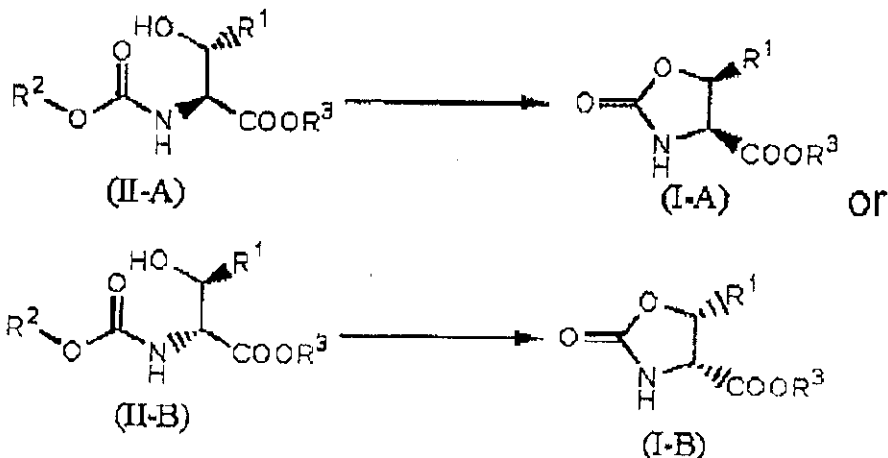


- wherein R^1 is as described above, and Y is an optionally substituted alkyl, the method comprising the step of obtaining a compound represented by the general formula (III-A) or the general formula (III-B) by a method according to claim 4 and subjecting the obtained compound represented by the general formula (III-A) or the general formula (III-B) to a peptide bond formation.
8. A method for production according to claim 4, wherein R^1 is phenyl, 5-imidazolyl, methyl, isopropyl, ethynyl, or 1-propynyl.
9. A method for production according to claim 4, wherein R^2 is a lower alkyl, an aralkyl, or a heteroarylalkyl.
10. A method for production according to claim 4, wherein R^2 is an aralkyl.
11. A method for production according to claim 4, wherein R^1 is methyl and R^2 is benzyl.

- 33(a) -

Amended Claims

- 5 12(new). A method for production of a compound represented
by the general formula (I-A) or the general formula (I-B),
comprising the step of treating a compound represented by
the general formula (II-A) or the general formula (II-B)
with 1.0 to 5.0 equivalents of thionyl chloride in a solvent
10 of toluene or ethyl acetate, as follows:



- wherein R¹ is an optionally substituted lower alkyl, an
optionally substituted aryl, an alkynyl, or an optionally
substituted heteroaryl; R² is a lower alkyl, an optionally
substituted aralkyl, or an optionally substituted
15 heteroarylalkyl; and R³ is a lower alkyl.

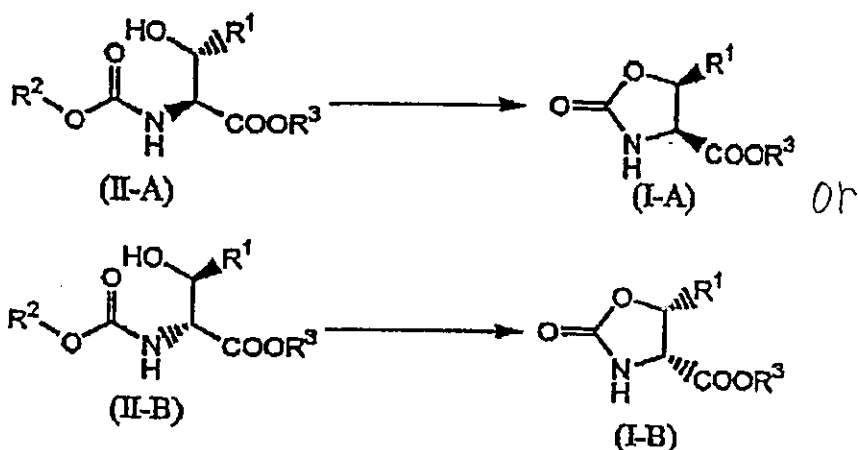
ABSTRACT

TITLE : "PROCESSES FOR THE PREPARATION OF OXO-OXAZOLINE OR
ALLOAMINO ACID DERIVATIVES"

[Problem] A method for producing oxo-oxazoline derivatives
is provided.

[Means for Solving the Problem] A method for producing a
compound represented by a general formula (I-A) or a general
formula (I-B), comprising the following step:

[Chemical Formula 1]



wherein R^1 is an optionally substituted lower alkyl, and the
like; R^2 is a lower alkyl or an optionally substituted aralkyl,
and the like; R^3 is a lower alkyl, characterized in that a compound
represented by a general formula (II-A) or a general
formula (II-B) is treated with thionyl chloride.

[Selected Figure] None