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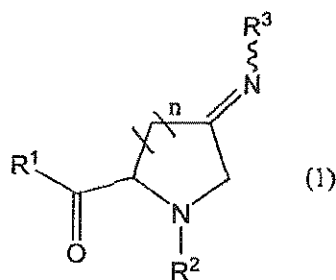
MEANS FOR SOLVING THE PROBLEMS

[0007]

Under the above-described circumstance, as a result of intensive study, the present inventors discovered that it is possible to produce a trans isomer of a cyclic amine compound efficiently by performing a reduction reaction of an imine derivative in the presence of a sulfonic acid, and accomplished the present ~~invention~~ disclosure.

[0008] - [0014]

In one aspect, there is provided a process for producing a cyclic amine compound, comprising the step of reacting an imine derivative represented by the following formula (1):

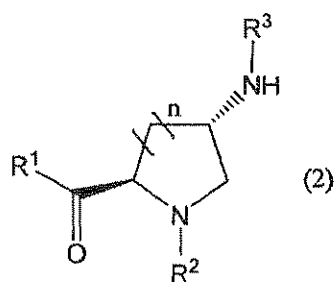


wherein R¹ is

C₁₋₁₂ alkyloxy group, C₂₋₁₂ alkenyloxy group, C₇₋₂₁ aralkyloxy group, C₆₋₁₈ aryloxy group, C₃₋₃₆ trialkylsilyloxy group, amino group, C₁₋₁₂ alkylamino group, C₂₋₁₂ alkenylamino group, C₇₋₂₁ aralkylamino group, C₆₋₁₈ arylamino group, C₂₋₂₄ dialkylamino group, C₄₋₂₄ dialkenylamino group, C₁₄₋₄₂ diaralkylamino group, C₁₂₋₃₆ diarylamino group, thiol group, C₁₋₁₂ alkylthio group, C₂₋₁₂ alkenylthio group, C₇₋₂₁ aralkylthio group, or C₆₋₁₈ arylthio group;
R² is hydrogen atom, C₁₋₁₂ alkyl group, C₂₋₁₂ alkenyl group, C₇₋₂₁ aralkyl group, or C₆₋₁₈ aryl group; R³ is hydrogen atom, C₁₋₁₂ alkyl

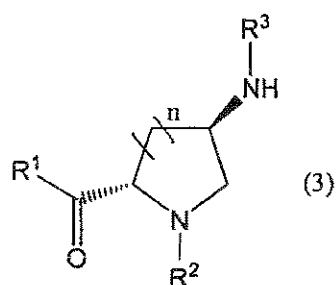
group, C₂₋₁₂ alkenyl group, C₇₋₂₁ aralkyl group, C₆₋₁₈ aryl group, hydroxy group, C₁₋₁₂ alkyloxy group, C₂₋₁₂ alkenyloxy group, C₇₋₂₁ aralkyloxy group, or C₆₋₁₈ aryloxy group; and n is an integer of 1, 2, or 3,

5 with a reducing agent in the presence of a sulfonic acid, wherein the cyclic amine compound is represented by the following formula (2):



wherein R¹, R², R³ and n are the same as the above

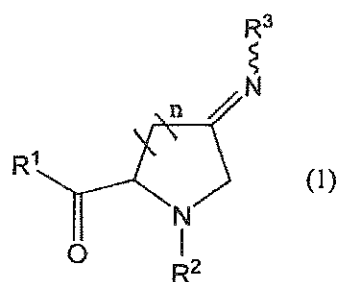
10 or the following formula (3):



wherein R¹, R², R³ and n are the same as the above.

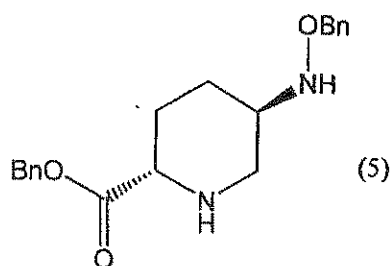
The present ~~invention~~ disclosure relates to a process for producing a cyclic amine compound, comprising the step of reacting an imine derivative represented by the following formula (1):

15



wherein R^1 is an organic group forming an ester bond, an amide bond, or a thioester bond with the carbonyl group binding to R^1 itself; R^2 is hydrogen atom, C_{1-12} alkyl group, C_{2-12} alkenyl group, C_{7-21} aralkyl group, or C_{6-18} aryl group; R^3 is hydrogen atom, C_{1-12} alkyl group, C_{2-12} alkenyl group, C_{7-21} aralkyl group, C_{6-18} aryl group, hydroxy group, C_{1-12} alkyloxy group, C_{2-12} alkenyloxy group, C_{7-21} aralkyloxy group, or C_{6-18} aryloxy group; and n is an integer of 1, 2, or 3, with a reducing agent in the presence of a sulfonic acid, wherein the cyclic amine compound is represented by the

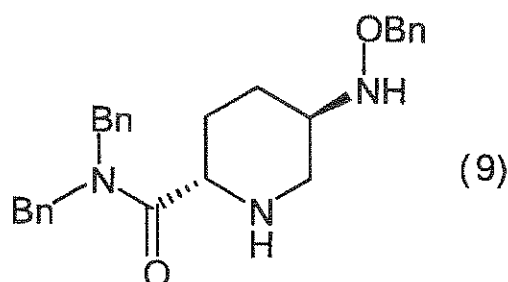
The present ~~invention~~-disclosure includes, for example, a process for producing a trans isomer (50) of 5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester, wherein R^1 is benzyloxy group, R^2 is hydrogen atom, R^3 is benzyloxy group, and n is 2; and more preferably a process for producing (2S,5R)-5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester represented by the following formula (5):



wherein R^1 is benzyloxy group, R^2 is hydrogen atom, R^3 is benzyloxy group, n is 2, and the carbon atom to which the group R^1CO is connected is in the S configuration.

[0019] - [0020]

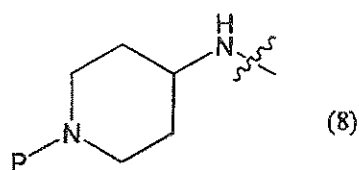
The present ~~invention~~-disclosure also includes a process for producing a trans isomer (90) of 5-benzyloxyamino-piperidine-2-carboxylic acid dibenzylamide, wherein R^1 is dibenzylamino group, R^2 is hydrogen atom, R^3 is benzyloxy group, and n is 2; and more preferably a process for producing (2S,5R)-5-(benzyloxyamino)-piperidine-2-carboxylic acid dibenzylamide represented by the following formula (9):



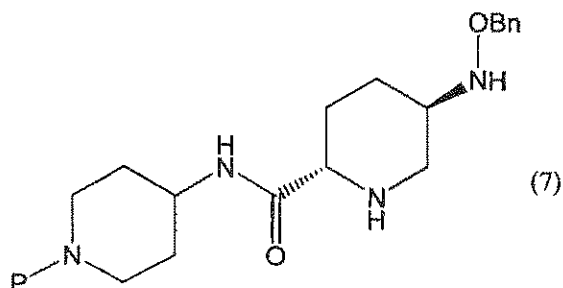
wherein R^1 is dibenzylamino group, R^2 is hydrogen atom, R^3 is benzyloxy group, n is 2, and the carbon atom to which the group R^1CO is connected is in the S configuration.

[0021] - [0025]

5 | The present ~~invention~~-disclosure includes, for example, a process for producing a trans isomer (70) of a 5-(benzyloxyamino)-piperidine-2-carboxylic acid derivative in which R^1 is a group represented by the following formula (8):



10 | wherein P represents a protecting group for the amino group, preferably benzyloxycarbonyl group; R^2 is hydrogen atom; R^3 is benzyloxy group; and n is 2; and more preferably a process for producing a (2*S*,5*R*)-5-(benzyloxyamino)-piperidine-2-carboxylic acid derivative represented by the following formula (7):



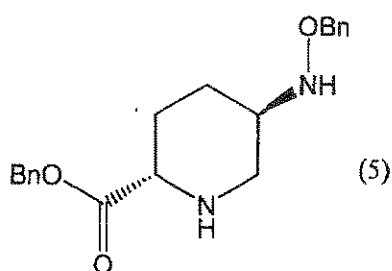
15 | wherein R^1 is a group represented by the previous formula (8), R^2 is hydrogen atom, R^3 is benzyloxy group, n is 2, and the carbon atom to which the group R^1CO is connected is in the S configuration.

[0026] - [0028]

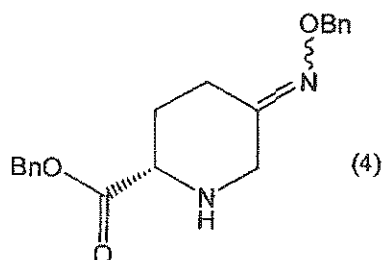
20 | The obtained trans isomer (50) can form a salt with oxalic acid, to precipitate a solid in either one of the solvents selected from methanol, ethanol, isopropanol, a mixed solvent containing

methanol, a mixed solvent containing ethanol, and a mixed solvent containing isopropanol.

Further, the present ~~invention~~-disclosure includes a process for producing a solid of (2S,5R)-5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester oxalate, wherein a salt is formed from (2S,5R)-5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester represented by the following formula (5):



containing (2S,5S)-5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester as an impurity, and oxalic acid, to precipitate a solid in methanol or in a mixed solvent containing methanol. It is possible in the production process of the present ~~invention~~-disclosure to use a compound which is obtained by reacting (S)-5-(benzyloxyimino)-piperidine-2-carboxylic acid benzyl ester represented by the following formula (4):

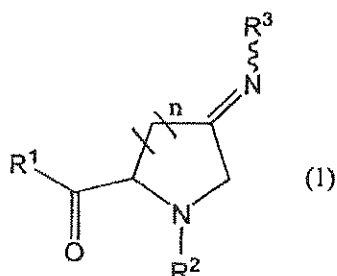


with a reducing agent in the presence of a sulfonic acid, as the compound represented by the above formula (5).

EFFECT OF THE INVENTION

CLAIMS

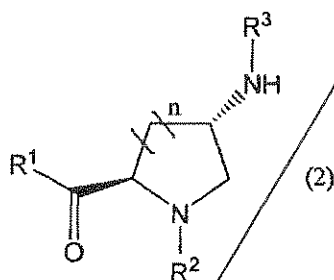
1. A process for producing a cyclic amine compound, comprising the step of reacting an imine derivative represented by the following formula (1):



wherein R¹ is an organic group forming an ester bond, an amide bond, or a thioester bond with the carbonyl group binding to R¹ itself; R² is hydrogen atom, C₁₋₁₂ alkyl group, C₂₋₁₂ alkenyl group, C₇₋₂₁ aralkyl group, or C₆₋₁₈ aryl group; R³ is hydrogen atom, C₁₋₁₂ alkyl group, C₂₋₁₂ alkenyl group, C₇₋₂₁ aralkyl group, C₆₋₁₈ aryl group, hydroxy group, C₁₋₁₂ alkyloxy group, C₂₋₁₂ alkenyloxy group, C₇₋₂₁ aralkyloxy group, or C₆₋₁₈ aryloxy group; and n is an integer of 1, 2, or 3,

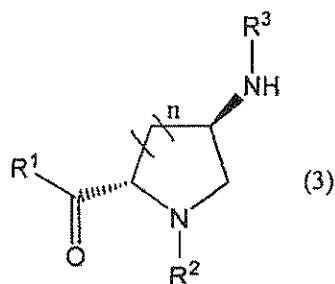
with a reducing agent in the presence of a sulfonic acid,

wherein the cyclic amine compound is represented by the following formula (2):



wherein R¹, R², R³ and n are the same as the above or the reduced form thereof,

or the following formula (3):



wherein R^1 , R^2 , R^3 and n are the same as the above or the reduced form thereof.

2. The process according to claim 1, wherein R^1 is C_{1-12} alkyloxy group, C_{2-12} alkenyloxy group, C_{7-21} aralkyloxy group, C_{6-18} aryloxy group, C_{3-36} trialkylsilyloxy group, amino group, C_{1-12} alkylamino group, C_{2-12} alkenylamino group, C_{7-21} aralkylamino group, C_{6-18} arylamino group, C_{2-24} dialkylamino group, C_{4-24} dialkenylamino group, C_{14-42} diaralkylamino group, C_{12-36} diarylamino group, thiol group, C_{1-12} alkylthio group, C_{2-12} alkenylthio group, C_{7-21} aralkylthio group, or C_{6-18} arylthio group.

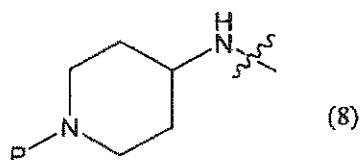
3. The process according to claim 1 or 2, wherein the sulfonic acid is sulfuric acid or camphorsulfonic acid; and the reducing agent is borane.

4. The process according to any one of claims 1 to 3, wherein R^1 is benzyloxy group or dibenzylamino group; R^2 is hydrogen atom; R^3 is benzyloxy group; and n is 2.

5. The process according to claim 4, further comprising the steps of forming a salt of said cyclic amine compound and oxalic acid, and precipitating the salt as a solid in methanol, in ethanol, in isopropanol, in a mixed solvent containing methanol, in a mixed

solvent containing ethanol, or in a mixed solvent containing isopropanol.

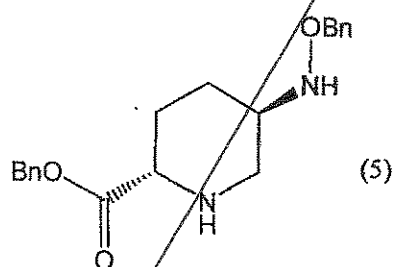
6. The process according to any one of claims 1 to 3, wherein R¹ is a group represented by the following formula (8):



wherein P represents a protecting group for the amino group; R² is hydrogen atom; R³ is benzyloxy group; and n is 2.

7. The process according to claim 6, wherein P is benzyloxycarbonyl group.

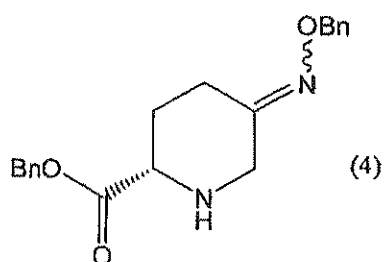
8. A process for producing a solid of (2S,5R)-5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester oxalate, comprising the step of forming a salt in a mole ratio of about 1:1 from (2S,5R)-5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester represented by the following formula (5):



- containing (2S,5S)-5-(benzyloxyamino)-piperidine-2-carboxylic

acid benzyl ester as an impurity and oxalic acid,
to precipitate a solid in methanol or in a mixed solvent containing
methanol.

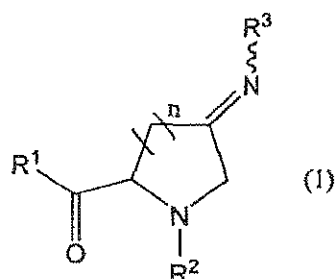
- 5 9. The process according to claim 8, wherein (2S,
5R)-5-(benzyloxyamino)-piperidine-2-carboxylic acid benzyl ester
represented by the above formula (5) is obtained by reacting
(S)-5-(benzyloxyimino)-piperidine-2-carboxylic acid benzyl ester
represented by the following formula (4):



- 10 with a reducing agent in the presence of a sulfonic acid.

CLAIMS

1. A process for producing a cyclic amine compound, comprising the step of reacting an imine derivative represented by the following formula (1):

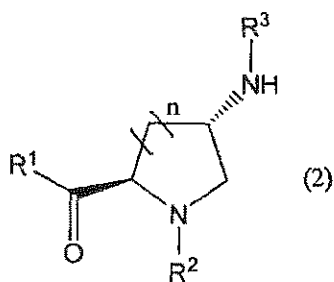


wherein R¹ is

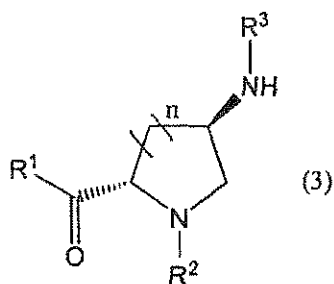
C₁₋₁₂ alkyloxy group, C₂₋₁₂ alkenyloxy group, C₇₋₂₁ aralkyloxy group, C₆₋₁₈ aryloxy group, C₃₋₃₆ trialkylsilyloxy group, amino group, C₁₋₁₂ alkylamino group, C₂₋₁₂ alkenylamino group, C₇₋₂₁ aralkylamino group, C₆₋₁₈ arylamino group, C₂₋₂₄ dialkylamino group, C₄₋₂₄ dialkenylamino group, C₁₄₋₄₂ diaralkylamino group, C₁₂₋₃₆ diarylamino group, thiol group, C₁₋₁₂ alkylthio group, C₂₋₁₂ alkenylthio group, C₇₋₂₁ aralkylthio group, or C₆₋₁₈ arylthio group;

R² is hydrogen atom, C₁₋₁₂ alkyl group, C₂₋₁₂ alkenyl group, C₇₋₂₁ aralkyl group, or C₆₋₁₈ aryl group; R³ is hydrogen atom, C₁₋₁₂ alkyl group, C₂₋₁₂ alkenyl group, C₇₋₂₁ aralkyl group, C₆₋₁₈ aryl group, hydroxy group, C₁₋₁₂ alkyloxy group, C₂₋₁₂ alkenyloxy group, C₇₋₂₁ aralkyloxy group, or C₆₋₁₈ aryloxy group; and n is an integer of 1, 2, or 3,

with a reducing agent in the presence of a sulfonic acid, wherein the cyclic amine compound is represented by the following formula (2):



wherein R^1 , R^2 , R^3 and n are the same as the above
or the following formula (3):



5 wherein R^1 , R^2 , R^3 and n are the same as the above.

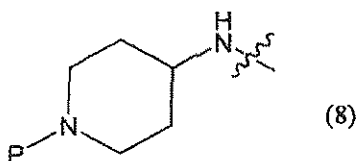
2. The process according to claim 1, wherein the sulfonic acid is sulfuric acid or camphorsulfonic acid; and the reducing agent is borane.

10 3. The process according to claim 1 or 2, wherein R^1 is benzyloxy group; R^2 is hydrogen atom; R^3 is benzyloxy group; and n is 2.

15 4. The process according to claim 3, further comprising the steps of forming a salt of said cyclic amine compound and oxalic acid, and precipitating the salt as a solid in methanol, in ethanol, in isopropanol, in a mixed solvent containing methanol, in a mixed solvent containing ethanol, or in a mixed solvent containing isopropanol.

20

5. The process according to claim 1 or 2, wherein R^1 is a group represented by the following formula (8):



wherein P represents a protecting group for the amino group;

R^2 is hydrogen atom; R^3 is benzyloxy group; and n is 2.

6. The process according to claim 5, wherein P is benzyloxycarbonyl group.

7. The process according to claim 1, wherein the sulfonic acid is any one of sulfuric acid, methanesulfonic acid, trifluoromethanesulfonic acid, ethanesulfonic acid, n-propanesulfonic acid, n-butanesulfonic acid, n-pentanesulfonic acid, n-hexanesulfonic acid, isopropanesulfonic acid, cyclobutanesulfonic acid, cyclopentanesulfonic acid, cyclopropanesulfonic acid, tert-butanesulfonic acid, adamantylsulfonic acid, camphorsulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, p-fluorobenzenesulfonic acid, and 2,4,6-trimethylbenzenesulfonic acid.

8. The process according to claim 1, wherein the reducing agent is any one of lithium aluminum hydride, diisobutyl aluminum hydride, lithium borohydride, sodium borohydride, potassium borohydride, calcium borohydride, sodium cyanoborohydride, sodium triacetoxymethylborohydride, lithium triethylborohydride, lithium

tri(sec-butyl)borohydride, potassium tri(sec-butyl)borohydride, sodium bis(2-methoxy-ethoxy)aluminium hydride, tributyltin hydride, and borane.

5 9. The process according to claim 1, wherein the reducing agent is any one of diborane, borane-tetrahydrofuran complex, borane-dimethylsulfide complex, borane-pyridine complex, borane-picoline complex, and borane-triethylamine complex.

10 10. The process according to claim 1, wherein R^1 is dibenzylamino group; R^2 is hydrogen atom; R^3 is benzyloxy group; and n is 2.