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(54) Title: PROCESS FOR PREPARING ALPHA-AMINO ACIDS AND THEIR DERIVATIVES INCLUDING PHENYLALANINE AND HOMOPHENYLALANINE AND THEIR INTERMEDIATES

(57) Abstract: The invention relates to (D)- or (L)-alpha-amino acids and their derivatives comprising phenylalanine or homophenylalanine having formula (I) or (II) and a process for the preparation thereof by stereoselective synthesis from aziridine having formula (V). The products maintain the stereochemistry of an optically pure aziridine used as starting material, and have many useful applications in industry.



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**PROCESS FOR PREPARING ALPHA-AMINO ACIDS AND THEIR DERIVATIVES
INCLUDING PHENYLALANINE AND HOMOPHENYLALANINE AND THEIR
INTERMEDIATES**

5 **Technical Field**

The invention relates to a process for preparing alpha-amino acids and their derivatives comprising phenylalanine or homophenylalanine, and their intermediates.

Background Art

Alpha-amino acids and their derivatives comprising phenylalanine or
10 homophenylalanine are of value as fine chemicals, particularly as medicaments or their intermediates, and methods of the preparations thereof are well known in the art.

The most commonly used methods of preparation include converting conventional imines into nitriles, and subjecting hydrolysis to produce alpha-amino acid (*cf.* A. Strecker, Justus Liebigs. *Ann. Chem.*, 1850, 75, 27) or hydrogenating N-acyleneamino acid (*cf.* W. S.
15 Knowles, *Acc. Chem. Res.* 1983, 16, 106).

EP No. 132999 discloses a process for producing phenylalanine comprising phenylpyruvic acid or phenylpyruvate in immobilized cells having transaminase activity in the presence of an amine donor, which asymmetrically incorporates an amine into an alpha-keto acid, using an enzyme.

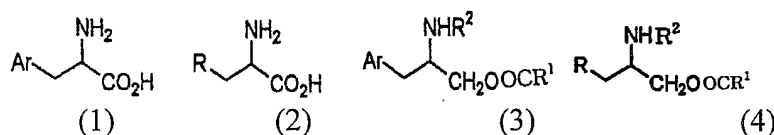
20 This invention relates to a process for producing a variety of optically pure amino acids from optically pure aziridines, which quite differs from conventional methods of preparation.

Disclosure of the Invention

The present invention is directed to a process for producing alpha-amino acids and
25 their derivatives in the optically pure (*D*) or (*L*) form as required, by reacting various compounds with aziridines, while maintaining the optically pure original stereochemistry of the starting material aziridines. The obtained alpha-amino acid and their derivatives *per se* are useful, and are further transformed into other fine chemicals including medicaments and their intermediates.

The present invention is directed to a process for producing various (*D*)- or (*L*)-alpha-amino acids and their derivatives from aziridines via stereoselective synthesis, and their intermediates. (*D*)- or (*L*)-alpha-amino acids and their derivatives contain phenylalanine, in which substituted phenylalanine having several substituents on phenyl group, homophenylalanine or substituted homophenylalanine having several substituents on phenyl group, wherein homophenylalanine contains one more carbon chain than phenylalanine.

An object of the present invention is to provide a substituted phenylalanine of formula (1) and its intermediate of formula (3) used to produce the substituted phenylalanine. Another object of the present invention is to provide homophenylalanine having formula (2) and its intermediates having formula (4) used to produce homophenylalanine.



wherein Ar is selected from a group consisting of phenyl, 4-methoxyphenyl, 2,4-dimethoxyphenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,3,4,5,6-pentafluorophenyl, 4-cyanophenyl, 2-cyanophenyl, 1-naphthyl or 2-naphthyl, preferably Ar is phenyl, 4-methoxyphenyl or 4-fluorophenyl;

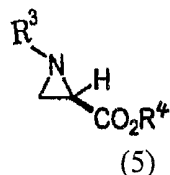
R is selected from a group consisting of alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl, dodecyl; cycloalkyl such as cyclohexyl, cyclopentyl; benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 4-fluorobenzyl or 2,3,4,5,6-pentafluorobenzyl, preferably R is benzyl or n-hexyl;

R¹ is alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl or dodecyl, preferably R¹ is methyl;

R² is alkyl carbamate such as methyl carbamate, ethyl carbamate, n-propyl carbamate, isopropyl carbamate, n-butyl carbamate, isobutyl carbamate; 9-fluoromethylcarbamate (Fmoc); or aryl carbamate such as phenyl carbamate, preferably R² is methyl carbamate, ethyl

carbamate or 9-fluoromethylcarbamate.

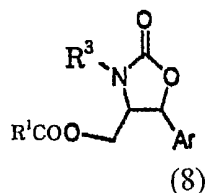
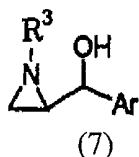
Both formulae (1) and (3) are synthesized via stereoselective reactions from (2R)- or (2S)-[N-R³]aziridine-2-carboxylic acid ethyl ester having formula (5).



wherein R³ is selected from the group consisting of hydrogen; alkyl; cycloalkyl; phenyl; 4-chlorophenyl; 4-methoxyphenyl; 3-triazinyl or pyridinyl acyl; benzyl; hydrocarbon residue which may be substituted with a substituent selected from the group consisting of hydroxy, alkoxy, dialkylamino, phenyl, 4-chlorophenyl and 4-methoxyphenyl; 2,4-dimethoxyphenyl; substituted phenyl such as (1R)-phenylethyl or (1S)-phenylethyl, preferably (1R)-phenylethyl or (1S)-phenylethyl;

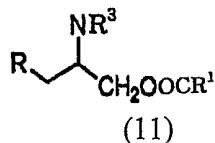
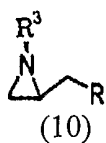
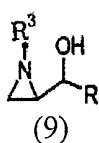
R⁴ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, isoheptyl, n-octyl or isooctyl.

Specifically, one embodiment of the present invention provides compounds having formula (7) or (8) and a process for producing them.



wherein Ar, R¹ and R³ are as defined hereinbefore.

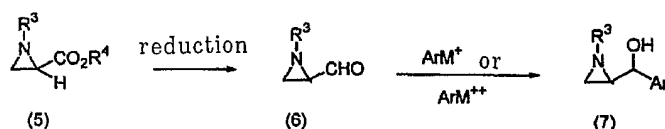
In another embodiment, the present invention provides compounds having formula (9), (10) or (11) and a process for producing them.



wherein R, R¹ and R³ are as defined hereinbefore.

In still another embodiment, the present invention provides a process for producing (*D*)-amino acids of formula (1), which maintain the stereochemistry of starting material, from (2*R*)-[*N*-*R*³]aziridine-2-carboxylic acid ester of formula (5). A compound of formula (3) is produced as intermediate by this process. This process is shown in detail below.

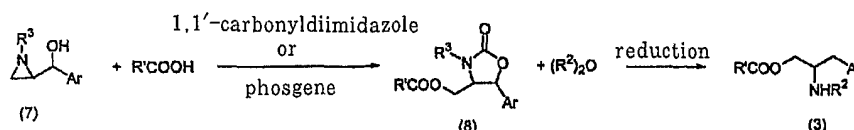
Scheme 1



wherein Ar and *R*³ are as defined hereinbefore, M⁺ is an alkali metal and M⁺⁺ is an alkali earth metal.

As can be seen in Scheme 1, (2*R*)-[*N*-*R*³]aziridine-2-carboxylic acid ester of formula (5) may be reduced to aldehyde of formula (6) by a conventional ester reducing agent. In this step, the used reduction method is a well known process and can be easily adopted by those skilled in the art. Typical reducing agents include lithium aluminum hydride, sodium borohydride, lithium borohydride, calcium borohydride etc. Bouveault-Blanc reaction, which is a reduction using sodium in ethanol, may be used. Further, the ester of formula (5) can be reduced using DIBAL (diisobutyl aluminum hydride) by a known method (Gwon-Il Hwang, *J. Org. Chem.*, 1996, 61, 6183). An aldehyde of formula (6) is produced by this reduction process, and then reacted with aryl alkali metal (ArM⁺) or aryl alkali earth metal (ArM⁺⁺) to produce aminoalcohol of formula (7). Preferred alkali metal is lithium, and preferred alkali earth metal is magnesium.

Scheme 2



wherein Ar, *R*¹, *R*² and *R*³ is as defined hereinbefore.

As can be seen in Scheme 2, a compound of formula (7) obtained from Scheme 1 reacts with $R^1\text{COOH}$ to stereoselectively open the aziridine ring, and reacts with 1,1'-carbonyldiimidazole or phosgene to produce oxazolin-2-one of formula (8).

The resulting compound of formula (8) reacts with $(R^2)_2\text{O}$ under a reducing condition to produce a compound of formula (3). The reducing condition is a conventional hydrogenation reduction, which can be easily adopted by those skilled in the art. Preferred reducing condition is a hydrogenating condition under 1 atmosphere pressure. Typical examples of a compound having formula (3) include 1-acetyloxy-2-*tert*-butoxycarbonylamino-3-arylpropane.

(*D*)-phenylalanine (formula 1) can be provided from formula (3) by known methods. There are several methods for the production, and the present invention uses the following known process for producing amino acid as follows. (*cf.*, Jae-Won Chang, *Tetrahedron Letters*, 1998, 39, 9193).

The compound of formula (3) was dissolved in EtOH. KOH was added to the dissolved solution, and it was stirred at 0°C for 10 minutes. After completing the reaction, water was added to this solution. The solution was extracted twice each with CH_2Cl_2 and the organic extracts were rinsed with water and saturated brine. After distilling this solution under reduced pressure, the residue was dissolved in a mixture solvent consisting of $\text{CCl}_4/\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (1:1:1.5 v:v) and thoroughly stirred. RuCl_3 and NaIO_4 were added to this solution, and it was stirred at ambient temperature for 7 hours. After completing the reaction, water was added to this solution, and the solution was extracted twice with CH_2Cl_2 . The combined organic extracts were rinsed with water and saturated brine. After distilling this solution under reduced pressure, the residue was dissolved in 6N HCl solution and then hydrolyzed by stirring at reflux for 4 hours. Upon using up the reactants, the solution was distilled under reduced pressure, and was recrystallized in acetone to give the desired amino acid phenylalanine.

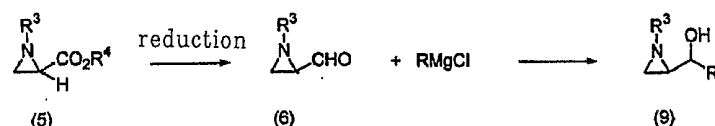
Also, (*L*)-phenylalanine can be effectively synthesized by starting with (2*S*)-compound which has a stereocenter on C-2 of compound of formula (5) and repeating the above steps.

In another embodiment, the present invention provides a process for producing a compound of formula (2) via an intermediate of formula (4) from aziridine having formula (5).

More specifically, the present invention provides a process for producing an optically pure amino acids, maintaining stereochemistry of (2R)- or (2S)-[N-R³]aziridine-2-carboxylic acid ester.

As described above, an aldehyde of formula (6) was produced by reducing (2R)- or (2S)-[N-R³]aziridine-2-carboxylic acid esters having formula (5) using the conventional reducing processes.

Scheme 3



wherein R³ is as defined hereinbefore.

R-hydroxyaziridine of formula (9) was produced by reacting the compound of formula (6) with R-MgCl, wherein R is selected from the group consisting of alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl, dodecyl; cycloalkyl such as cyclohexyl, cyclopentyl; benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl; preferred R is benzyl or n-hexyl.

Scheme 4



wherein R and R³ are as defined hereinbefore.

As can be seen in Scheme 4, R-aziridine of formula (10) was produced by reducing

the hydroxy group of formula (9) as shown in the Scheme 4. This reduction is a conventional process which can be easily chosen and carried out by those skilled in the art. For example, reduction after mesylation can be done. The mesylation is a process preceding reduction of a hydroxy group and is used in substitution and elimination processes.

- 5 Conventionally, those skilled in the art can easily carry out the mesylation using methanesulfonates. The hydroxy group was mesylated and then reduced with a reducing agent by a conventional reduction process. The term "conventional reduction" means a process using a reducing agent such as lithium aluminum hydride, sodium borohydride, lithium borohydride, calcium borohydride, etc. Further, sodium reduction in ethanol may be used. Preferred reducing agents include lithium aluminum hydride.

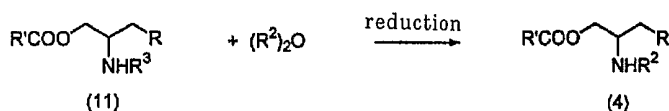
Scheme 5



wherein R, R¹ and R³ are as defined hereinbefore.

As can be seen in Scheme 5, an alkylaziridine of formula (10) was subjected to ring opening with R¹COOH to produce beta-aminoacetyloxyalkane of formula (11).

Scheme 6



wherein R, R¹, R² and R³ are as defined hereinbefore.

As can be seen in Scheme 6, reduction of a compound of formula (11) was carried out in the presence of (R²)₂O to produce a compound of formula (4). A conventional reduction process, for example, reduction with lithium aluminum hydride, may be used.

The amino acid of formula (2) can be produced from the resulting compound of formula (4) by a known process (*cf.* Jae-Won Chang, *Tetrahedron Letters*, 1998, 39, 9193).

Example

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

Example 1

Synthesis of 1-p-methoxyphenyl-[1-((S)-1-phenylethyl)-aziridine-2-yl]methanol

Solution of 4-bromoanisole (1.013 g, 5.42 mmol) in 13.0 ml of THF was cooled to -78 °C, and n-BuLi (1.35 M, 4.00 ml, 5.42 mmol) was added to the solution. After stirring the solution for 30 minutes, aziridine-2-carboxyaldehyde (634 mg, 3.62 mmol) obtained by the reduction of aziridine ester in THF (5.0 ml) was added. The obtained reaction solution was stirred at -78 °C for 3 hours, and then allowed to raise to room temperature. Water (10.0 ml) was added to quench the reaction and separate the solution into an organic solvent phase and an aqueous phase. And then the aqueous phase was extracted with ethyl acetate (10.0 ml x 3). The organic extracts were dried to remove the solvent and purified by silica gel chromatography to give 916 mg of the titled adduct (89%).

¹H NMR(500MHz, CDCl₃) δ 7.35-7.33(m, 5H), 7.01 (d, J=8.8 Hz, 2H), 6.71 (d, J=8.7 Hz, 2H), 4.17(q, J=5.0 Hz, 1H), 3.74 (s, 3H), 2.51 (q, J=6.5 Hz, 1H), 2.38 (s, 3H), 1.76 (m, 1H), 1.53 (d, J=3.4Hz, 1H), 1.45 (d, J=6.5 Hz, 1H).

Example 2

Synthesis of 4-acetyloxymethyl-5-p-methoxyphenyl-3-[(S)-1-phenylethyl]oxazolin -2-one

The compound obtained from Example 1 (821 mg, 2.89 mmol) was dissolved in 14.0 ml of CH₂Cl₂, and then AcOH(0.80 ml, 14.4 mmol) was added to this solution. The solution was stirred at room temperature for 6 hours, and an aqueous saturated NaHCO₃ solution (15 ml) was added to quench the reaction. The solution was separated into an organic phase and an aqueous phase, and the aqueous phase was extracted with CH₂Cl₂ (10.0

ml x 3). The combined organic extracts were dried *in vacuo* to remove the solvent. The residue was subjected to silica gel chromatography to give the major product. The major product was dissolved in 9.2 ml of CH₂Cl₂. CDI (447 mg, 2.76 mmol) was added to the solution, which was then stirred at room temperature for 24 hours. Water (10 ml) was added to quench the reaction, and the solution was separated into an organic phase and an aqueous phase. Then the aqueous phase was extracted with CH₂Cl₂ (10 ml x 3). The combined organic extracts were dried under MgSO₄ *in vacuo* to remove the solvent, and then purified by silica gel chromatography to give cyclic carbamate (613 mg, 90%) as a white solid.

¹H NMR(CDCl₃) δ 7.08(m, 9H), 5.06(q, J=7.2 Hz, 1H), 5.00(d, J=5.1 Hz, 1H), 3.72(m, 1H), 3.62(s, 3H), 3.51(m, 1H), 1.76(s, 3H), 1.51(d, J=7.2 Hz, 3H). mp: 105 °C.

Example 3

Synthesis of 1-acetyloxy-(2S)-tert-butoxycarbonylamino-3-p-methoxyphenyl propane

Part of the solid (233 mg, 0.63 mmol) obtained in Example 2 was dissolved in 4.0 ml of MeOH/CH₂Cl₂ (3/1), and then 30% by weight of catalyst Pd/C based on the reactant, and Boc₂O (275 mg, 2.18 mmol) were added to the solution. The mixture was stirred under 1 atmosphere pressure of hydrogen for 24 hours, and the catalyst was filtered out. After removing the solvent, the residue was purified by chromatography to give 205 mg of 1-acetyloxy-2-tert-butoxycarbonylamino-3-phenylpropane as a white solid.

¹H (300 MHz, CDCl₃) δ 7.02-6.72 (m, 5H), 4.71 (br, 1H), 3.93 (s, 2H), 3.67 (s, 3H), 2.65 (m, 2H), 1.98 (s, 3H), 1.33 (s, 9H). mp: 98 °C

Example 4

Synthesis of 2-phenyl-1-[1-((S)-1-phenylethyl)-aziridine-2-yl]-ethanol

186 mg of activated magnesium was added to 6.0 ml of ethyl ether, and then a small

amount of dibromoethane was added to this solution. While being thoroughly stirred at ambient temperature, 0.72 ml of benzyl bromide was added into this solution for 20 minutes and stirred for 2 more hours. After cooling this solution to -78°C, a solution of (S)-1-[(1S)-phenylethyl]-aziridine-2-carboxyaldehyde (875 mg) in ethyl ether (3.0 ml) was slowly added to this solution, which was further stirred at -78°C for 4 hours. The solution was slowly warmed up to ambient temperature, and 3 ml of saturated ammonium chloride solution was added to the solution. The reaction product was extracted three times each with 5.0 ml of ethyl ether, and the organic extracts were combined. The obtained organic extracts were dried to remove the solvent, purified by silica gel chromatography to give the titled adduct of formula (9) (700 mg).

TLC (EtOAc : n-hexane = 25 : 75), Rf= 0.21.

¹H (300 MHz, CDCl₃) δ : 7.21-7.35 (m, 10H), 3.62 (q, 1H), 2.93 (m, 2H), 2.78 (br, 1H), 2.52 (q, 1H), 1.73 (m, 1H), 1.59 (d, J=6.0Hz, 1H), 1.46 (d, J=11.33 Hz, 3H), 1.30 (d, J=10.67 Hz, 1H).

Example 5

Synthesis of 2-phenyl-1-[1-((S)-1-phenylethyl)-aziridine-2-yl]-ethane

To a solution of 2-phenyl-1-[1-(1-phenylethyl)-aziridine-2-yl]-ethanol (217 mg) in methylene chloride (4.0 ml), 0.17 ml of triethylamine and 0.09 ml of methanesulfonyl chloride were added at 0°C. This mixture solution was stirred for 2 hours and 1.0 ml of water was added to quench the reaction. The reaction product was extracted three times each with 3 ml of methylene chloride, and the organic extracts were combined. Thus obtained organic extracts were rinsed with brine, dried under reduced pressure to remove solvent and then purified by silica gel chromatography to give 196 mg of 2-phenyl-1-[1-(1-phenylethyl)-aziridine-2-yl]-ethylmethanesulfonate.

TLC (EtOAc : n-hexane = 25 : 75), Rf= 0.33.

¹H (500 MHz, CDCl₃) δ : 7.27 (m, 10H), 4.40 (q, 1H), 3.12 (d, J=7.0Hz, 1H),

2.85 (s, 3H), 2.45 (q, 1H), 1.84 (m, 1H), 1.44 (d, $J=3.5$ Hz, 1H), 1.42 (d, $J=8.5$ Hz, 3H), 1.30 (d, $J=7.0$ Hz, 1H).

Thus obtained 2-phenyl-1-[1-(1-phenylethyl)-aziridine-2-yl]-ethylmethane sulfonate (191 mg) was dissolved in 3 ml of ether. 63 mg of LiAlH_4 was added to this solution. The solution was stirred at ambient temperature for 4 hours and 1 ml of water was added to quench the reaction. Then the reaction product was extracted three times each with 5 ml of ether, and the organic extracts were combined. The obtained organic extracts were dried under reduced pressure to remove the solvent, and purified by silica gel chromatography to give the titled product (101 mg).

TLC (EtOAc : n-hexane = 30 : 70), R_f = 0.65.

^1H (500 MHz, CDCl_3) δ : 7.27 (m, 10H), 2.88 (m, 1H), 2.75 (m, 1H), 2.37 (q, 1H), 1.83 (m, 1H), 1.73 (m, 1H), 1.49 (m, 1H), 1.45 (d, $J=3.5$ Hz, 1H), 1.44 (d, $J=6.5$ Hz, 3H), 1.24 (d, $J=6.5$ Hz, 1H).

Example 6

Synthesis of 1-acetyloxy-2-[1-(1-phenylethyl)-amino-2-yl]-4-phenylbutane

To a solution of 2-phenyl-1-[1-(1-phenylethyl)-aziridine-2-yl]-ethane (97 mg) in 2.0 ml of methylene chloride, a solution of acetic acid (0.11 ml) in methylene chloride (1.93 ml) was added. This mixture was stirred for a day. 1 ml of saturated NaHCO_3 solution was added to the mixture. The reaction product was extracted three times each with 2 ml of ethyl acetate, and the organic extracts were combined. Thus obtained organic extracts were dried under reduced pressure to remove the solvent and purified by silica gel chromatography to give titled compound (116 mg).

TLC (EtOAc : n-hexane = 30 : 70), R_f = 0.14.

^1H (500 MHz, CDCl_3) δ : 7.29-7.15 (m, 10H), 4.04 (dd, $J=11$ Hz $J=4.5$ Hz 1H), 3.94 (dd, $J=11$ Hz $J=6$ Hz, 1H), 3.84 (q, $J=6.5$ Hz, 1H) 2.68 (m, 2H) 2.59 (m, 1H) 2.91 (s,

3H), 1.76 (m, 2H), 1.5(br, 1H) 1.31(d, $J=6.0\text{Hz}$ 1H).

Example 7

Synthesis of 1-acetyloxy-2-tert-butoxycarbonylamino-4-phenylbutane

1-acetyloxy-2-[1-(1-phenylethyl)-amino-2-yl]-4-phenylbutane (27 mg) was dissolved in 0.4 ml of methanol. 5 mg of $\text{Pd}(\text{OH})_2$ (10 wt%) and 36 mg of $(\text{Boc})_2\text{O}$ were added to the solution. This mixed solution was stirred for 7 hours, and the catalyst was filtered out. The solution was concentrated *in vacuo*, and purified by chromatography to give the titled compound (26 mg)..

^1H (300 MHz, CDCl_3) δ : 7.31-7.16 (m, 5H), 4.58 (br, 1h), 4.06 (m, 2H), 3.90 (br, 1H), 2.68 (m, 2H), 2.06 (s, 3H), 1.78 (m, 2H), 1.46(s, 9H).

Example 8

Synthesis of 2R-tert-butoxycarbonylamino-1-hydroxy-4-phenylbutane

26 mg of 1-acetyloxy-2-tert-butoxycarbonylamino-4-phenylbutane obtained in Example 7 was dissolved in 0.4 ml of methanol. 22 mg of KOH was added to this solution. The reaction mixture was stirred at 0°C for 30 minutes, and 1 ml of water was added to quench the reaction. The reaction product was extracted three times each with 2 ml of methylene chloride, and the organic extracts were combined. The obtained organic extracts were dried *in vacuo* to remove the solvent, and purified by silica gel chromatography to give 10 mg of the titled product.

^1H (300 MHz, CDCl_3) δ : 7.25-7.11 (m, 5H), 4.75 (br, 1H), 3.65 (m, 3H), 2.74 (m, 2H), 2.69 (br, 1H), 1.84 (m,2H), 1.95 (m, 1H), 1.49 (m, 9H).

Example 9

Synthesis of 1-[1-(1-phenylethyl)-aziridine-2-yl]-1-heptanol

154 mg of activated magnesium and a small amount of dibromoethane were added to

6 ml of ethyl ether. While thoroughly stirring this solution at ambient temperature, 0.8 ml of 1-bromohexane was added for 20 minutes and stirred for 2 more hours. After cooling the solution to 0 °C, a solution of 1-[(1S)-1-phenylethyl]-aziridine-2(S)-carboxyaldehyde (552 mg) in ethyl ether (15 ml) was added slowly, and this solution was stirred at room temperature for 4 more hours. 3 ml of saturated ammonium chloride solution was added. The reaction product was extracted three times each with 5 ml of ethyl ether, and the organic extracts were combined. The obtained organic extracts were dried to remove the solvent and purified by silica gel chromatography to give 700 mg of titled adduct.

TLC (EtOAc : n-hexane = 30 : 70), Rf= 0.44.

¹H (200 MHz, CDCl₃) δ : 8.55 (m, 10H), 4.96 (br, 1H), 4.77 (t, J=6.6 Hz, 1H), 4.70 (br, 1H), 4.25 (br, 1H), 3.76 (q, J=6.3 Hz, 1H), 3.70 (q, J=6.3 Hz, 1H), 2.92-2.40 (m, 30H), 2.07(m, 6H).

Example 10

Synthesis of 1-[1-(1-phenylethyl)-aziridine-2-yl]-hexylmethanesulfonate

To a solution of 1-[1-(1-phenylethyl)-aziridine-2-yl]-1-heptanol (401 mg) in methylene chloride (8.0 ml), 0.43 ml of triethylamine and 0.18 ml of methanesulfonyl chloride were added at 0 °C. The mixed solution was stirred for 2 hours and 3 ml of water was added to quench the reaction. The reaction product was extracted three times each with 3 ml of methylene chloride, and the organic extracts were combined. The obtained extracts were rinsed with brine, dried *in vacuo* to remove the solvent, and purified by silica gel chromatography to give 478 mg of 1-[1-(1-phenylethyl)-aziridine-2-yl]-hexylmethanesulfonate.

TLC (EtOAc : n-hexane = 30 : 70), Rf= 0.56,

¹H (300 MHz, CDCl₃) δ : 7.64 (m, 10H), 4.80 (q, J=6.0Hz, 1H), 4.49 (q, J=6.0 Hz, 1H), 3.54 (s, 3H), 3.43 (s, 1H), 2.89 (q, J=6.6 Hz, 1H), 2.82 (q, J=6.6 Hz, 1H) 2.40 (s, 1H) 2.18 (m, 7H) 2.04 (d, J=2.0 Hz, 1H) 1.81-1.60 (m, 28H) 1.24 (m, 6H).

Example 11**Synthesis of 2-heptyl-1-(1-phenylethyl)-aziridine**

478 mg of 1-[1-(1-phenylethyl)-aziridine-2-yl]-hexylmethanesulfonate was dissolved in 7.0 ml of ether, and 134 mg of LiAlH_4 was added thereto. The solution was stirred at ambient temperature for 4 hours, and 4 ml of water was added to quench the reaction. The reaction product was extracted three times each with 5 ml of ether, and the organic extracts were combined. The obtained organic extracts were dried *in vacuo* to remove the solvent, and purified by silica gel chromatography to give 261 mg of the titled compound.

TLC (EtOAc : n-hexane = 30 : 70), R_f =0.71.

^1H (300 MHz, CDCl_3) δ : 8.03 (m, 5H), 3.04 (q, J =6.6Hz, 1H), 2.15-1.88 (m, 19H), 1.55 (m, 3H).

Example 12**Synthesis of 1-acetoxy-2-((R)-1-phenylethyl)aminononane**

To a solution of [1-(1-phenylethyl)-aziridine-2-yl]-heptane (145 mg) in methylene chloride (3.0 ml), 0.4 ml of acetic acid in 1.0 ml of methylene chloride was added. After stirring for 5 hours, 3 ml of a saturated NaHCO_3 solution was added to the mixture. The reaction product was extracted three times each with 2 ml of methylene chloride, and the organic extracts were combined. The obtained extracts were dried *in vacuo* to remove the solvent, and purified by silica gel chromatography to give 179 mg of the titled compound.

TLC (EtOAc : n-hexane = 30 : 70), R_f = 0.31.

^1H (300 MHz, CDCl_3) δ : 7.23 (m, 5H), 3.94 (dd, J =11 Hz, J =4.2 Hz , 1H), 3.82 (m, 2H), 2.53 (m, 2H), 1.95 (s , 3H), 1.35-1.20 (m , 28H) 0.82 (m, 3H).

Example 13**Synthesis of 1-hydroxy-1-[1-(1-phenylethyl)-aziridine-2-yl]-2-methylpropane**

To a solution cooled to 0°C of 1-[(1S)-1-phenylethyl]-aziridine-2(S)-

carboxyaldehyde (344 mg) in 10.0 ml of ethyl ether, 2 M of isopropylmagnesium chloride ether solution (2.0 ml) was slowly added, and the solution was stirred at room temperature for 4 more hours. Further, 3 ml of saturated ammonium chloride solution was added. The reaction product was extracted three times each with 5 ml of ethyl ether, and the organic
5 extracts were combined. The obtained organic extracts were dried to remove the solvent, and purified by silica gel chromatography to give the titled compound of formula (9) (395 mg).

Physical properties of one isomer

10 TLC (EtOAc : n-hexane = 30 : 70), Rf=0.48.

^1H (500 MHz, CDCl_3) δ : 7.37-7.23 (m, 5H), 3.60 (dd, $J=6.5$ Hz $J=2.5$ Hz 1H), 2.90 (br, 1H), 1.65 (q, $J=6.5$ Hz, 1H), 1.80 (m, 1H), 1.71 (m, $J=6.5$ Hz, 1H) 1.4 (d, $J=4.0$ Hz, 3H), 1.28 (m, 1H), 1.02 (d, $J=7$ Hz, 3H), 0.98(d, $J=7$ Hz, 3H).

Physical properties of the other isomer

15 TLC (EtOAc : n-hexane = 30 : 70), Rf=0.41

^1H (500 MHz, CDCl_3) δ : 7.37-7.24 (m, 5H), 2.91(t, $J=5.5$ Hz, 1H), 2.68 (br, 1H), 2.53 (q, $J=6.5$ Hz, 1H), 1.81 (m, $J=7$ Hz, 1H), 1.73 (m, 1H), 1.67 (d, $J=3.5$ Hz, 1H), 1.45 (d, $J=6.5$ Hz, 3H), 1.40 (d, $J=6.5$ Hz, 1H), 1.05 (d, $J=6$ Hz, 3H), 1.0 (d, $J=7$ Hz, 3H).

20

Example 14

Synthesis of 1-[1-(1-phenylethyl)-aziridine-2-yl]-2-methyl-propylsulfonate

To a solution of 1-hydroxy-1-[1-(1-phenylethyl)-aziridine-2-yl]-2-methyl propane (283 mg) in methylene chloride (4.0 ml), 0.27 ml of triethylamine and 0.15 ml of
25 methanesulfonyl chloride were added at 0°C. This mixed solution was stirred for 2 hours, and 3 ml of water was added to quench the reaction. The reaction product was extracted three times each with 3 ml of methylene chloride, and the organic extracts were combined. The obtained organic extracts were rinsed with brine, dried *in vacuo* to remove the solvent, and purified by silica gel chromatography to give 245 mg of 1-[1-(1-phenylethyl)-aziridine-

2-yl]-2-methyl-propylsulfonate.

TLC (EtOAc : n-hexane = 30 : 70), R_f = 0.65

¹H (300 MHz, CDCl₃) δ : 7.40-7.30 (m, 10H), 4.47 (m, 1H), 4.01 (dd, J=9 Hz, J=5.4 Hz, 1H), 3.23 (s, 3H), 3.16 (s, 3H), 2.60 (q, J=6.5Hz, 1H), 2.53 (q, J=6.5Hz, 1H), 2.22 (m, 2H), 1.91 (m, 3H), 1.74 (d, J=3.3Hz, 1H), 1.47 (m, 6H), 1.14 (m, 9H)

Example 15

Synthesis of 1-[1-(1-phenylethyl)-aziridine-2-yl]-2-methylpropane

235 mg of 1-[1-(1-phenylethyl)-aziridine-2-yl]-2-methyl-propylsulfonate was dissolved in 4 ml of ether, and 90 mg of LiAlH₄ was added thereto. The solution was stirred at ambient temperature for 4 hours, and 3 ml of water was added to quench the reaction. The reaction product was extracted three times each with 3 ml of ether, and the organic extracts were combined. The obtained organic extracts were dried *in vacuo* to remove the solvent, and purified by silica gel chromatography to give 210 mg of the titled compound.

¹H (300 MHz, CDCl₃) δ : 7.30-7.16 (m, 5H), 2.34 (q, J=6.3Hz, 1H), 1.44 (m, 1H), 1.42 (m, 2H), 1.38 (m, 4H), 1.89 (m, 3H), 0.91 (m, 5H).

Example 16

Synthesis of 1-phenyl-[1((S)-1-phenylethyl)-aziridine-2-yl]methanol

A solution of phenyl bromide (0.856 ml, 8.22 mmol) in 13 ml of THF was cooled to -78°C, and n-BuLi (1.6 M, 3.4 ml, 5.48 mmol) was added to the solution. The solution was stirred for 30 minutes, and aziridine-2-carboxyaldehyde (480 mg, 2.74 mmol) which was obtained by reduction of aziridine ester in 5 ml of THF was added. The reaction solution was stirred at -78°C for 3 hours, and warmed up to room temperature. Water (2 ml) was added to this solution to quench the reaction, and the solution was separated into an organic phase and an aqueous phase. The aqueous phase was extracted with ethyl acetate (7 ml x 3). The organic extracts were dried to remove the solvent, and purified by silica gel

chromatography to give the titled adduct (554 mg, 80 %).

^1H NMR(300 MHz, CDCl_3) δ 7.31-7.07(m, 10H), 4.23(d, $J=5.5\text{Hz}$, 1H), 2.52(q, $J=6.6\text{Hz}$, 1H), 2.03(d, $J=3.5\text{Hz}$, 1H), 1.78(td, $J=6.0\text{Hz}$, 3.5Hz 1H), 1.57(d, $J=6.5\text{Hz}$, 1H),
5 1.46(d, $J=6.6\text{Hz}$, 3H).

Example 17

Synthesis of 4-acetyloxymethyl-5-phenyl-3-[(S)-1-phenylethyl]oxazolin-2-one

The compound obtained in Example 16 (729 mg, 2.88 mmol) was dissolved in 14 ml
10 of CH_2Cl_2 . AcOH (0.84 ml, 14.4 mmol) was added to this solution. The solution was stirred at room temperature for 6 hours, and an aqueous saturated NaHCO_3 solution (15 ml) was added to quench the reaction. The solution was separated into an organic phase and an aqueous phase. The aqueous phase was extracted with CH_2Cl_2 (10 ml x 3). The organic
15 extracts were combined and dried *in vacuo* to remove the solvent. The residue was purified by silica gel chromatography to give the major product. The major product was dissolved in 13 ml of CH_2Cl_2 . CDI (849mg, 5.24 mmol) was added to the solution, and stirred at room temperature for 24 hours. Water (10 ml) was added to quench the reaction and the solution was separated into an organic phase and an aqueous phase. The aqueous phase was
20 extracted with CH_2Cl_2 (10 ml x 3). The combined organic extracts were dried under MgSO_4 *in vacuo* to remove the solvent, and purified by silica gel chromatography to give cyclic carbamate (845 mg, 85%) as a white solid.

^1H NMR(500 MHz, CDCl_3) δ 7.42-7.26(m, 10H), 5.23(q, $J=7.0\text{Hz}$, 1H), 5.20(d, $J=5.0\text{Hz}$, 1H), 3.83(m, 1H), 3.77(dd, $J=12\text{Hz}$, 3.5Hz, 1H), 3.66(dd, $J=12\text{Hz}$, 6Hz, 1H), 1.93(s,
25 3H), 1.63(d, $J=7.5\text{Hz}$, 3H). mp: 91-92°C.

Example 18

Synthesis of 1-acetyloxy-(2S)-tert-butoxycarbonylamino-2-phenylpropane

Part of the obtained solid (428 mg, 1.26 mmol) was dissolved in 6.3 ml of

MeOH/CH₂Cl₂ (3/1), 30 % by weight of catalyst Pd/C based on the reactant and Boc₂O (825 mg, 3.78 mmol) were added to the solution. The mixture was stirred at 1 atm of hydrogen for 24 hours and the catalyst was filtered. After removing the solvent, the residue was purified by chromatography to give 1-acetyloxy-2-tert-butoxycarbonylamino-3-phenylpropane (446 mg) as a gray solid.

¹H NMR(300 MHz, CDCl₃) δ 7.32-7.17(m, 5H), 4.67(br, 1H), 4.03(m, 3H), 2.79(m, 2H), 2.08(s, 3H), 1.41(s, 9H). mp: 82 °C

Example 19

Synthesis of 1-p-fluorophenyl-[1((S)-1-phenylethyl)-aziridine-2-yl]methanol

A solution of 1-bromo-4-fluorobenzene (368 mg, 2.10 mmol) in 10 ml of THF was cooled to -78 °C, and n-BuLi (1.6 M, 1.25 ml, 2.00 mmol) was added to the solution. The solution was stirred for 30 minutes, and aziridine-2-carboxyaldehyde(175 mg, 1.00 mmol) obtained by reduction of aziridine ester in 5 ml of THF was added to the solution. The reaction solution was stirred at -78 °C for 3 hours, and warmed up to room temperature. Water (2 ml) was added to quench the reaction and the solution was separated into an organic phase and an aqueous phase. The aqueous phase was extracted with ethyl acetate (3 ml x 3). The combined organic extracts were dried to remove the solvent and purified by silica gel chromatography to give the titled adduct (208 mg, 77 %).

¹H NMR(200 MHz, CDCl₃) δ 7.29-6.90(m, 9H), 4.24(d, J=4.9Hz, 1H), 2.51(q, J=6.5Hz, 1H), 2.00(d, J=3.5Hz, 1H), 1.75(ddd, J=6.0Hz, 4.9, 3.5Hz 1H), 1.56(d, J=6.5Hz, 1H), 1.46(d, J=6.6Hz, 3H).

Example 20

Synthesis of 4-acetyloxymethyl-5-p-fluorophenyl-3-[(S)-1-phenylethyl] oxazolin-2-one

The compound obtained in Example 19 (782 mg, 2.88 mmol) was dissolved in 14 ml

of CH_2Cl_2 , and AcOH (0.82 mL, 14.4 mmol) was added to this solution. The solution was stirred at room temperature for 6 hours, and an aqueous saturated NaHCO_3 solution (15 mL) was added to quench the reaction. The solution was separated into an organic phase and an aqueous phase. The aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried *in vacuo* to remove solvent. The major product was obtained by silica gel chromatography, and dissolved in 13 mL of CH_2Cl_2 . CDI (840 mg, 5.18 mmol) was added to the solution and stirred at room temperature for 24 hours. Water (10 mL) was added to quench the reaction, and the solution was separated into an organic phase and an aqueous phase. The aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried (MgSO_4) *in vacuo* to remove the solvent, and purified by silica gel chromatography to give cyclic carbamate (842 mg, 81%) as a white solid.

^1H NMR(500 MHz, CDCl_3) δ 7.42-7.06(m, 10H), 5.21(q, $J=7.0\text{Hz}$, 1H), 5.18(d, $J=2\text{Hz}$, 1H), 3.81(m, 1H), 3.77(dd, $J=9\text{Hz}$, 3H, 1H), 3.67(dd, $J=12\text{Hz}$, 5.5Hz, 1H), 1.94(s, 3H), 1.65(d, $J=7.5\text{Hz}$, 3H), mp: 127°C.

Example 21

Synthesis of 1-acetyloxy-(2S)-tert-butoxycarbonylamino-3-p-fluoropropane

Part of the obtained solids (121 mg, 0.34 mmol) was dissolved in 1.7 mL of MeOH/ CH_2Cl_2 (3/1), 30 % by weight of catalyst Pd/C based on the reactant and subsequently Boc_2O (222 mg, 1.01 mmol) were added to this solution. The mixture was stirred at 1 atm of hydrogen for 24 hours, and the catalyst was filtered out. After removing the solvent, the residue was purified by chromatography to give 1-acetyloxy-2-tert-butoxycarbonylamino-3-phenylpropane (97 mg) as a gray solid.

^1H NMR(300 MHz, CDCl_3) δ 7.17-7.12(m, 4H), 4.70(br, 1H), 4.03(m, 3H), 2.77(m, 2H), 2.08(s, 3H), 1.41(s, 9H). mp: 80°C

The present invention is directed to a process for producing alpha-amino acids and their derivatives in optically pure (*D*) or (*L*) forms, by reacting various compounds with aziridines, while maintaining the optically pure original stereochemistry of the starting material aziridines. The obtained alpha-amino acids and their derivatives *per se* are useful,
5 and can be transformed into fine chemicals including medicines and their intermediates.

Claims:

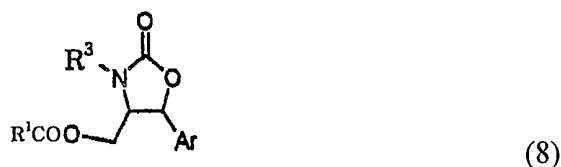
1. A compound having formula (7) :



wherein R³ is selected from a group consisting of hydrogen; alkyl; cycloalkyl; phenyl; 4-chlorophenyl; 4-methoxyphenyl; 3-triazinyl or pyridinyl acyl; benzyl; hydrocarbon residue which may be substituted by a substituent selected from a group consisting of hydroxy, alkoxy, dialkylamino, phenyl, 4-chlorophenyl, 4-methoxyphenyl; 2,4-dimethoxyphenyl; substituted phenyl including (1R)-phenylethyl or (1S)-phenylethyl, and

Ar is phenyl, 4-methoxyphenyl, 2,4-dimethoxyphenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,3,4,5,6-pentafluorophenyl, 4-cyanophenyl, 2-cyanophenyl, 1-naphthyl or 2-naphthyl.

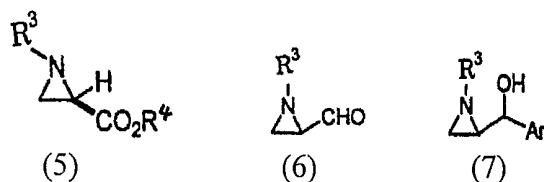
2. A compound having formula (8) :



wherein Ar and R³ are as defined in Claim 1,

R¹ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl or dodecyl.

3. A process for producing an alcohol having formula (7), comprising reducing (2R)- or (2S)-[N-R³]aziridine-2-carboxylic acid ester of formula (5) to aldehyde of formula (6), and adding aryl alkali metal (ArM⁺) or aryl alkali earth metal (ArM⁺⁺) thereto :



wherein Ar and R³ is as defined in Claim 1.

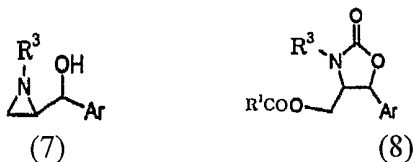
R⁴ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, isoheptyl, n-octyl or isooctyl,

M⁺ is alkali metal, and

M⁺⁺ is alkali earth metal.

4. The process according to Claim 3, wherein Ar is phenyl, 4-methoxyphenyl or 4-fluorophenyl, and R³ is (1R)-phenylethyl or (1S)-phenylethyl, M⁺ is lithium, and M⁺⁺ is magnesium.

5. A process for producing an oxazolin-2-one of formula (8), comprising reacting a compound of formula (7) with R¹COOH, and then with 1,1-carbonyldiimidazol or phosgene :



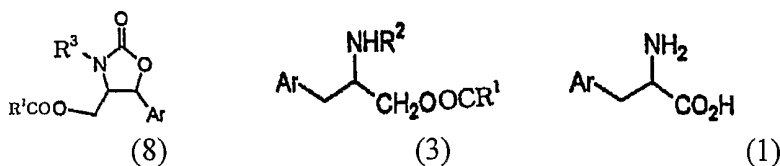
wherein Ar and R³ are defined as in Claim 1, and R¹ is defined as in Claim 2.

6. The process according to Claim 5, wherein Ar is phenyl, 4-methoxyphenyl or 4-fluorophenyl, R¹ is methyl, and R³ is (1R)-phenylethyl or (1S)-phenylethyl.

7. A process for producing (*D*)- or (*L*)-amino acids and their derivatives including phenylalanine or homophenylalanine by stereoselective synthesis, comprising the steps of:

(a) reducing an oxazolin-2-one of formula (8) in the presence of (R²)₂O to produce a compound of formula (3); and

(b) producing (*D*)- or (*L*)-amino acids of formula (1) from the compound of formula (3) :



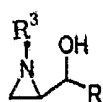
wherein Ar and R³ are as defined in Claim 1,

R¹ is as defined in Claim 2, and

R^2 is alkyl carbamate such as methyl carbamate, ethyl carbamate, n-propyl carbamate, isopropyl carbamate, n-butyl carbamate, isobutyl carbamate; 9-fluoromethylcarbamate(Fmoc); or aryl carbamate such as phenyl carbamate.

8. The process according to Claim 7, wherein Ar is phenyl, 4-methoxyphenyl or 4-fluorophenyl, R^1 is methyl, R^2 is methyl carbamate, ethyl carbamate or 9-fluoromethylcarbamate (Fmoc), and R^3 is (1R)-phenylethyl or (1S)-phenylethyl.

9. A compound having formula (9) :

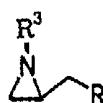


(9)

wherein R is alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl, dodecyl; cycloalkyl such as cyclohexyl or cyclopentyl; benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 4-fluorobenzyl or 2,3,4,5,6-pentafluorobenzyl,

R^3 is selected from a group consisting of hydrogen; alkyl; cycloalkyl; phenyl; 4-chlorophenyl; 4-methoxyphenyl; 3-triazinyl or pyridinyl acyl; benzyl; hydrocarbon residue which may be substituted by a substituent selected from a group consisting of hydroxy, alkoxy, dialkylamino, phenyl, 4-chlorophenyl, 4-methoxyphenyl; 2,4-dimethoxyphenyl; and substituted phenyl including (1R)-phenylethyl or (1S)-phenylethyl.

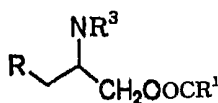
10. A compound having formula (10) :



(10)

wherein R and R^3 are as defined in Claim 9.

11. A compound having formula (11) :

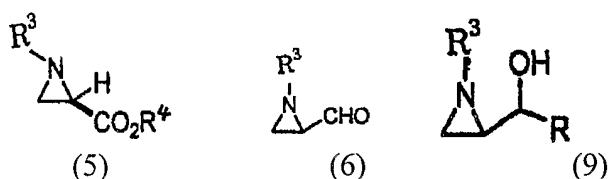


(11)

wherein R and R^3 are as defined in Claim 9,

R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl or dodecyl.

12. A process for producing R-hydroxyaziridine of formula (9), comprising reducing (2R)- or (2S)-[N- R^3]aziridine-2-carboxylic acid esters of formula (5) to a compound of formula (6), and reacting the compound of formula (6) with R-MgCl :



wherein R and R^3 are as defined in Claim 9, and

R^4 is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, isoheptyl, n-octyl or isooctyl.

13. The process according to Claim 12, wherein R is benzyl or n-hexyl, and R^3 is (1R)-phenylethyl or (1S)-phenylethyl.

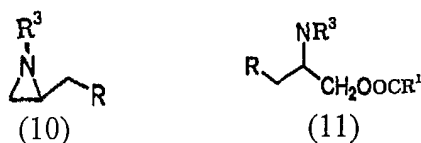
14. A process for producing R-aziridine of formula (10), comprising reducing R-hydroxy functional group of formula (9) :



wherein R and R^3 are as defined in Claim 9.

15. The process according to Claim 14, wherein R is benzyl or n-hexyl, and R^3 is (1R)-phenylethyl or (1S)-phenylethyl.

16. A process for producing beta-amino alcohol derivatives of formula (11), comprising reacting R-aziridine of formula (10) with $R^1\text{COOH}$:



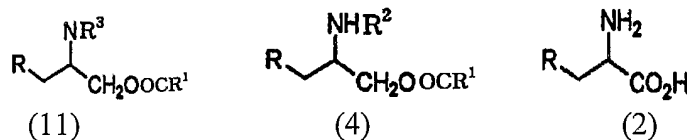
wherein R and R³ are as defined in claim 9, R¹ is as defined in Claim 1.

17. The process according to Claim 16, R is benzyl or n-hexyl, R¹ is methyl, and R³ is (1R)-phenylethyl or (1S)-phenylethyl.

18. A process for producing (*D*)- or (*L*)-alpha-amino acids and their derivatives including phenylalanine or homophenylalanine by stereoselective synthesis, comprising the steps of:

(a) reducing beta-amino alcohol derivatives of formula (11) in the presence of (R²)₂O to produce a compound of formula (4); and

(b) producing (*D*)- or (*L*)-amino acids of formula (2) from a compound of formula (4) :



wherein R and R³ are as defined in Claim 9,

R¹ is as defined in Claim 11, and

R² is alkyl carbamate such as methyl carbamate, ethyl carbamate, n-propyl carbamate, isopropyl carbamate, isopropyl carbamate, n-butyl carbamate, isobutyl carbamate; 9-fluoromethylcarbamate(Fmoc); or aryl carbamate such as phenyl carbamate.

19. The process according to Claim 18, wherein R is benzyl or n-hexyl, R¹ is methyl, R² is methyl carbamate, ethyl carbamate or 9-fluoromethylcarbamate (Fmoc), and R³ is (1R)-phenylethyl or (1S)-phenylethyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/01361

A. CLASSIFICATION OF SUBJECT MATTER		
IPC7 C07D 203/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) Korean Patents and applications for inventions since 1975 Korean Utility models and applications for utility models since 1975		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP.A 1989-228946호 [Santori co,LTD], 12 Sep 1989 see the whole document	2
A	JP.A 1992-293928호, 19 Oct 1992 see the whole document	1, 3 - 8
A	EP 0,736,509.A2, 09 Oct 1996 see the whole document	1, 3 - 8
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR01/01361

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