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(54) **METHOD OF ENANTIOSELECTIVE NUCLEOPHILIC ADDITION REACTION OF AN ENAMIDE TO A GLYOXYLIC ACID ESTER**

VERFAHREN EINER ENANTIOSELEKTIVEN NUKLEOPHILEN ADDITION EINES ENAMIDS AN EINEN GLYOXYLSÄUREESTER

PROCEDE D'ADDITION NUCLEOPHILE ENANTIOSELECTIVE D'UN ENAMIDE A UN ESTER D'ACIDE GLYOXYLIQUE

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Description

Technical Field

[0001] The present invention relates to a method of an enantioselective nucleophilic addition reaction of enamide to a carbonyl group which enables an asymmetric synthesis of an optically active compound which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like and, as an application thereof, a synthesis method of an optically active α-hydroxy-γ-keto acid ester, hydroxydiketone or the like.

Background Art

[0002] Conventionally, a method of a nucleophilic addition reaction to an aldehyde group of an aldehyde compound or an imino group of an imine compound derived from the aldehyde compound has been studied and, in recent years, this nucleophilic addition reaction has drawn attention as a measure for efficiently and asymmetrically synthesizing an amino acid derivative, a hydroxycarboxylic acid or the like as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like.

[0003] Under these circumstances, the present inventors have developed and disclosed a method for synthesizing an N-acylated amino acid derivative by a nucleophilic addition reaction to an N-acylimino ester compound by using a polymer-carrying catalyst (Journal of Combinatorial Chemistry, 2001, Vol. 3, No. 5, 401 to 403) and, further, a method for enantioselectively synthesizing these compounds by using a chiral copper catalyst (Org. Lett. Vol. 4, No. 1, 2002, 143 to 145; J. Am. Chem. Soc. Vol. 125, No. 9, 2003, 2507 to 2515).

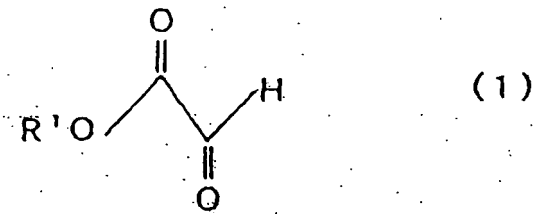
[0004] However, the nucleophilic addition reaction on which the present inventors have studied is limited to such nucleophilic reactants as a silyl enol ether and an alkyl vinyl ether and, accordingly, a subject to which the nucleophilic addition reaction is applied and such application thereof have inevitably been restricted.

[0005] J. Organic Chemistry, vol. 63, No. 22, 9 October 1998, pp. 7764-7769 relates to the chemoenzymatic synthesis of 4-amino-2-hydroxy acids. Organic Letters, vol. 4, No. 20, 7 September 2002, pp. 3379-3382 describes a method for the enantioselective synthesis of pantolactone derivatives.

[0006] Then, under these circumstances, the present invention has an object of providing a method of an enantioselective nucleophilic addition reaction to a carbonyl group which enables an asymmetric synthesis of an α-hydroxyγ-keto acid compound, an α-hydroxy-γ-amino acid compound or the like which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like and, further, as an application thereof, a novel synthesis method of the α-hydroxy-γ-keto acid ester or the like.

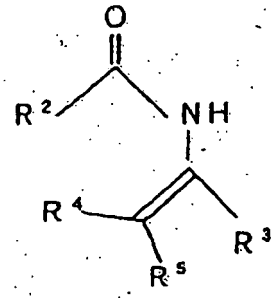
Disclosure of Invention

[0007] In order to solve these problems, according to a first aspect of the present invention, there is provided a method of an enantioselective nucleophilic addition reaction of enamide, characterised by being a method of a nucleophilic addition reaction of an enamide compound accompanied by generation of a hydroxyl group (-OH) to a carbonyl group, performed on a compound having a carbonyl group which is a glyoxylic acid ester represented by the following formula (1):



(1)

wherein R^1 represents a hydrocarbon group which may have a substituent;
and wherein said enamide compound is represented by the following formula (2):

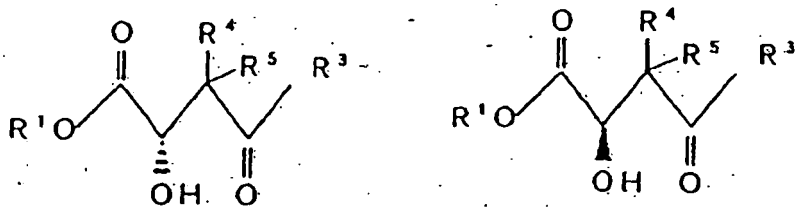


(2)

wherein R^2 represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom;
R^3 represents a hydrocarbon group which may have a substituent;
R^4 and R^5 may be same with or different from each other and each represent
a hydrogen atom or a hydrocarbon group which may have a substituent, wherein at least one of them represents a hydrogen atom;
and performing the reaction in the presence of a chiral catalyst comprising copper or nickel.

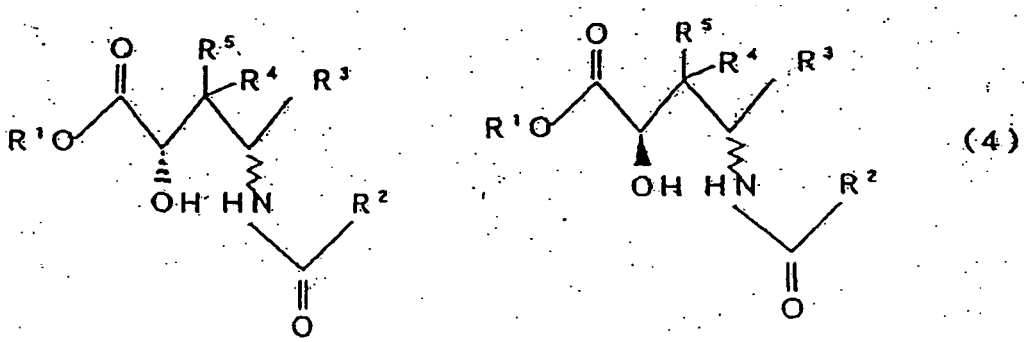
[0008] Then, with reference to the above-described method, according to a second aspect of the invention, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the chiral catalyst is constituted by a copper compound or a nickel compound which is a salt of an organic or inorganic acid or a complex or composite of the salt, and a chiral diamine ligand and, according to a third aspect of the invention, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the chiral diamine ligand has an ethylene diamine structure as a portion thereof.

[0009] According to a fourth aspect of the invention, there is provided a method for synthesizing an optically active α-hydroxy-γ-keto acid ester which is characterized in that, after the above-described nucleophilic addition reaction, an acid treatment is performed, to thereby generate a compound represented by at least one of the following formulae (3):



(3)

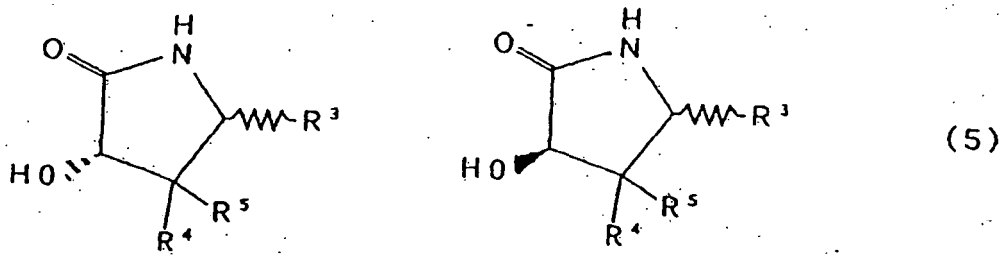
wherein R^1, R^3, R^4 and R^5 are each as defined above, and, according to a fifth aspect of the invention, there is provided a method for synthesizing an optically active α-hydroxy-γ-amino acid ester which is characterized in that, after the above-described nucleophilic addition reaction, a reduction treatment is performed, to thereby generate a compound represented by at least one of the following formulae (4):



(4)

wherein R^1, R^2, R^3, R^4 and R^5 are each as defined above, and, further, according to a sixth aspect of the invention, there is provided a method for synthesizing optically active α-hydroxy-γ-lactams which is characterized in that an optimally active α-hydroxy-γ-amino acid ester is synthesized by the method of the fifth aspect above, a substituent (R^2 CO-) on a γ-amino group of the thus-synthesized optically active α-hydroxy-γ-amino acid ester is removed, and thereafter a cyclization reaction is performed, to thereby generate a compound represented by at least one of the following formulae

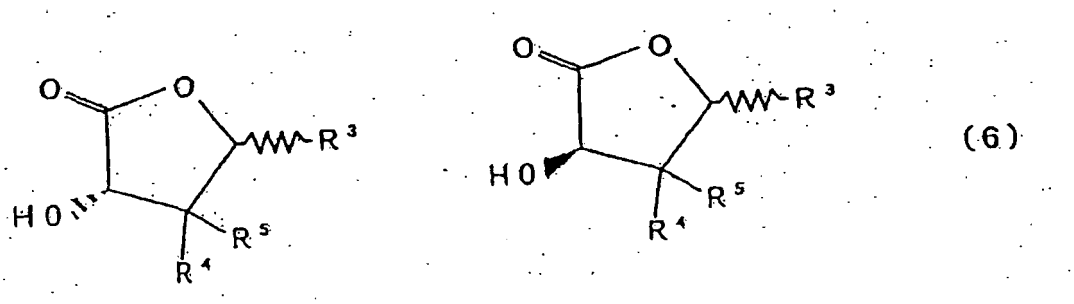
(5):



(5)

wherein R^3, R^4 and R^5 are each as defined above.

[0010] Still further, according to a seventh aspect of the invention, there is provided a method for synthesizing any one of optically active α-hydroxy-γ-lactones which is characterized in that the optically active α-hydroxy-γ-keto acid ester is synthesized by the above-described fourth aspect of the invention, and the optically active α-hydroxy-γ-keto acid ester is subjected to a reduction reaction and, subsequently, to a cyclization reaction, to thereby generate a compound represented by at least one of the following formulae (6):



(6)

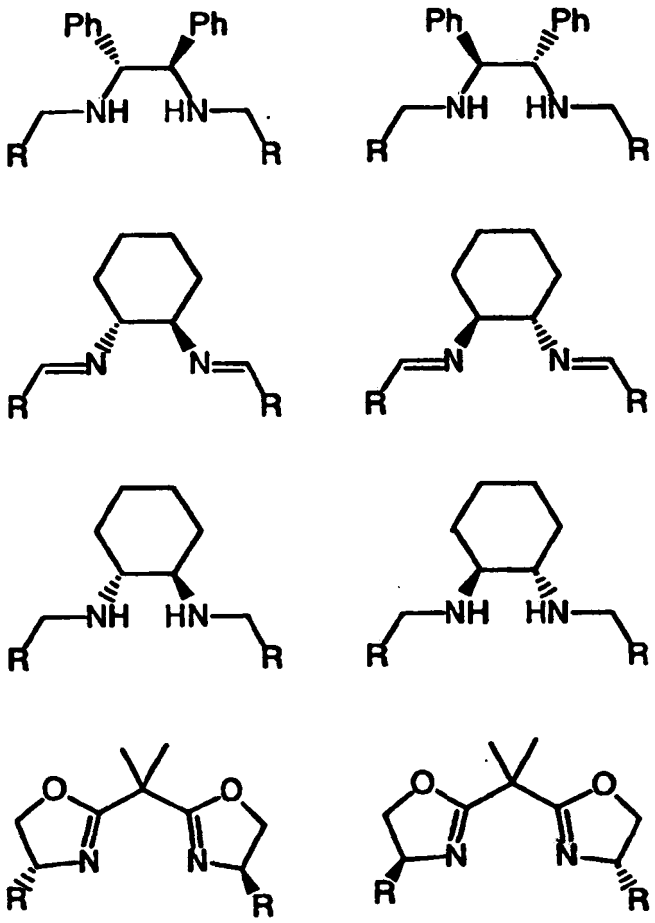
wherein R^3, R^4 and R^5 are each as defined above.

Best Mode for Carrying Out the Invention

[0011] The present invention has characteristics as described above and is, further, described with reference to embodiments thereof.

[0012] In a method of an enantioselective nucleophilic addition reaction of enamide to a carbonyl group according to the invention, a chiral copper catalyst or a chiral nickel catalyst is used as a catalyst. As for the chiral catalyst on this occasion, various types of such chiral catalysts in each of which a copper (Cu) or nickel (Ni) atom is indispensable for a constitution thereof and to each of which a chiral organic molecular structure is attached are considered. Ordinarily, the chiral catalyst is constituted by a copper compound or nickel compound and a chiral organic compound and, more practically, from the standpoint of reaction yield and enantioselectivity, the chiral catalyst constituted by a copper compound or nickel compound and a chiral diamine ligand compound is favorably considered. The copper compound or nickel compound may be selected from among various types of salts, complex salts, organic metal compounds and the like as a monovalent or bivalent compound and, among other things, a salt with an organic or inorganic acid, a complex or organic composite of the salt is favorably mentioned. Among these compounds, a salt with a strong acid, for example, a salt of (per)fluoroalkyl sulfonic acid, perchloric acid or sulfonic acid, a complex or an organic composite of the salt is favorably illustrated. For example, $Cu(OTf)_2$, $CuClO_4$, $CuClO_4 \cdot 4CH_3CN$, Cu(ClO4)2·$6H_2O$, $Ni(OTf)_2$, and NiX_2+AgOTf (X being a halogen atom) are mentioned.

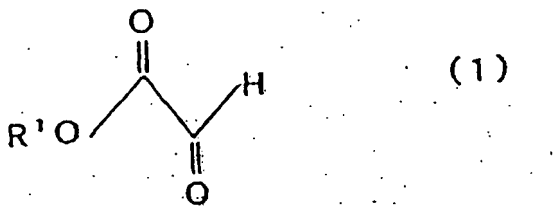
[0013] As for the chiral diamine ligand as a counterpart, an article having an ethylene diamine structure in a molecular constitution as a portion thereof is favorably used. On this occasion, an amino group may contain an imine bond. For example, as representatives, various types represented by the following formulae are illustrated:



[0014] On this occasion, R in the formulae represents a hydrocarbon group which may have a substituent. The hydrocarbon group may be any one of various types in a chain state or a cyclic state and may have, as a substituent, a halogen atom, a hydrocarbon group of an alkyl group or the like, an alkoxy group or the like. Further, Ph (phenyl group) and a cyclohexyl group in the formulae may each have a substituent.

[0015] With reference to the chiral catalyst containing copper or nickel as described above according to the invention, a complex may previously be prepared by using a copper compound or a nickel compound and a chiral organic molecule and, then, used as a catalyst, or the copper compound or the nickel compound and the chiral organic molecule may be mixed with each other in a reaction system and, then, used. As far as a ratio in use as a catalyst is concerned, the copper compound or nickel compound or the complex of the copper compound or nickel compound and the chiral organic molecule is used at a rate of ordinarily from about 0.5 to about 30 % by mol against the carbonyl compound.

[0016] The carbonyl compound to be used in the reaction is a glyoxylic acid ester represented by the following formula (1):



wherein R^1 represents a hydrocarbon group which may have a substituent.

[0017] As for the compound having a carbonyl group, a glyoxylic acid ester represented by the formula (1) is illustrated. This article has an ester bond portion and reference mark R^1 in the formula represents a hydrocarbon group which may have a substituent. The hydrocarbon group may be any one of various types of hydrocarbon groups, for example, a chain or an alicyclic hydrocarbon group, an aromatic hydrocarbon group and mixtures thereof. As for such substituents, so long as they do not interfere with the nucleophilic addition reaction, the hydrocarbon group may appropriately have

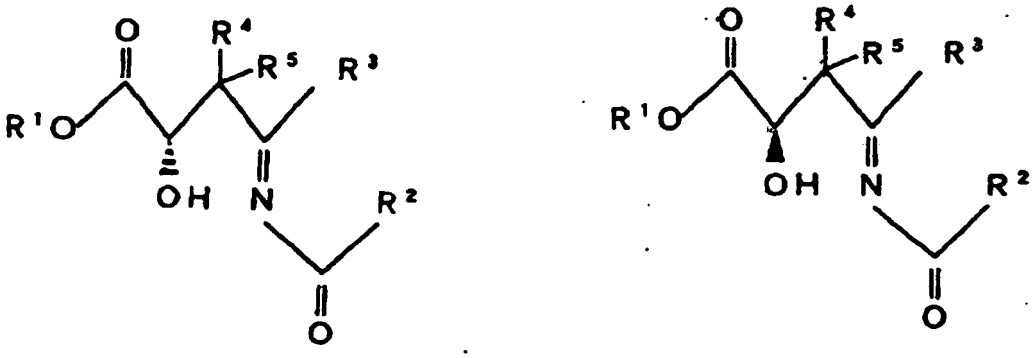
any one of various types of substituents such as a hydrocarbon group such as an alkyl group, an alkoxy group, a sulfide group, a cyano group, a nitro group, and an ester group.

[0018] The enamide compound as a counterpart, is represented by the above-described formula (2). As for characteristics thereof, it has an amide bond or a carbamate bond. As for reference marks in the formula, R^2 represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom; R^3 represents a hydrocarbon group which may have a substituent; and R^4 and R^5 may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon group which may have a substituent, in which at least one of them represents a hydrogen atom.

[0019] The hydrocarbon group may be any one of various types of hydrocarbon groups in a same manner as described above, for example, an aliphatic hydrocarbon group, an alicyclic hydrocarbon group, an aromatic hydrocarbon group and mixtures thereof. As for such substituents, various types of substituents such as a hydrocarbon group such as an alkyl group, a halogen atom, an alkoxy group, a sulfide group, a cyano group, a nitro group, and an ester group are appropriately be considered.

[0020] Further, as for reference mark R^2, a hydrocarbon group which is bonded via an oxygen atom such as -OEt, -O^{t}Bu, or -OBn is appropriately illustrated. As for reference mark R^3, an article having a substituent such as a phenyl group, a naphthyl group, or any one of these groups each having a substituent such as a halogen atom, an alkyl group, or an alkoxy group is favorably illustrated. In the nucleophilic addition reaction of the enamide compound to the aldehyde group (-CHO) of the glyoxylic acid ester, an appropriate organic solvent, for example, a halogenated hydrocarbon, any one of nitriles such as acetonitrile, or any one of ethers such as THF may be used and, in a reaction temperature, a range of from about -20°C to about 40°C can appropriately be adopted. A ratio of the aldehyde compound to the enamide compound to be used in an atmosphere of the air or in an inert atmosphere can appropriately be set to be in the range of from about 0.1 to about 10 in terms of a molar ratio.

[0021] In the nucleophilic addition reaction of the enamide compound, when a reaction between the glyoxylic acid ester represented by the above-described formula (1) and the enamide compound represented by the above-described formula (2) is taken as an example, an optically active α-hydroxy-γ-imino acid ester represented by at least one of the following formulae is enantioselectively generated:



[0022] Then, particularly, when enecarbamate is used as a type of the enamide compound, a high stereoselectivity can also be realized. A syn-adduct and an anti-adduct can be obtained from a Z-body and an E-body at high diastereoselectivity and high enantioselectivity, respectively. By either without isolating or isolating the above-described imino acid ester compound, an acid treatment, for example, an acid treatment by using an aqueous solution of HCl, HBr or the like is performed, to thereby obtain the optically active α-hydroxy-γ-keto acid ester represented by the above-described formula (3) at high yield and with excellent enantioselectivity.

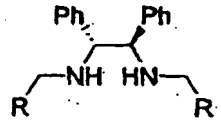
[0023] Further, on the other hand, without performing the acid treatment but performing a reduction treatment, the optically active α-hydroxy-γ-amino acid ester represented by the above-described formula (4) can be obtained at high yield and with excellent enantioselectivity in a same manner as described above. The reduction treatment on this occasion can use, for example, a boron reducing agent compound such as Et_2BOMe-$NaBH_4$, any one of other metal hydrides or a metallic hydrogen complex compound. Then, the thus-generated optically active α-hydroxy-γ-amino acid ester is subjected to a cyclization reaction to remove an acyl group on a γ-amino group therefrom (freeig from protection), to thereby being favorably converted into any one of optically active α-hydroxy-γ-lactams represented by the formula (5). For example, when the acyl group is a benzyloxycarbonyl group, protection freeing-cyclization reaction can be performed by catalytic hydrogen reduction.

[0024] Further, in the present invention, it is possible to synthesize the optically active α-hydroxy-γ-lactams as represented by the above-described formula (6) by subject the optically active -hydroxy- -keto acid ester as described above firstly to a reduction reaction and, then, to a cyclization reaction.

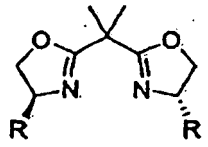
[0025] Hereinafter, the present invention is described in detail with reference to embodiments. It goes without saying that the present invention is not limited to these embodiments.

EXAMPLES

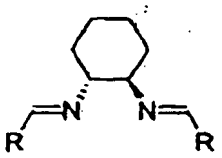
[0026] In Examples described below, unless stated otherwise, reference numerals and marks of chiral diamine ligands are denoted as follows:



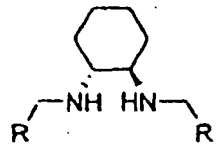
3a: R = 1-nap
3b: R = (3,5-(^{t}Bu)$_2$)-Ph
3c: R = ^{t}Bu
3d: R = Ph
3e: R = (*o*-F)-Ph
3f: R = (*o*-OMe)-Ph



3g: R = Ph
3h: R = ^{t}Bu



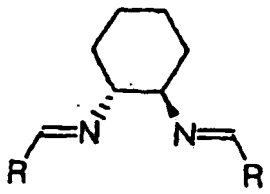
3i: R = Ph
3j: R = 1-nap
3k: R = 2-nap
3l: R = (3,5-di^{t}Bu)-C_6H_3
3m: R = *o*-Tol
3n: R = *m*-Tol
3o: R = *p*-Tol
3p: R = *p*-Et-C_6H_4
3q: R = *p*-^{i}Pr-C_6H_4
3r: R = *p*-F-C_6H_4
3s: R = *p*-Cl-C_6H_4
3t: R = *p*-Br-C_6H_4



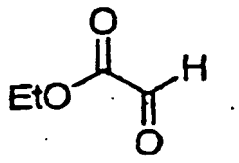
3v: R = Ph
3w: R = 2-nap
3x: R = (3,5-(^{t}Bu)$_2$)-Ph

<Example 1>

[0027] In the formula described below, a CH_2Cl_2 (1.5 ml) solution of chiral diamine ligand (9.9 mg, 0.022 mmol) in which R represents 4-BrC_6H_4 is added to $CuClO_4 \cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) in an argon atmosphere and the resultant excellent yellow solution was stirred for 8 hours or more and, then, cooled to 0°C.



[0028] Next, into the resultant mixed solution, a CH_2Cl_2 (0.8 ml) solution of ethyl glyoxylate (100 μl, 0.40 mmol) represented by the formula described below was added and, further, a CH_2Cl_2 (0.8 ml) solution of enamide (0.20 mmol) represented by the formula (2) as shown in Table 1 was added.



[0029] The resultant reaction mixed solution was stirred for one hour at 0°C and, then, added with a saturated aqueous solution of $NaHCO_3$, to thereby terminate a reaction. Thereafter, the resultant reaction mixed solution was allowed to have room temperature and, then, subjected to extraction by using CH_2Cl_2. The resultant organic phase was rinsed and, then, dried. After a solvent was evaporated, a residue was dissolved in EtOH (3.0 ml), added with a 48% aqueous HBr solution (0.3 ml) and, then, stirred for 1.5 minute at room temperature.

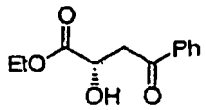
[0030] The resultant reaction mixture was subjected to extraction by using CH_2Cl_2. The resultant organic phase was rinsed and, then, dried. After a solvent was evaporated, a crude product was obtained. This crude product was purified by using silica gel chromatography.

[0031] In Table 1, the reaction yield and ee (%) in accordance with the type of enamide are shown. On this occasion, the ee (%) was determined by an HPLC analysis.

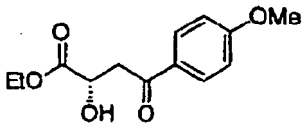
Table 1

No.	R^2	R^3	R^4, R^5	Yield (%)	ee (%)
1-1	BnO	Ph	H, H	93	97
1-2	BnO	4-MeO-Ph	H, H	94	93
1-3	BnO	4-Cl-Ph	H, H	97	97
1-4	BnO	4-Me-Ph	H, H	quantum	96
1-5	BnO	2-naphthyl	H, H	91	96

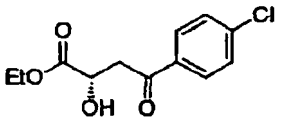
[0032] Identification values of products in the case of Nos. 1-1 to 1-5 are shown below.



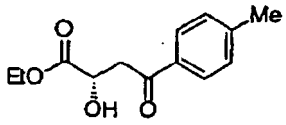
(2S)-2-Hydroxy-4-oxo-4-$_P$henyl-butyric acid ethyl ester: ^{1}H NMR ($CDCl_3$) δ = 1.27 (t, 3H, *J* = 7.1 Hz), 3.29 (brs, 1H), 3.44 (dd, 1H, *J* = 6.1, 17.6 Hz), 3.52 (dd, 1H, *J* = 3.9,17.6 Hz), 4.25 (q, 2H, *J* = 7.1 Hz), 4.61-4.67 (m, 1H). 7.44-7.50 (m, 2H). 7.54-7.60 (m, 1H), 7.92-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 14.0, 42.1, 61.8,67.1, 128.1,128.6,133.5, 136.4, 173.7, 197.5. IR (neat) 3475, 3063, 2983, 1737, 1687, 1597, 1580, 1449, 1368, 1213, 1098, 1045, 860, 759, 690, 582,499 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{12}H_{15}O_4$ IM+H]$^+$, 223.0970. Found 223.0972.; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH = 4/1, flow rate = 0.5 mL/min : t_R = 19.9 min (*S*), t_R = 22.2 min (R).



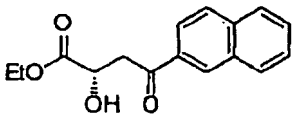
(2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-4-oxo-butyric acid ethyl ester: ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 3.41 (dd, 1H, *J* = 5.9, 17.4 Hz), 3.48 (dd, 1H, *J* = 4.0, 17.4 Hz), 3.48 (brd, 1H, *J* = 6.8 Hz), 3.87 (s, 3H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.60-4.70 (m, 1H), 6.91-6.97 (m, 2H), 7.90-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 14.0, 41.7, 55.4, 61.7, 67.3, 113.8, 129.5, 130.4, 163.8, 173.8, 196.1. IR (neat) 3483, 2979, 2841, 1739, 1677, 1600, 1575, 1512, 1465, 1421, 1368, 1265, 1172, 1099, 1027, 988, 895, 834, 737, 579 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_5$ [M+H]$^+$, 253.1076. Found 253.1097.; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH = 4/1, flow rate = 0.4 mL/min : ^{t}R = 43.1 min (*S*), t_R = 45.7 min (*R*).



(2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-4-oxo-butyric acid ethyl ester: ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 3.42 (dd, 1H, *J* = 6.1, 17.3 Hz), 3.49 (dd, 1H, *J* = 3.9, 17.3 Hz), 3.41-3.47 (brd, 1H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.62-4.70 (m, 1H), 7.42-7.48 (m, 2H), 7.86-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 14.1, 42.2, 62.0, 67.1, 129.0, 129.6, 134.8, 140.1, 173.7, 196.3. IR (neat) 3480, 2982, 1739, 1684, 1590, 1573, 1402, 1213, 1093, 1045, 820, 531 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{12}H_{14}ClO_4$ $[M+H]^+$. 257.0580. Found 257.0584.; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH = 4/1, flow rate = 0.5 mL/min : t_R = 24.2 min (*S*), t_R = 26.5 min (*R*).



(2S)-2-Hydroxy-4-oxo-4-p-tolyl-butyric acid ethyl ester: ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 2.41 (s, 3H), 3.44 (dd, 1H, *J* = 5.9,17.4 Hz), 3.51 (dd, 1H, *J* = 4.0, 17.4 Hz), 3.45-3.55 (brs, 1H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.66 (dt, 1H, *J* = 4.2, 5.5 Hz), 7.26 (apparent d, 2H, *J* = 8.0 Hz), 7.85 (apparent d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ = 14.0, 21.6, 42.0, 61.7, 67.2, 128.2, 129.3,133.9, 144.4, 173.7, 197.1. IR (neat) 3483, 2981, 1742, 1682, 1606, 1405, 1365, 1212, 1098, 1044, 813, 578 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1120.; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH = 4/1, flow rate = 0.3 mL/min : ^{t}R = 36.1 min (*S*), t_R = 38.2 min (R).



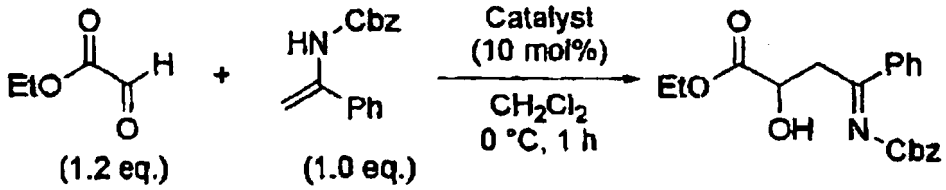
(2*S*)-2-Hydroxy-4-naphthalen-2-yl-4-oxo-butyric acid ethyl ester: ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 3.52 (d, 1H, *J* = 5.9 Hz), 3.59 (dd, 1H, *J* = 6.1, 17.3 Hz), 3.66 (dd, 1H, *J* = 3.9, 17.3 Hz), 4.28 (q, 2H, *J* = 7.1 Hz), 4.73 (dt, 1H, *J* = 4.2, 5.4 Hz), 7.50-7.65 (m, 2H), 7.82-8.20 (m, 4H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ = 14.1, 42.3, 61.9, 67.3, 123.6, 126.9, 127.8, 128.6, 128.8, 129.6, 130.2, 132.4, 133.8, 135.8, 173.9, 197.5. IR (neat) 3481, 3058, 2982, 1741, 1681, 1627, 1469, 1369, 1209, 1097, 1045, 859, 824, 749, 477 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{16}H_{17}O_4$ $[M+H]^+$, 273.1127. Found 273.1125.; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH = 4/1, flow rate = 0.5 mL/min : t_R = 27.0 min (*S*), t_R = 30.4 min (R).

<Example 2>

[0033] An nucleophilic addition reaction of enamide was performed by various types of chiral diamine ligands and $CuClO_4 \cdot 4CH_3CN$, while using No. 1-1 enamide and ethyl glyoxylate in Example 1 and, to thereby synthesize an α-hydroxy-γ-imino acid ester.

[0034] The results are shown in Table 2.

Table 2



entry	metal	ligand	yield (%)	ee (%)[a]
1	$CuClO_4 \cdot 4CH_3CN$	**3a**	90	35[a]
2	$CuClO_4 \cdot 4CH_3CN$	**3i**	94	93
3	$CuPF_6 \cdot 4CH_3CN$	**3i**	94	82

(continued)

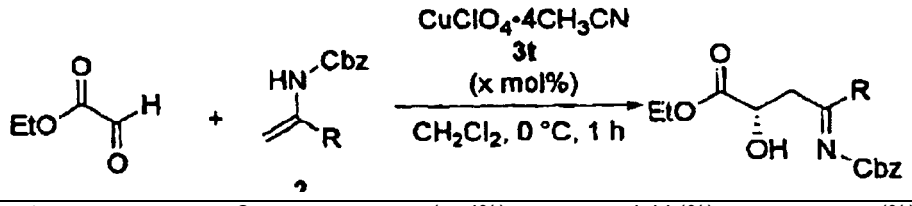
entry	metal	ligand	yield (%)	ee (%)[a]
4	$CuOTf{\cdot}0.5C_6H_5CH_3$	**3i**	66	78
5	$CuClO_4{\cdot}4CH_3CN$	**3j**	92	73
6	$CuOlO_4{\cdot}4CH_3CN$	**3k**	52	68
7[b]	$CuClO_4{\cdot}4CH_3CN$	**3i**	48	91
8[c]	$CuClO_4{\cdot}4CH_3CN$	**3i**	97	93
9[d]	$CuClO_4{\cdot}4CH_3CN$	**3i**	quant	94
10[d]	$CuClO_4{\cdot}4CH_3CN$	**3m**	97	81
11[d]	$CuClO_4{\cdot}4CH_3CN$	**3n**	quant	86
12[d]	$CuClO_4{\cdot}4CH_3CN$	**3o**	98	95
13[d,]	$CuClO_4{\cdot}4CH_3CN$	**3p**	87	94
10[d,]	$CuClO_4{\cdot}4CH_3CN$	**3q**	93	94
15[d]	$CuClO_4{\cdot}4CH_3CN$	**3r**	97	96
16[d]	$CuClO_4{\cdot}4CH_3CN$	**3s**	93	96.5
17[d]	$CuClO_4{\cdot}4CH_3CN$	**3t**	93	97.0

[a] The absolute configuration is *S* except in entry 1 (*R*). [b] -78 °C. [c] Ethyl glyoxylate (1.5 equiv) was used. [d] Ethyl glyoxylate (2.0 equiv) was used.

<Example 3>

[0035] A reaction was performed in a same manner as in Example 2 except that various types of enamides were used and an amount of $CuClO_4{\cdot}4CH_3CN$ to be used was changed. The results are shown in Table 3. It is found that results of high yield and high ee % can be obtained even with a low concentration of a chiral copper catalyst.

Table 3



entry	**2**	× (mol%)	yield (%)	ee (%)
1	**2a** (R = Ph)	10	93	97
2	**2a**	5	94	96
3	**2a**	2	96	95
4	**2a**	1	90	94
5	**2b** (R = PMP)	10	94	93
6	**2c** (R = PCP)	10	97	97
7	**2d** (R = PMeP)	10	quant	96
8	**2e** (R = 2-Nap)	10	91	96

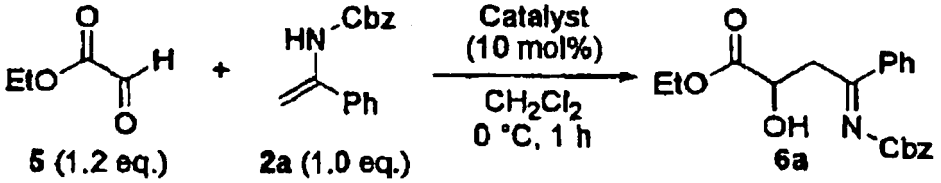
Cbz = Benzyloxycarbonyl, PMP = *p*-Methoxyphenyl. PCP = *p*-Chlorophenyl, PMeP = *p*-Methylphenyl. 2-Nap = 2-Naphthyl.

<Example 4>

[0036] A reaction was performed in a same manner as in Example 2 except that $Cu(OTf)_2$ or the like was used in place of the copper compound.

[0037] The results are shown in Table 4. An absolute configuration of the product was R.

Table 4



entry	metal	ligand	yield (%)	ee (%)[d]
1	$Cu(OTf)_2$	**3a**	93	55
2[a]	$Cu(OTf)_2$	**3a**	91	54
3[b]	$Cu(OTf)_2$	**3a**	89	58
4	$Cu(OTf)_2$	**3b**	74	59
5	$Cu(OTf)_2$	**3c**	58	57
6	$Cu(OTf)_2$	**3d**	96	46
7	$Cu(OTf)_2$	**3e**	97	37
8	$Cu(OTf)_2$	**3h**	70	73
9	$Cu(OTf)_2$	**3i**	65	70
10	$Cu(OTf)_2$	**3j**	66	28
11	$Cu(OTf)_2$	**3k**	71	52
12	$Cu(OTf)_2$	**3l**	68	17
13	$Cu(OTf)_2$	**3v**	89	51
14	$Cu(OTf)_2$	**3w**	91	50
15	$Cu(OTf)_2$	**3x**	quant	62
16	$Cu(SbP_6)_2$	**3b**	77	44

[a] Catalyst (30 mol%) was used. [b] -20 °C.

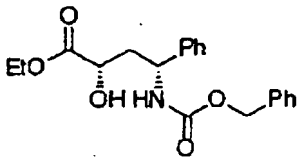
<Example 5>

[0038] A treatment as described below was performed in place of the acid treatment by using the aqueous HBr solution in Example 1-1.

[0039] Namely, the residue was added with a mixed solution of THF (2.0 ml) and MeOH (0.5 ml) and, then, cooled to -78°C and, thereafter, added with Et_2BOMe (79 μl, 0.6 mmol) and, subsequently, stirred for 15 minutes. The resultant mixed solution was added with $NaBH_4$ (22.7 mg, 0.6 mmol) and, then, cooled to -78°C and stirred for 2 hours at this temperature.

[0040] Then, a reaction was terminated by being added with AcOH (0.3 μl) and, then, allowed to have room temperature.

[0041] The compound described below was obtained in an amount of 46.5 mg at a yield of 65 %. A ratio of syn/anti was 94/6.

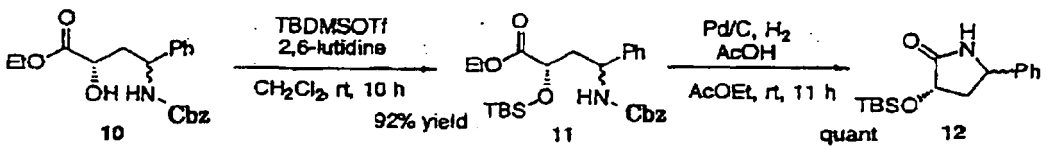


4-Benzyloxycarbonylamino-2-hydroxy-4-phenyl-butyric acid ethyl ester: (10, *syn*/*anti* = 94/6): ^1H NMR ($CDCl_3$) δ = 1.23 (t, 3H x 19/20, *J* = 7.1 Hz), 1.25 (t, 3H x 1/20, *J* = 7.0 Hz), 1.95-2.40 (m, 2H). 3.33 (brs, ^1H x 19/20), 3.51 (brs, ^1H x 1/20), 4.00-4.40 (m, 3H), 4.85-5.20 (m, 3H), 5.52 (d, ^1H x 1920, *J* = 7.3 Hz), 5.96 (d, 1H x 1/20, *J* = 8.2 Hz), 7.00-7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) *syn*: δ = 14.1, 40.3, 52.6, 61.8, 66.8, 68.4, 126.4, 127.6, 128.1, 128.4, 128.7, 136.3, 141.4, 155.7, 174.4; ***anti*:** (distinguishable peak) 40.2, 52.4, 67.8, 126.2, 127.4, 141.1, 156.0, 174.3; LRMS (FAB) *m*/*z* = 358 ($M+H^+$)

[0042] In the same manner as described above, when a reaction was performed for 3 hours in the solvent of Et_2O by using $Zn(BH_4)_2$ (one equivalent), the results in which the yield was 66% and a ratio of syn/anti was 78/22 were obtained.

<Example 6>

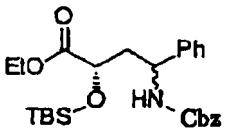
[0043] In accordance with the following reaction formulae, γ-lactams (12) were synthesized from the product obtained in Example 5:



[0044] 1) A CH_2Cl_2 (0.6 ml) solution of the above-described product (10) (31.3 mg, 0.08 mmol) was added with a CH_2Cl_2 (0.2 ml) solution of 2.6-lutidine (12.0 mg, 0.114 mmol) and a CH_2Cl_2 solution of tert-butyl dimethyl silyl trifluoromethane sulfonate: TBDMSOTf (27.8 mg, 0.105 mmol) at a temperature of 0°C.

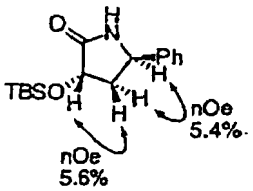
[0045] A reaction mixture was stirred for 10 hours at room temperature.

[0046] After the resultant reaction mixture was added with water, it was subjected to extraction by using CH_2Cl_2 and, then, the resultant organic phase was rinsed and, then, dried and, thereafter, a solvent therein was evaporated. The resultant crude product was purified by using silica gel chromatography, to thereby obtain 37.9 mg (with a yield of 92 %) of a next compound (11).

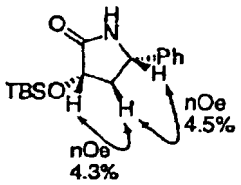


4-Benzyloxycarbonylamino-2-(*tert*-butyl-dimethyl-silanylozy)-4-phenyl-butyric acid ethyl ester (11, diastereomer mixture): ^{1}H NMR ($CDCl_3$) δ = ***syn*:** -0.03 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 1.15-1.27 (m, 3H), 2.00-2.35 (m, 2H), 3.90-4.30 (m, 3H), 4.80-5.15 (m, 3H), 5.50 (brs, 1H), 7.15-7.40 (m, 10 H); ***anti*:** (distinguishable peak) δ = -0.02 (s, 3H), 0.03 (s, 3H), 5.62 (brd, 1H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$) syn: δ = -5.4, -5.0, 14.0, 18.1, 25.7, 41.0, 52.9, 61.0, 66.6, 70.3, 126.4, 127.4, 128.0, 128.1, 128.4, 128.6, 136.4, 141.8, 155.3, 173.2; ***anti:*** (distinguishable peak) -5.0, 14.1, 41.8, 52.3, 69.8, 126.0, 127.3, 128.6, 142.2, 155.6, 173.1; IR (neat) 3343, 2940, 1720, 1518, 1254, 1131, 1038, 839, 781, 699cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{26}H_{38}NO_5Si$ $[M+H]^+$, 472.2519. Found 472.2508.

[0047] 2) An AcOEt (2.0 ml) solution of the above-described product (11) (21.4 mg, 0.454 mmol) was added with AcOH (16.8 mg, 0.0272 mmol) and a 5% Pd/C (9.7 mg, 10% by mol) at room temperature. After an argon gas in the atmosphere of the resultant mixture was replaced with an H_2 gas, the mixture was stirred for 11 hours, to thereby obtain a next compound (12) (13.4 mg, quantitative yield). A diastereomer (12) can be separated by using silica gel chromatography.



(3*S*, 5*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-major): ^{1}H NMR ($CDCl_3$) δ = 0.14 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 2.21 (ddd, 1H, *J* = 5.1, 7.1, 13.2 Hz), 2.46 (ddd, 1H, *J* = 5.1, 7.5, 13.2 Hz), 4.38 (dd, 1H, *J* = 5.1, 7.1 Hz), 4.83 (dd, 1H, *J* = 5.0, 7.5 Hz), 6.02 (brs, 1H), 7.20-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = -5.1, -4.5, 18.3, 25.8, 41.5, 55.1, 69.9, 125.5, 127.9, 129.0, 142.1, 176.3; IR (neat) 3226, 2927, 2892, 2855, 1715, 1496,1471, 1331, 1253, 1151, 1091, 1028, 963, 880, 839, 780, 699 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1733.;



(3*S*, 5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-minor): ^{1}H NMR ($CDCl_3$) δ = 0.15 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 1.94 (dt, 1H, *J* = 9.2, 12.6 Hz), 2.75-2.87 (m. 1H), 4.42 (dd, 1H, *J* = 7.9, 9.2 Hz), 4.53 (dd, 1H, *J* = 6.2,8.6 Hz), 5.76 (brs, 1H), 7.30-7.40 (m, 5H); ^{13}CNMR ($CDCl_3$) δ = -5.1, -4.5, 118.3, 25.8, 42.0, 53.9, 70.8, 126.1, 128.2, 128.9, 176.0; IR (neat) 3220, 2936, 2858, 2359, 1717, 1463, 1330, 1247, 1151, 882, 838, 781, 698 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1736.;

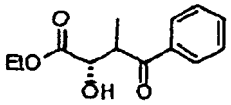
<Example 7>

[0048] A reaction was performed in a same manner as in Example 1 except that various types of enecarbamates shown in Table 10 as enamides represented by the above-described formula (2), were used. In Table 5, yield (%), a syn/anti ratio, and ee (%) of a reaction product are shown. Identification values of 7-1/7-2, 7-3/7-4, 7-5/7-6 and 7-7/7-8 of the reaction products are also shown.

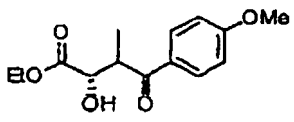
[0049] From the results of this reaction, it was confirmed that an anti-adduct and a syn-adduct were obtained from an E-body and a Z-body at high diastereoselectivity and high enantioselectivity, respectively.

Table 5

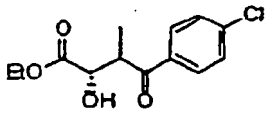
No.	R^2	R^3	R^4·R^5	Yield (%)	Syn/anti	ee (%)
7-1	BnO	Ph	Me, H (E)	83	1/99	98
7-2	BnO	Ph	H, Me (Z)	82	98/2	98
7-3	BnO	4-MeO-Ph	Me, H (E)	96	2/98	98
7-4	BnO	4-MeO-Ph	H, Me (Z)	97	98/2	98
7-5	EtO	4-MeO-Ph	Me, H (E)	82	3/97	96
7-6	EtO	4-MeO-Ph	H, Me (Z)	96	99/1	98
7-7	BnO	4-Cl-C_6H_4	Me, H (E)	85	2/98	98
7-8	BnO	4-Cl-C_6H_4	H, Me (Z)	79	99/1	98



(2*S*)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (*syn*/*anti* mixture): ^{1}H NMR *syn* ($CDCl_3$) δ = 1.26 (t, 3H, *J* = 7.0 Hz), 1.29 (d, 3H, *J*= 7.0 Hz), 3.28 (br, 1H), 3.93 (dq, 1H, *J* = 4.2, 7.0 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 4.58 (d, 1H, *J*= 4.2 Hz), 7.40-7.65 (m, 3H), 7.90-8.05 (m, 2H); ***anti*** ($CDCl_3$) δ = 1.20 (t, 3H, *J* = 7.1 Hz), 1.36 (d, 3H, *J* = 7.3 Hz), 3.61 (d, 1H, *J* = 8.3 Hz), 3.98 (dq, 1H, *J* = 4.6, 7.1 Hz), 4.10-4.25 (m, 2H), 4.39 (dd, 1H, *J* = 4.6, 8.3 Hz), 7.40-7.65 (m, 3H); ^{13}CNMR ***syn*** ($CDCl_3$) δ = 12.1, 14.0, 44.3, 61.9, 71.6, 128-4, 128.7, 133.3, 135.7, 173.1, 201.6; ***anti*** ($CDCl_3$) δ = 14.0, 14.1, 44.0, 61.5, 73.1, 128.3, 128.7, 133.4, 135.9, 173.1; IR (neat) ***syn*** 3480, 3063, 2978, 2936, 1734, 1678, 1596, 1579, 1449, 1369,1217, 1133, 1062, 1023, 1001, 975, 952, 862, 794, 708; ***anti*** 3481, 3059, 2981, 2941, 1738, 1685, 1588, 1454, 1372, 1255, 1209, 1144, 1092, 1024, 973, 701 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1118.; HPLC, Daicel Chiralcel AS + ADH + AD, hexane/^{i}PrOH = 4/1, flow rate = 0.5 mL/min : t_R = 46.7 min (2*S*, 3*S*), t_R = 50.6 min (2*R*, 3*R*), t_R = 54.3 min (2*S*, 3*R*), t_R = 61.9 min (2*R*, 3*S*).



(2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester (*syn*/*anti* mixture): ^{1}H NMR ***syn*** ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 1.29 (d, 3H, *J*= 7.1 Hz), 335 (br, 1H), 3.84-3.96 (m, 4H), 4.27 (q, 2H, *J*= 7.1 Hz), 4.58 (t, 1H, *J* = 4.2 Hz), 6.96 (apparent d, 2H, *J* = 9.0 Hz), 730-7.45 (m, 5H), 7.95 (apparent d, 2H, *J*= 8.8 Hz); ***anti*** ($CDCl_3$) δ = 1.19 (t, 3H, *J* = 7.1 Hz), 1.36 (d, 3H, *J* = 7.3 Hz), 3.75 (d, 1H, *J* = 9.3 Hz), 3.88 (s, 3H), 3.94 (dq,1H, *J*= 4.6, 7.3 Hz), 4.15 (apparent dq, 2H, *J*= 3.2, 7.1 Hz), 436 (dd, 1H, *J*= 4.6, 9.3 Hz), 692-6.99 (m, 2H), 7.90-7.97 (m, 2H); ^{13}C NMR ***syn*** ($CDCl_3$) δ = 12.3, 14.0, 43.7, 55.4, 61.8, 71.7, 113.9, 128.5, 130.7, 163.7, 173.1, 200.4; ***anti*** ($CDCl_3$) δ = 74.0, 14.6, 43.2, 55.5, 61.4, 73.4, 113.9, 128.7, 130.8, 163.8, 173.2, 201.9; IR (neat) ***syn*** 3477, 2979, 2935, 2850, 1730, 1670, 1600, 1573, 1510, 1463, 1420, 1308, 1261, 1173, 1125, 1027, 976, 843, 770, 604; ***anti*** 3478, 2979, 2941, 2843, 1738, 1671, 1599, 1580, 1510, 1457, 1419, 1370, 1308, 1257, 1216, 1172, 1092, 1026, 974, 841 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{14}H_{19}O_5$ $[M+H]^+$, 267.1232. Found 267.1232.; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH = 4/1, flow rate = 0.2 mL/min : t_R = 60.5 min (2R, *3R), t_R* = 65.4 min (2S, 2S), t_R = 75.2 min (2R, 3S), t_R = 78.9 min (2*S*, 3*R*).



(2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester (*syn*/*anti* mixture): ^{1}H NMR ***syn*** ($CDCl_3$) δ = 1.26 (t, 3H, *J* = 7.0 Hz), 1.28 (d, 3H, *J* = 7.0 Hz), 3.27 (brs, 1H), 3.87 (dq, 1H, *J* = 4.4, 7.0 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 4.55 (d, 1H, *J* = 4.4 Hz), 7.40-7.55 (m, 2H), 7.84-7.97 (m, 2H); ***anti*** ($CDCl_3$) δ = 1.21 (t, 3H, *J*= 7.1 Hz), 1.34 (d, 3H, *J* = 7.1 Hz), 3.53 (d, 1H, *J* = 8.2 Hz), 3.91 (dq, 1H, *J* = 5.0, 7.1 Hz), 4.08-4.24 (m, 2H), 4.38 (dd, 1H, *J*= 5.0, 8.2 Hz), 7.42-7.52 (m, 2H), 7.80-7.95 (m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ = 12.1, 14.0, 44.4, 62.0, 71.5, 129.0, 129.8, 134.1, 139.7, 173.1, 200.3; *anti* ($CDCl_3$) δ = 13.9, 14.0, 44.1, 61.6, 73.0, 129.0, 129.8, 134.3, 139.9, 173.0, 201.8; IR (neat) ***syn*** 3485, 2982, 2938, 1730, 1682, 1589, 1571, 1488, 1455, 1401, 1217, 1132, 1092, 1013, 977, 843, 758, 692, 533, 478; ***anti*** 3478, 3092, 2982, 2935, 1738, 1686, 1589, 1455, 1402,1255, 1208, 1144, 1092, 1022, 976, 842, 751, 527 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{13}H_{16}ClO_4$ $[M+H]^+$, 271.0737. Found 271.0745.; HPLC, Daicel Chiralcel AS, hexane/^{i}PrOH = 4/1, flow rate = 0.5 mL/min : t_R = 15.1 min (2S, 3S), t_R = 16.6 min (2S, 3*R*), t_R = 21.4 min (2*R*, 3*S*), t_R = 23.9 min (2*R,* 3*R*).

<Example 8>

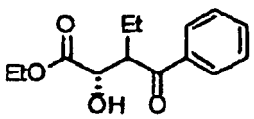
[0050] A reaction was performed in a same manner as in Example 7 except that various types of enecarbamates as shown in Table 6 were used. In Table 6, yield (%), a syn/anti ratio, and ee (%) of a reaction product are shown. Identification values of 8-1/8-2 and 8-3/8-4 of the reaction products are also shown.

[0051] It was confirmed that, in a same manner as in Example 7, an anti-adduct and a syn-adduct were obtained from an E-body and a Z-body at high diastereoselectivity and high enantioselectivity, respectively.

Table 6

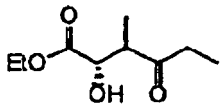
No.	R^2	R^3	R^4·R^5	Yield (%)	Syn/anti	ee (%)
8-1	BnO	Ph	Et, H (E)	90	1/99	98
8-2	BnO	Ph	H, Et (Z)	92	99/1	98
8-3	BnO	Et	Me, H (E)	83	3/97	97
8-4	BnO	Et	H, Me (Z)	89	92/8	98

(2*S*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester (*syn*/*anti* mixture): ^{1}H



NMR ***syn*** ($CDCl_3$) δ = 0.93 (t, 3H, *J* = 7.5 Hz), 1.19 (t, 3H, *J*= 7.1 Hz), 1.70-2.05 (m, 2H), 3.18 (brs, 1H), 3.83 (dt, 1H, *J* = 5.3, 8.3 Hz), 4.19 (q, 2H, *J*= 7.1 Hz), 4.51 (d, 1H, *J*= 5.3 Hz), 7.42-7.54 (m, 2H), 7.54-7.62 (m, 1H), 7.90-8.02 (m, 2H); ***anti*** ($CDCl_3$) δ =1.04 (t, 3H, *J*= 7.6 Hz), 1.15 (t, 3H, *J*= 7.1 Hz), 1.80-1.95 (m, 2H), 3.70 (d, 1H, *J*= 9.5 Hz), 3.83 (dt, 1H, *J*= 4.2, 7.1 Hz), 4.09 (q, 2H, *J*= 7.1 Hz), 4.43 (dd, 1H, *J*=4.2, 9.5 Hz), 7.46-7.52 (m, 2H), 7.56-7.63 (m, 1H), 7.88-7.95

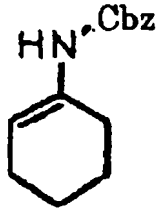
(m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ =12.0, 13.9, 21.3, 51.2, 61.9, 71.1, 128.3, 128.6, 133.2, 137.0, 173.6, 201.5; ***anti*** ($CDCl_3$) δ = 12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.6, 173.4, 203.9; IR (neat) *syn* 3477, 2972, 2876, 1738, 1675, 1596, 1447, 1372, 1255, 1220, 1118, 1023, 931, 849, 779, 701; ***anti*** 3485, 3062, 2966, 2941, 2875, 1738, 1682, 1596, 1579, 1448, 1368, 1268, 1208, 1134, 1100, 1028, 914, 849, 785, 699 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{14}H_{19}O_4$ $[M+H]^+$, 251.1283. Found 251.1277.; HPLC, Daicel Chiralcel AS, hexane/^{i}PrOH = 4/1, flow rate = 0.5 mL/min : t_R = 13.7 min (2*S*, 3*S*), t_R = 15.3 min (2S, *3*R), t_R = 17.6 min (2*R*, 3*R*), t_R = 23.1 min (2*R*, 3*S*).



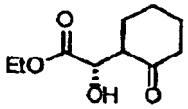
(2,*S*')-2-Hydroxy-3-methyl-4-ozo-hexanoic acid ethyl ester (*syn*/*anti* mixture): ^{1}H NMR ***syn*** (C_6D_6) δ = 0.89 (t, 3H, *J* = 7.1 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 1.97-2.08 (m, 2H), 2.70 (dq, 1H, *J* = 4.9, 7.2 Hz), 3.39 (d, 1H, *J*= 6.7 Hz), 3.80-4.00 (m, 2H), 4.11 (dd, 1H, *J*= 4.9, 6.7 Hz); ***anti*** (C_6D_6) δ = 0.87 (t, 3H, *J* = 7.1 Hz), 0.93 (t, 3H, *J* = 7.3 Hz), 1.02 (d, 3H, *J* = 7.2 Hz), 1.95-2.22 (m, 2H), 2.65 (dq, 1H, *J* = 4.4, 7.2 Hz), 3.05-3.23 (m, 1H), 3.80-4.00 (m, 2H), 4.38-4.47 (m, 1H); ^{13}C NMR ***syn*** ($CDCl_3$) δ = 7.58,12.8, 14.0, 34.6, 49.4, 61.3, 73.0, 173.5, 211.3; ***anti*** (C_6D_6) δ = 7.7, 11.0, 14.0, 34.0, 49.5, 61.6, 71.7, 173.7, 209.9; IR (neat) ***syn*** 3484, 2981, 2940, 1739, 1716, 1459, 1409, 1375, 1268, 1209, 1108, 1066, 1025, 975, 862, 808, 748; ***anti*** 3488, 2981, 2940, 1733, 1716, 1459, 1373, 1218, 1145, 1025, 977, 862, 800,752 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_9H_{17}O_4$ $[M+H]^+$, 189.1127. Found 189.1120.;

<Example 9>

[0052] A reaction was performed in a same manner as in Example 7 except that an enecarbamate represented by the following formula as an enamide:



Thus, a next compound was obtained at a yield of 85% with a syn/anti of 16/84 and 94 ee (%).

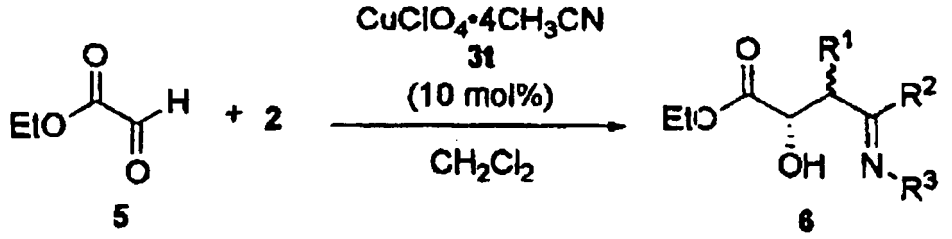


(1*S*)-Hydroxy-(2-oxo-cyclohexyl)-acetic acid ethyl ester (*syn*/*anti* mixture): ^{1}H NMR ***anti*** (1*S*, 1'*R*), tentatively assignment) (C_6D_6) δ = 0.95 (t, 3H, *J*= 7.1 Hz), 0.94-1.20 (m, 2H), 1.30-1.42 (m, 2H), 1.56-1.84 (m, 3H), 2.02-2.12 (m, 1H), 2.60-2.70 (m, 1H), 3.35 (d, 1H, *J* = 7.2 Hz), 3.84 (dd, 1H, *J*= 3.2, 7.2 Hz), 4.02 (dq, 2H, *J* = 1.9, 7.1 Hz); **distingishable syn peaks** δ = 0.88 (t, 3H, *J* = 7.1 Hz), 2.12-2.21 (m, 1H), 2.48-2.57 (m,1H), 2.94 (d, 1H, *J* = 5.0 Hz), 4.60 (dd, 1H, *J* = 3.2, 5.0 Hz); ^{13}C NMR *anti* ($CDCl_3$) δ = *14.1,* 24.8, 26.9, 30.1, 42.0, 53.7, 61.6, 71.1, 173.4, 211.2; **distinguishable syn peaks** δ = 14.2, 24.6, 27.1, 41.9, 53.8, 61.7, 69.2, 173.6, 210.4; HRMS (FAB); Exact mass calcd for $C_{10}H_{17}O_4$ $[M+H]^+$, 201.1127. Found 201.1127.;

<Example 10>

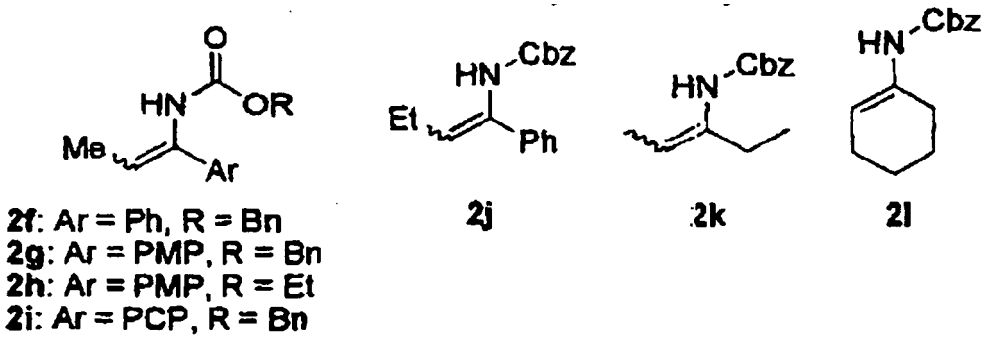
[0053] A reaction was performed in a same manner as in Example 7 except that an enamide (2) having an α-substituent as shown in Table 7 was used. The results are also shown in Table 7.

Table 7



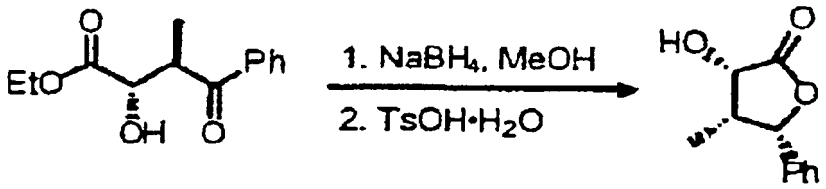
entry	2	product	yield (%)[a]	*syn*/*anti*[b]	ee (%)[c]
1	**2f*E***	**7f**	83	1/99	98
2[d]	**2f*E*[e]**	**7f**	93	1/99	97
3[d]	**2f*E*[f]**	**7f**	95	1/99	98
4	**2f*Z***	**7f**	82	98/2	98
5	**2f*Z*[e]**	**7f**	93	98/2	98
6	**2f*Z*[f]**	**7f**	96	98/2	98
7	**2g*E***	**7g**	96	2/98	98
8	**2g*Z***	**7g**	97	98/2	98
9	**2h*E***	**7g**	82	3/97	96
10	**2h*Z***	**7g**	96	99/1	98
11	**2i*E***	**7i**	85	2/98	98
12	**2i*Z***	**7i**	79	99/1	98
13	**2j*E*[g]**	**7j**	58	1/99	98
14	**2j*Z***	**7j**	92	99/1	98
15[d]	**2k*E***	**7k**	83	3/97[h]	97
16[d]	**2k*Z***	**7k**	89	92/8[h]	98
17	**2l**	**7l**	85	16/84[h]	94

[a] isolated yield of ketone product. [b] Determined by HPLC. [c] Ee of the major diastereomer, determined by HPLC.
[d] -20 °C. [e] 1 mol% of catalyst was used. 0.1 mol% of catalyst was used. [g] 1 (1.0 eq.) and 2 (2.0 eq.) were used. [h] Determined by NMR analysis.



<Example 11>

[0054] From the reaction product obtained in Example 7, an optically active α-hydroxy-γ-lactone was synthesized in accordance with the following reaction formulae:

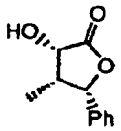


[0055] Namely, MeOH (1.0 ml) of the anti-body (45.6 mg, 0.193 mmol) of the reaction product was added with $NaBH_4$ (14.6 mg, 0.39 mmol) at 0°C, stirred for 10 minutes, added with acetone, stirred further for 5 minutes and, then, added with a saturated aqueous solution of NH_4Cl.

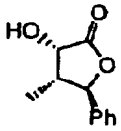
[0056] The resultant mixture was subjected to extraction by using CH_2Cl_2, dried and, then, a solvent was evaporated. Thereafter, the resultant CH_2Cl_2 solution (1 ml) was added with $TsOH \cdot H_2O$and, then, stirred for 13.5 hours at room temperature.

[0057] The resultant reaction product was added with a saturated aqueous solution of $NaHCO_3$, subjected to extraction by using CH_2Cl_2, dried and, then, subjected to a solvent-evaporation treatment. The resultant crude product was purified by using silica gel chromatography. As a product, the lactone compound as shown in the above-described reaction formulae and an epi-body thereof (ratio: 55/45) were obtained as a diastereomer mixture in an amount of 19.8 mg at a yield of 53 %.

[0058] Identification values of the products are shown below.



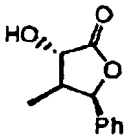
(3*S*, 4*R*, 5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one : Mp. 150-151 °C; ^{1}H **NMR** ($CDCl_3$) δ = 0.65 (d, 3H, *J* = 7.3 Hz), 2.75 (brs, 1H), 2.98-3.08 (m, 1H), 4.79 (d, 1H, *J*= 6.8 Hz), 5.57 (d, 1H, *J*= 4.6 Hz), 7.25-7.30 (m, 2H), 7.30-7.38 (m, 1H), 7.38-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 7.4, 41.1, 72.1, 80.2, 125.2, 128.2, 128.6, 135.1 177.0; IR (neat) 3443,2963, 1758, 1452, 1414, 1294, 1194, 1148, 1051, 956, 754, 701, 622, 478 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.;



(3*S*, 4*R*, 5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (epi-): ^{1}H NMR ($CDCl_3$) δ = 1.22 (d, 3H, *J* = 7.1 Hz), 2.62 (tq, 1H, *J* = 5.1, 6.8 Hz), 2.86 (brs, 1H), 4.47 (d, 1H, *J* = 6.8 Hz), 5.26 (d, 1H, *J* = 5.1 Hz), 7.20-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = 10.8, 43.2, 69.7, 85.8, 125.3, 128.6, 128.8, 137.7, 176.9; IR (neat) 3430, 3039, 2924, 2857, 1772, 1455, 1275, 1202, 1143, 1093, 986, 889, 805, 742, 702 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0864.;

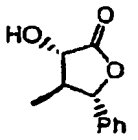
[0059] In a same manner as described above, by using the syn-body of the product in Example 7 as a raw material, a lactone compound and an epi-body thereof (ratio: 86/14) were obtained at a yield of 84 %.

[0060] Identification values of the products are shown below.



(3*S*, 4*S*, 5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one : ^{1}H NMR ($CDCl_3$) δ = 0.87 (d, 3H, *J* = 7.0 Hz), 2.70-2.92 (m, 1H), 3.18 (brs, 1H), 4.24 (d, 1H, *J* = 9.9 Hz), 5.63 (d, 1H, *J*= 8.1 Hz), 7.05-7.18 (m, 2H), 7.30-7.45 (m, 3H); ^{13}C NMR ($CDCl_3$) δ = 13.3, 42.1, 72.2, 82.4, 125.7, 128.5, 128.6, 135.5, 177.5; IR (neat) 3362, 2970, 1776 1455, 1334, 1184, 1145, 1096, 991, 897, 755, 701, 464 cm^{-1}; HRMS (FAB); Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865.

Found 193.0872.;



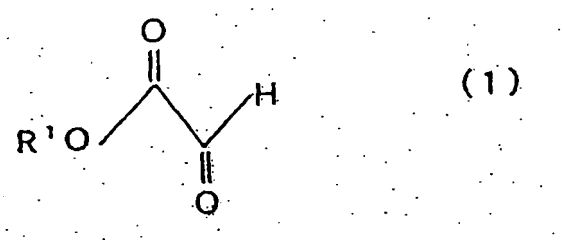
(3*S*, 4*S*, 5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (epi-): ^{1}H NMR ($CDCl_3$) δ = 1.24 (d, 3H, *J* = 6.4 Hz), 2.41 (tq, 1H, *J*= 6.4,10.6 Hz), 3.24 (brs, 1H), 4.25 (d, 1H, *J*= 11.0 Hz), 4.87 (d, 1H,

Industrial Applicability

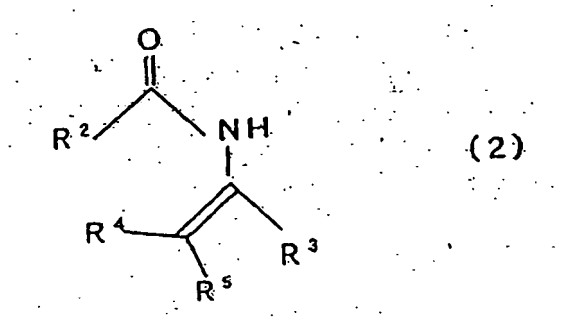
[0061] As has been described above in detail, according to the present invention, there is provided a method of an enantioselective nucleophilic addition reaction to an aldehyde group which enables an asymmetric synthesis of an optically active α-hydroxy-γ-keto acid ester, an optically active α-hydroxy-γ-amino acid ester, an optically active hydroxydiketone or the like which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like. Then, according to the invention, high stereoselective reaction is made possible and, particularly in the case of an enecarbamate having an α-1 substitution, high diastereoselectivity and enantioselectivity are realized. Further, there is provided a novel method for synthesizing an optically active γ-lactam or any one of γ-lactones.

Claims

1. A method of an enantioselective nucleophilic addition reaction of enamide, **characterised by** being a method of a nucleophilic addition reaction of an enamide compound accompanied by generation of a hydroxyl group (-OH) to a carbonyl group, performed on a compound having a carbonyl group which is a glyoxylic acid ester represented by the following formula (1):



wherein R^1 represents a hydrocarbon group which may have a substituent; and wherein said enamide compound is represented by the following formula (2):



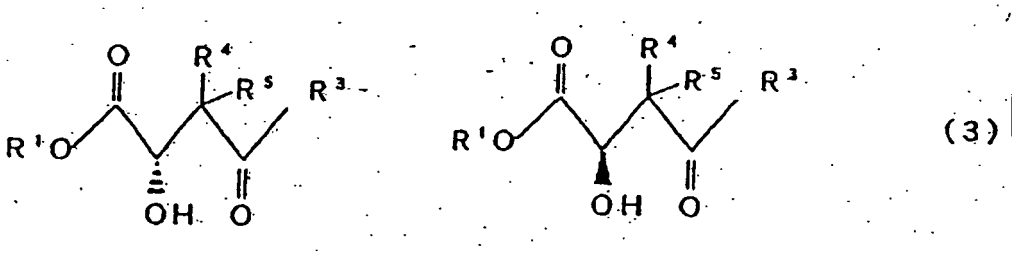
wherein R^2 represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom;
R^3 represents a hydrocarbon group which may have a substituent;
R^4 and R^5 may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon

group which may have a substituent, wherein at least one of them represents a hydrogen atom; and performing the reaction in the presence of a chiral catalyst comprising copper or nickel.

2. A method of an enantioselective nucleophilic addition reaction of enamide as claimed in claim 1, being **characterized in that** the chiral catalyst is constituted by a copper compound or a nickel compound which is a salt of an organic or inorganic acid or a complex or composite of the salt, and a chiral diamine ligand.

3. A method of an enantioselective nucleophilic addition reaction of enamide as claimed in claim 2, being **characterized in that** the chiral diamine ligand has an ethylene diamine structure as a portion thereof.

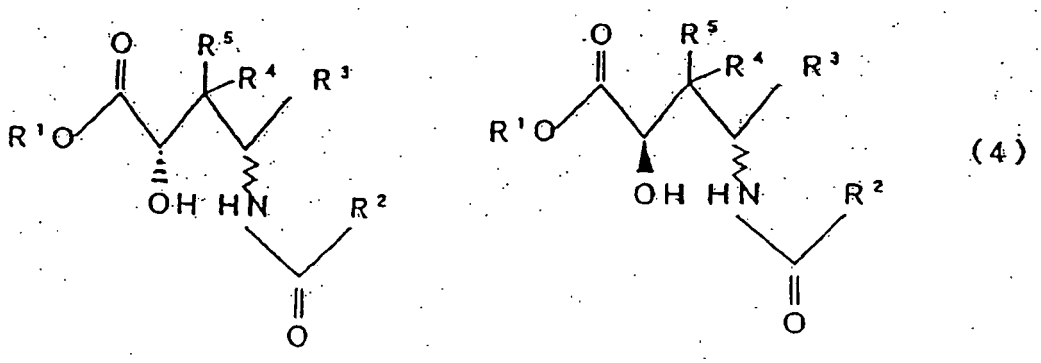
4. A method for synthesizing an optically active α-hydroxy-γ-keto acid ester, being **characterized in that**, after the nucleophilic addition reaction as claimed in any of the preceding claims, an acid treatment is performed, to thereby generate a compound represented by at least one of the following formulae (3):



(3)

wherein R^1, R^3, R^4 and R^5 are as defined in claim 1.

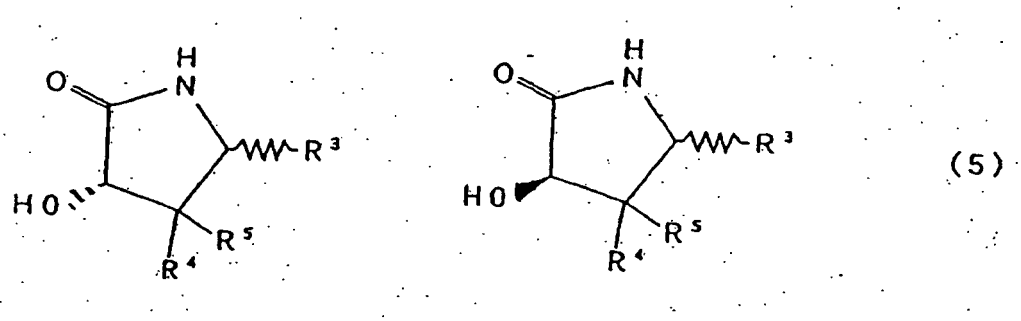
5. A method for synthesizing an optically active α-hydroxy-γ-amino acid ester, being **characterized in that**, after the nucleophilic addition reaction according to any one of claims 1 to 3, a reduction treatment is performed, to thereby generate a compound represented by at least one of the following formulae (4):



(4)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined in claim 1.

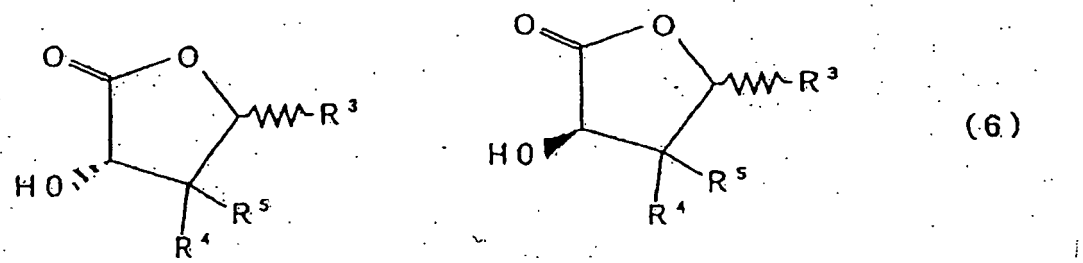
6. A method for synthesizing optically active α-hydroxy-γ-lactams, being **characterized in that** an optically active α-hydroxy-γ-amino acid ester is synthesized by the method according to claim 5, a substituent (R^2 CO-) on a γ-amino group of the optically active α-hydroxy-γ-amino acid ester is removed, and thereafter a cyclization reaction is performed, to thereby generate a compound represented by at least one of the following formulae (5):



(5)

wherein R^3, R^4 and R^5 are as defined in claim 1.

7. A method for synthesizing any one of optically active α-hydroxy-γ-lactones, being **characterized in that** an optically active α-hydroxy-γ-keto acid ester is synthesized by the method according to claim 4, and the optically active α-hydroxy-γ-keto acid ester is subjected to a reduction reaction and, subsequently, to a cyclization reaction, to thereby generate a compound represented by at least one of the following formulae (6):

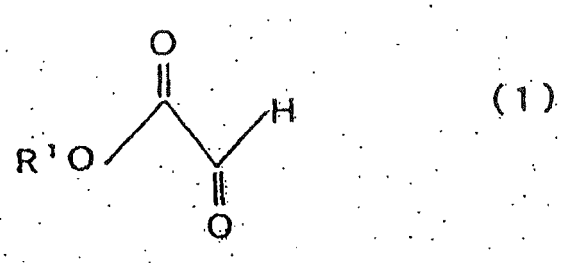


(6)

wherein R^3, R^4 and R^5 are as defined in claim 1.

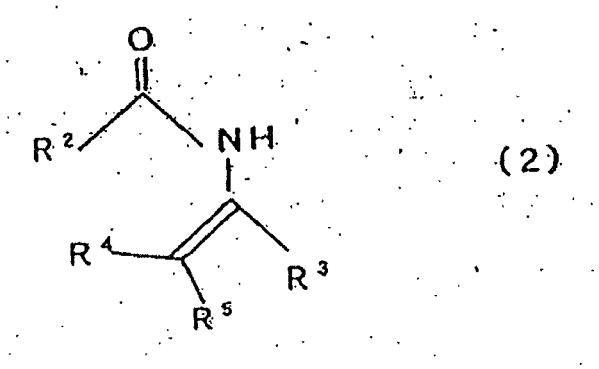
Patentansprüche

1. Verfahren einer enantioselektiven nukleophilen Additionsreaktion von Enamid, **dadurch gekennzeichnet, dass** es sich um ein Verfahren einer nukleophilen Additionsreaktion einer Enamidverbindung, begleitet von der Erzeugung einer Hydroxylgruppe (-OH), an eine Carbonylgruppe handelt, die an einer Verbindung durchgeführt wird, die eine Carbonylgruppe aufweist, die ein Glyoxylsäureester ist, dargestellt durch die folgende Formel (1):



(1)

wobei R^1 eine Kohlenwasserstoffgruppe darstellt, die einen Substituenten aufweisen kann; und wobei die Enamidverbindung durch die folgende Formel (2) dargestellt wird:



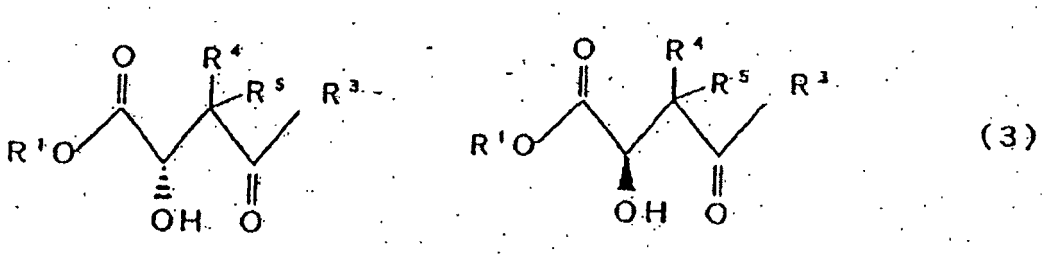
(2)

wobei R^2 eine Kohlenwasserstoffgruppe, die einen Substituenten aufweisen kann, oder eine Kohlenwasserstoffgruppe, die einen Substituenten aufweisen kann, darstellt, um über ein Sauerstoffatom gebunden zu werden;
R^3 eine Kohlenwasserstoffgruppe darstellt, die einen Substituenten aufweisen kann;
R^4 und R^5 gleich oder verschieden voneinander sein können und jedes ein Wasserstoffatom oder eine Kohlenwasserstoffgruppe darstellt, die einen Substituenten aufweisen kann, wobei mindestens eines davon ein Wasserstoffatom darstellt;
und Durchführen der Reaktion in Gegenwart eines chiralen Katalysators, der Kupfer oder Nickel umfasst.

2. Verfahren einer enantioselektiven nukleophilen Additionsreaktion von Enamid nach Anspruch 1, das **dadurch gekennzeichnet ist, dass** der chirale Katalysator aus einer Kupferverbindung oder einer Nickelverbindung, die ein Salz einer organischen oder anorganischen Säure oder ein Komplex oder Komposit des Salzes ist, und einem chiralen Diaminliganden besteht.

3. Verfahren einer enantioselektiven nukleophilen Additionsreaktion von Enamid nach Anspruch 2, das **dadurch gekennzeichnet ist, dass** der chirale Diaminligand eine Ethylen-Diamin-Struktur als einen Teil davon aufweist.

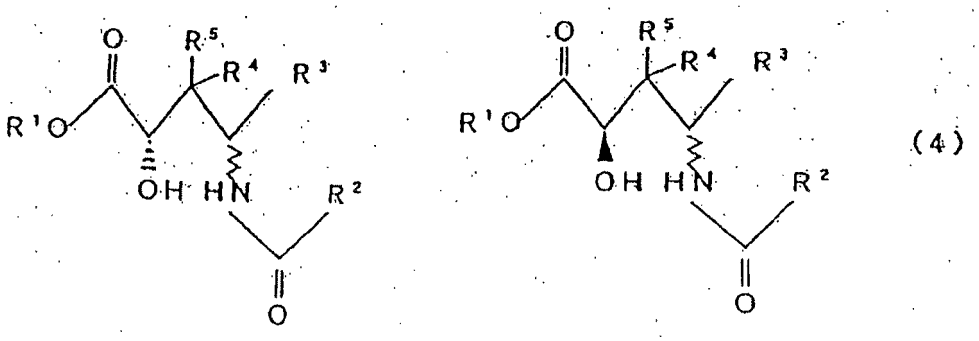
4. Verfahren zum Synthetisieren eines optisch aktiven α-Hydroxy-γ-ketosäureesters, das **dadurch gekennzeichnet ist, dass** nach der nukleophilen Additionsreaktion nach einem der vorhergehenden Ansprüche eine Säurebehandlung durchgeführt wird, um dadurch eine Verbindung zu erzeugen, die durch mindestens eine der folgenden Formeln (3) dargestellt wird:



(3)

wobei R^1, R^3, R^4 und R^5 wie in Anspruch 1 definiert sind.

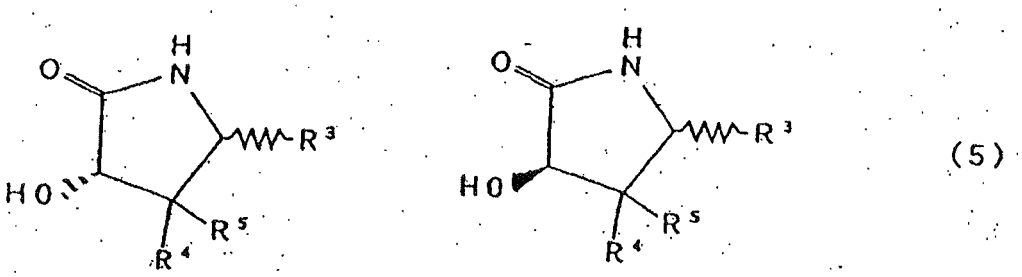
5. Verfahren zum Synthetisieren eines optisch aktiven α-Hydroxy-γ-aminosäureesters, das **dadurch gekennzeichnet ist, dass** nach der nukleophilen Additionsreaktion nach einem der Ansprüche 1 bis 3 eine Reduktionsbehandlung durchgeführt wird, um dadurch eine Verbindung zu erzeugen, die durch mindestens eine der folgenden Formeln (4) dargestellt wird:



(4)

wobei R^1, R^2, R^3, R^4 und R^5 wie in Anspruch 1 definiert sind.

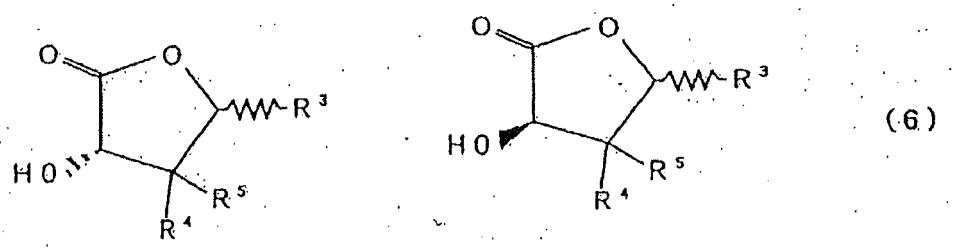
6. Verfahren zum Synthetisieren von optisch aktiven α-Hydroxy-γ-lactamen, das **dadurch gekennzeichnet ist, dass** ein optisch aktiver α-Hydroxy-γ-aminosäureester durch das Verfahren nach Anspruch 5 synthetisiert wird, ein Substituent (R^2CO-) auf einer γ-Aminogruppe des optisch aktiven α-Hydroxy-γ-aminosäureesters entfernt wird und danach eine Zyklisierungsreaktion durchgeführt wird, um dadurch eine Verbindung zu erzeugen, die durch mindestens eine der folgenden Formeln (5) dargestellt wird:



(5)

wobei R^3, R^4 und R^5 wie in Anspruch 1 definiert sind.

7. Verfahren zum Synthetisieren irgendeines der optisch aktiven α-Hydroxy-γ-lactone, das **dadurch gekennzeichnet ist, dass** der optisch aktive α-Hydroxy-γ-ketosäureester durch das Verfahren nach Anspruch 4 synthetisiert wird und der optisch aktive α-Hydroxy-γ-ketosäureester einer Reduktionsreaktion und anschließend einer Zyklisierungsreaktion unterzogen wird, um dadurch eine Verbindung zu erzeugen, die durch mindestens eine der folgenden Formeln (6) dargestellt wird:



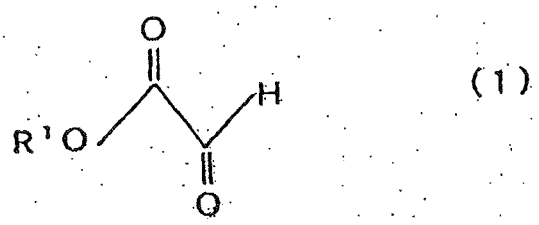
(6)

wobei R^3, R^4 und R^5 wie in Anspruch 1 definiert sind.

Revendications

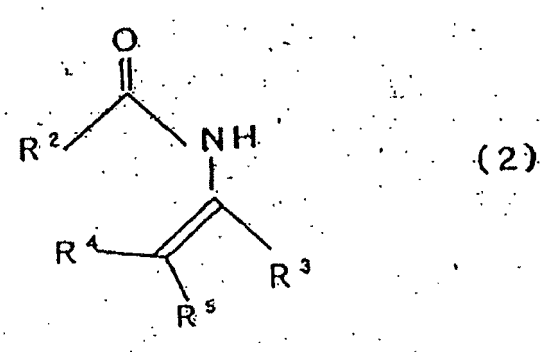
1. Procédé de réaction d'addition nucléophile énantiosélective d'un énamide, **caractérisé en ce qu'**il s'agit d'un procédé de réaction d'addition nucléophile d'un composé d'énamide accompagnée de la génération d'un groupement hydroxyle (-OH) à un groupement carbonyle, effectué sur un composé ayant un groupement carbonyle qui est un

ester de l'acide glyoxylique représenté par la formule suivante (1) :



(1)

dans laquelle R^1 représente un groupement hydrocarboné qui peut avoir un substituant ;
et dans lequel ledit composé d'énamide est représenté par la formule suivante (2) :



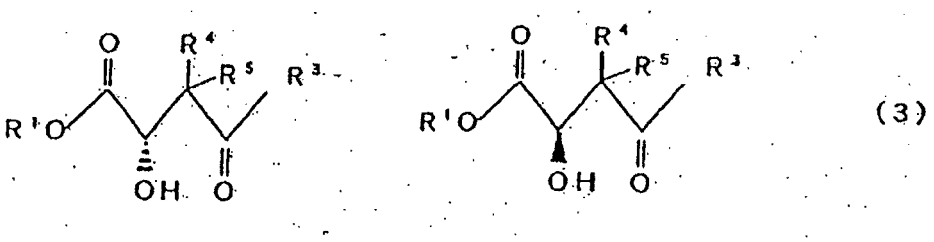
(2)

dans laquelle R^2 représente un groupement hydrocarboné qui peut avoir un substituant ou un groupement hydrocarboné qui peut avoir un substituant à lier via un atome d'oxygène ;
R^3 représente un groupement hydrocarboné qui peut avoir un substituant ;
R^4 et R^5 peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène ou un groupement hydrocarboné qui peut avoir un substituant, dans lequel au moins l'un d'eux représente un atome d'hydrogène ;
et en effectuant la réaction en présence d'un catalyseur chiral comprenant du cuivre ou du nickel.

2. Procédé de réaction d'addition nucléophile énantiosélective d'un énamide selon la revendication 1, **caractérisé en ce que** le catalyseur chiral est constitué d'un composé de cuivre ou d'un composé de nickel, qui est un sel d'un acide organique ou inorganique ou un complexe ou un composite du sel, et un ligand de diamine chiral.

3. Procédé de réaction d'addition nucléophile énantiosélective d'un énamide selon la revendication 2, **caractérisé en ce que** le ligand de diamine chiral a une structure d'éthylènediamine en tant que partie de celui-ci.

4. Procédé de synthèse d'un ester d'α-hydroxy-γ-cétoacide optiquement actif, **caractérisé en ce que**, après la réaction d'addition nucléophile selon l'une quelconque des revendications précédentes, un traitement à l'acide est effectué pour générer de la sorte un composé représenté par au moins l'une des formules suivantes (3) :

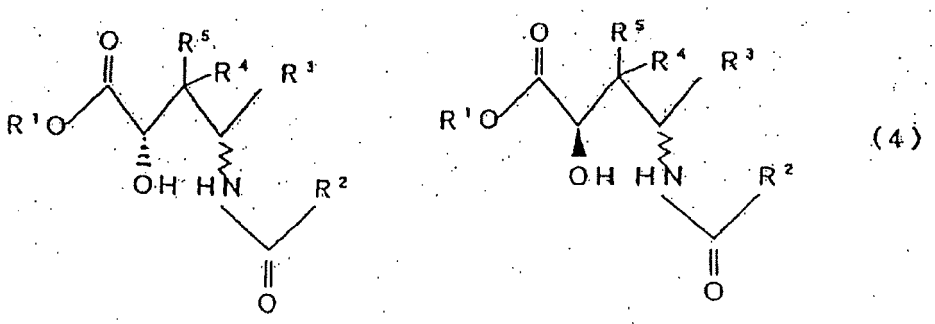


(3)

dans lesquelles R^1, R^3, R^4 et R^5 sont tels que définis dans la revendication 1.

5. Procédé de synthèse d'un ester d'α-hydroxy-γ-aminoacide optiquement actif, **caractérisé en ce que**, après la

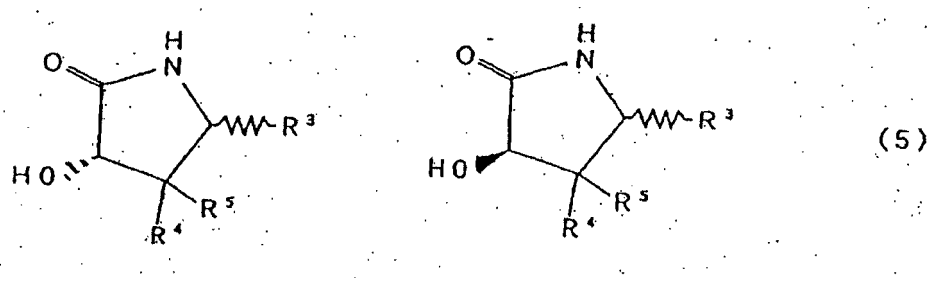
réaction d'addition nucléophile selon l'une quelconque des revendications 1 à 3, un traitement de réduction est effectué pour ainsi générer un composé représenté par au moins l'une des formules suivantes (4) :



(4)

dans lesquelles R^1, R^2, R^3, R^4 et R^5 sont tels que définis dans la revendication 1.

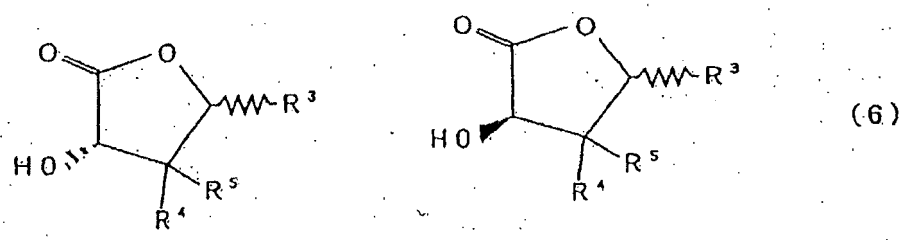
6. Procédé de synthèse d'α-hydroxy-γ-lactames optiquement actives, **caractérisé en ce qu'**un ester d'α-hydroxy-γ-aminoacide optiquement actif est synthétisé par le procédé selon la revendication 5, un substituant (R^2 CO-) qui se trouve sur un groupement γ-amino de l'ester d'α-hydroxy-γ-aminoacide optiquement optif est éliminé et, ensuite, une réaction de cyclisation est effectuée pour ainsi générer un composé représenté par au moins l'une des formules suivantes (5) :



(5)

dans lesquelles R^3, R^4 et R^5 sont tels que définis dans la revendication 1.

7. Procédé de synthèse de l'une quelconque d'α-hydroxy-γ-lactones optiquement actives, **caractérisé en ce qu'**un ester d'α-hydroxy-γ-cétoacide optiquement actif est synthétisé par le procédé selon la revendication 4 et l'ester d'α-hydroxy-γ-cétoacide optiquement actif est soumis à une réaction de réduction et, par la suite, à une réaction de cyclisation, pour ainsi générer un composé représenté par au moins l'une des formules suivantes (6) :



(6)

dans lesquelles R^3, R^4 et R^5 sont tels que définis dans la revendication 1.

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- *Journal of Combinatorial Chemistry,* 2001, vol. 3 (5), 401-403 **[0003]**
- *Org. Lett.,* 2002, vol. 4 (1), 143-145 **[0003]**
- *J. Am. Chem. Soc.,* 2003, vol. 125 (9), 2507-2515 **[0003]**
- *J. Organic Chemistry,* 09 October 1998, vol. 63 (22), 7764-7769 **[0005]**
- *Organic Letters,* 07 September 2002, vol. 4 (20), 3379-3382 **[0005]**