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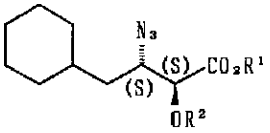
(54) **CYCLOHEXYL BUTYRIC ACID DERIVATIVE AND ITS PRODUCTION**

(57)Abstract:
PURPOSE: To safely produce the subject derivative having a high optical purity by asymmetrically hydrogenating a 4-cyclohexyl-2-halogeno-3-oxobutyric acid ester in the presence of an Ru complex catalyst, epoxidizing the product and subsequently reacting the reactional product with trimethylsilyl azide, etc.
CONSTITUTION: A 4-cyclohexyl-2-halogeno-3-oxobutyric acid ester of formula I (R1 is lower alkyl; X is halogen) is asymmetrically hydrogenated in the presence of a ruthenium-phosphine complex catalyst into a 4-cyclohexyl-2-halogeno-(3 R)-hydroxybutyric acid ester of formula II (the wave line exhibits 2S-configuration and/or 2R-configuration), and the compound of formula II is epoxidized in the presence of a base into a 4-cyclohexyl-(2S,2R)-epoxybutyric acid ester of formula III. The product of formula III is further reacted with a tri-lower alkylsilyl azide in the presence of a Lewis acid to produce a (3S)-azido-4-cyclohexyl-(2S)-substituted butyric acid ester of formula IV (R2 is H, lower trialkylsilyl).

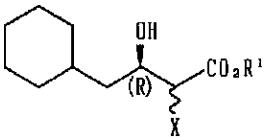
CLAIMS

[Claim(s)]
[Claim 1] The following general formula (4)
[Formula 1]



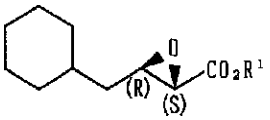
(4)

It is - azide-4-cyclohexyl expressed with (R1 shows a low-grade alkyl group among a formula, and R2 shows a hydrogen atom or a low-grade trialkylsilyl group) (3S). -(2S)- It is substitute butylate.
[Claim 2] The following general formula (2)
[Formula 2]



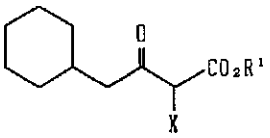
(2)

It is 4-cyclohexyl-2-halogeno [which is expressed with (R1 shows a low-grade alkyl group among a formula, X shows a halogen atom, and a wavy line means 2S-arrangement and/or 2R-arrangement)]. -(3R)- It is hydroxybutyric acid ester.
[Claim 3] The following general formula (3)
[Formula 3]



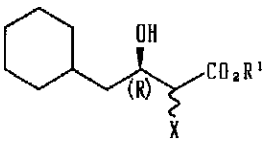
(3)

It is 4-cyclohexyl expressed with (R1 shows a low-grade alkyl group among a formula). -(2S and 3R)- It is epoxy butylate.
[Claim 4] General formula (1)
[Formula 4]



(1)

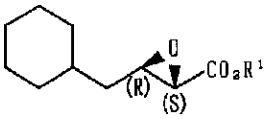
Dissymmetry hydrogenation of the 4-cyclohexyl-2-halogeno-3-oxo butylate expressed with (R1 shows a low-grade alkyl group among a formula, and X shows a halogen atom) is carried out under presence of a ruthenium-phosphine complex, and it is a general formula (2).
[Formula 5]



(2)

It is 4-cyclohexyl-2-halogeno [which is expressed with (R1 shows a low-grade alkyl group, X shows a halogen atom, and a wavy line means 2S-arrangement and/or 2R-arrangement)]. -(3R)- It makes with hydroxybutyric acid ester, subsequently a base carries out bottom epoxidation of presence of this, and it is a general formula (3).

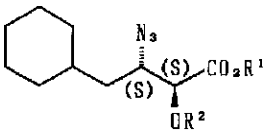
[Formula 6]



(3)

It is 4-cyclohexyl expressed with (R1 shows a low-grade alkyl group among a formula). -(2S and 3R)- They are epoxy butylate, nothing, and the general formula (4) characterized by making a low-grade-under presence of Lewis acid trialkylsilyl azide react to this further.

[Formula 7]

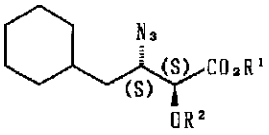


(4)

It is - azide-4-cyclohexyl expressed with (R1 shows a low-grade alkyl group among a formula, and R2 shows a hydrogen atom or a low-grade trialkylsilyl group) (3S). -(2S)- It is the manufacturing method of substitute butylate.

[Claim 5] General formula (4)

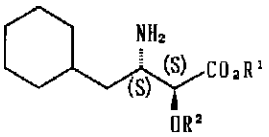
[Formula 8]



(4)

It is - azide-4-cyclohexyl expressed with (R1 shows a low-grade alkyl group among a formula, and R2 shows a hydrogen atom or a low-grade trialkylsilyl group) (3S). -(2S)- Catalytic reduction of the substitute butylate is carried out, and it is a general formula (5).

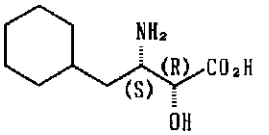
[Formula 9]



(5)

They are nothing [which are expressed with (R1 and R2 show the same thing as the above among a formula) (2S and 3S) / - cyclohexyl ********** derivative and nothing], and the formula (6) characterized by subsequently reversing the configuration of the 2nd place of this.

[Formula 10]

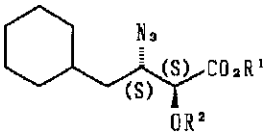


(6)

- cyclohexyl ********** come out of and expressed (2R and 3S), or the manufacturing method of the salt.

[Claim 6] General formula (4)

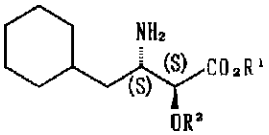
[Formula 11]



(4)

It is - azide-4-cyclohexyl expressed with (R1 shows a low-grade alkyl group among a formula, and R2 shows a hydrogen atom or a low-grade trialkylsilyl group) (3S). -(2S)- Substitute butylate is hydrocracked and it is a general formula (5).

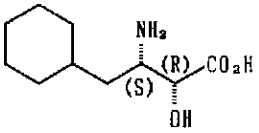
[Formula 12]



(5)

It makes with - cyclohexyl ********** derivative expressed with (R1 and R2 show the same thing as the above among a formula) (2S and 3S), subsequently the configuration of the 2nd place of this is reversed, and it is a formula (6).

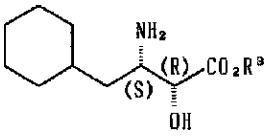
[Formula 13]



(6)

- cyclohexyl ********** come out of and expressed (2R and 3S), nothing, the formula characterized by making the alcohol of carbon numbers 1-7 react to this further (7)

[Formula 14]



(7)

It is the manufacturing method of - cyclohexyl ******** tin ester expressed with (R3 shows the alkyl group of carbon numbers 1-7 among a formula) (2R and 3S).

DETAILED DESCRIPTION

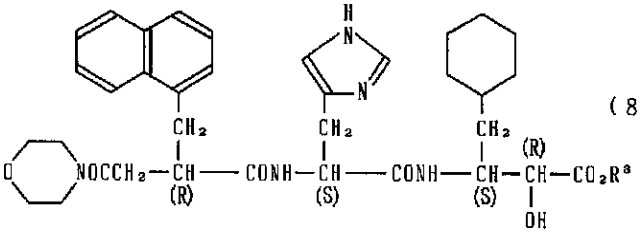
[Detailed Description of the Invention]

[0001]

[Field of the Invention] Homo-sapiens renin (Human renin) inhibitory action is shown, and this invention is the useful following formula (8) as a hypertension treatment agent.

[0002]

[Formula 15]

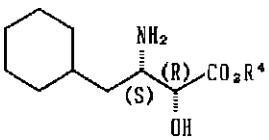


(8)

[0003] The peptide compound (JP,62-234071,A) expressed with (R3 shows the alkyl group of carbon numbers 1-7 among a formula) is constituted, and it is the following formula (9) especially important as the dissymmetry component.

[0004]

[Formula 16]



(9)

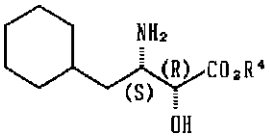
[0005] It is related with the new manufacturing method of optical-activity (2R and 3S)-cyclohexyl ************s expressed with (R4 shows a hydrogen atom or the alkyl group of carbon numbers 1-7 among a formula), and a cyclohexyl butyric-acid derivative useful as intermediate field of this manufacturing method.

[0006]

[Description of the Prior Art] The configuration of a peptide compound expressed with the above-mentioned general formula (8) affects activity, and it is checked that it is desirable that especially two asymmetrical carbons by the side of a carboxylate are (2R and 3S)-arrangement. Therefore, the following formula which constitutes the important dissymmetry fraction of the above-mentioned peptide compound (9)

[0007]

[Formula 17]



(9)

[0008] The method of manufacturing industrially advantageously optical-activity (2R and 3S)-cyclohexyl ************s expressed with (R4 shows the same thing as the above among a formula) was desired.

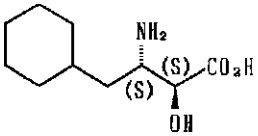
[0009] As technique of manufacturing (R and 32S)-cyclohexyl ************, conventionally J. Chem.Soc., Chem.Commun., 1989, and 1678 pages, Chem.Lett., 1990, 723 pages, J.Med.Chem., 1990, and 2707 pages, And it oxidizes, the technique of using a phenylalanine as a raw material, i.e., the alcohol guided from now on, is made into an aldehyde, and the technique of carrying out adding hydrocyanic acid gas etc. and making two optical-activity points is reported to JP,1-172365,A. However, since it had the process which uses oxidation reaction and a detrimental cyanide compound by this technique, while there was a problem in industrialization, the aldehyde generated in the interval was very unstable, and it was very difficult to be easy to carry out racemization and to obtain what has high optical purity.

[0010] Moreover, although the technique of manufacturing from a 4-cyclohexyl methyl-2-azetidinone derivative was reported to JP,2-121963,A, this technique was not satisfactory in yield and optical purity, either.

[0011] On the other hand, it is the following formula (10).

[0012]

[Formula 18]



(10)

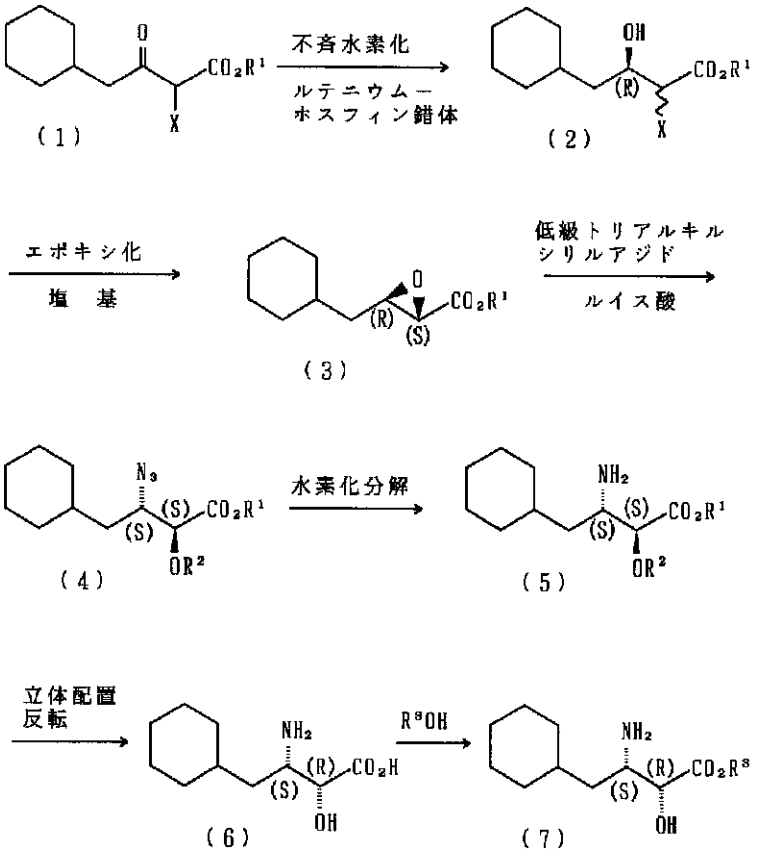
[0013] It comes out and the method (J.Med.Chem., 1990, and 2702 pages) of reversing the configuration, 2R and (3S)-field, of the 2nd place is learned as a process of optical-activity (2S and 3S)-cyclohexyl ************ expressed.

[0014]

[Problem(s) to be Solved by the Invention] Therefore, this invention aims at offering the technique of being easy operation and manufacturing - cyclohexyl ************s with high (2R, 3S) optical purity in a safety and a high yield.

[0015]

[Means for Solving the Problem] In such actual condition, as a result of inquiring zealously, this invention persons used 4-cyclohexyl-2-halogeno-3-oxo butylate as the start raw material, succeeded in manufacturing an optical-activity (2S, 3S)-cyclohexyl ********** derivative via a new cyclohexyl butyric-acid derivative, and completed this invention.
[0016] this invention technique is shown by the following reaction formula.
[0017]
[Formula 19]



[0018] (the inside of a formula, and R1 -- a low-grade alkyl group -- in R2, R3 shows the alkyl group of carbon numbers 1-7, X shows a halogen atom for a hydrogen atom or a low-grade trialkylsilyl group, and a wavy line means 2S-arrangement and/or 2R-arrangement)
[0019] Dissymmetry hydrogenation of the 4-cyclohexyl-2-halogeno-3-oxo butylate (1) is carried out under presence of a ruthenium-phosphine complex, and this invention technique is 4-cyclohexyl-2-halogeno. -(3R)- Hydroxybutyric acid ester (2) and nothing, Subsequently, a base carries out bottom epoxidation of presence of this, and it is 4-cyclohexyl. -(2S and 3R)- Epoxy butylate (3) and nothing, Furthermore, a low-grade-under presence of Lewis acid trialkylsilyl azide is made to react to this, and it is - (3S) azide-4-cyclohexyl. -(2S)- It is the technique of manufacturing substitute butylate (4).
[0020] Furthermore, this invention technique is (3S)-azide-4-cyclohexyl. -(2S)- Substitute butylate (4) is hydrocracked. - (2S and 3S) cyclohexyl ********** derivative (5) and nothing, The configuration of the 2nd place of this is reversed. Subsequently, - (2R and 3S) cyclohexyl ********** (6) Or they are the salt, and nothing and the method of making alcohol (R3OH) react to this by request further, and manufacturing - (2R and 3S) cyclohexyl ******** tin ester (7).
[0021] In this invention, as a low-grade alkyl group, the thing of carbon numbers 1-4 is usually shown, and a trimethylsilyl machine, a triethyl silyl machine, a ******** pill silyl machine, a triisopropyl silyl machine, a tributyl silyl

machine, a ******** butylsilyl machine, a **** sec-butylsilyl machine, a **** tert-butylsilyl machine, tert-butyldimethylsilyl machine, a dimethyl ******** silyl machine, etc. are mentioned as a low-grade trialkylsilyl group.

[0022] The compound (1) of a start raw material is obtained by halogenating 4-cyclohexyl-3-oxo butylate (J.Org.Chem., 29, 1964, and 1956 pages).

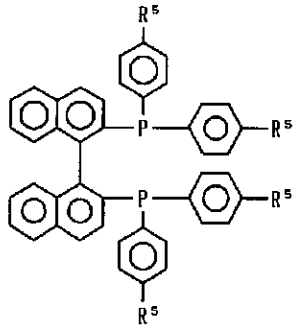
[0023] 4-cyclohexyl-2-halogeno -(3R)- Hydroxybutyric acid ester (2) is obtained by hydrogenating a ruthenium-phosphine complex for a compound (1) stereoselectively as a catalyst. As a ruthenium-phosphine complex, the ruthenium-phosphine complex of a publication and the thing specifically expressed with the following general formula (11) and (12) are mentioned to JP,61-63690,A and JP,2-191289,A.

[0024]

[Formula 20]

$Ru_2X_4(R^5\text{-BINAP})(NEt_3)$ (11)

〔式中、R^5-BINAPは一般式（13）で表わされる三級ホスフィン



(13)

を意味し、R^5は水素原子、メチル基、tertーブチル基又はメトキシ基を示し、Etはエチル基を示し、X はハロゲン原子を示す〕

[0025]

[Formula 21]

$[RuX(Y)(R^5\text{-BINAP})]X$ (12)

(式中、Y は置換基を有してもよいフェニル基を示し、R^5-BINAP及びX は前記と同じものを示す)

[0026] a ruthenium-phosphine complex -- a compound (1) -- receiving -- a 0.0002 - 0.01 times mol -- especially -- 0.001 - 0.005 time mol -- using is desirable As a solvent, the organic solvents usually used, such as a methanol, ethanol, propanol, an isopropanol, a butanol, tert-butyl alcohol, a methylene chloride, a tetrahydrofuran, and toluene, can be used. These solvents are similarly used in the following reactions. As for a solvent, in this reaction, it is desirable to use an amount (capacity) 2- 10 times to a compound (1). 0-50 degrees C of reaction temperature are 10-30 degrees C preferably, ten to 150 atm, hydrogen pressure is 50-100atm and it is preferably good to perform a reaction for 15 to 40 hours. For example, a silica gel column chromatography etc. can perform refining.

[0027] 4-cyclohexyl -(2S and 3R)- Epoxy butylate (3) is obtained by being -5 degrees C - 5 degrees C, and making a compound (2) and a base react preferably the reaction temperature of -20 degrees C - 30 degrees C in the reaction time 1 - 3 hours. As a base, alkali alkoxide, such as a sodium methylate, a sodium ethylate, sodium pro ********, sodium isopropylate, a sodium butyrate, a sodium tert-butyrate, a potassium methylate, potassium ethylate, potassium pro ********, potassium isopropylate, a potassium butyrate, and a potassium tert-butyrate, is

mentioned. a solvent -- the amount (capacity) of 1 - 3 times of a compound (2) -- to use is good Refining is performed by distilling, after extracting by solvents, such as toluene, ethyl acetate, the ether, a methylene chloride, and chloroform, after adding a phosphate buffer solution (pH 7.0) for example, after a reaction and distilling off a solvent, and distilling off a solvent.

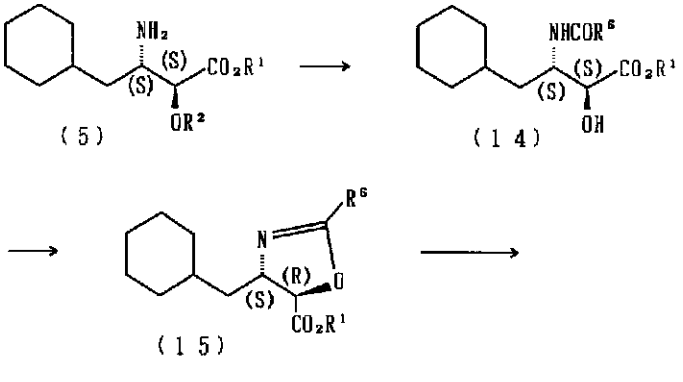
[0028] (3S)-azide-4-cyclohexyl -(2S)- Substitute butylate (4) is obtained by making a compound (3) and a low-grade trialkylsilyl azide react under presence of a Lewis acid. As a low-grade trialkylsilyl azide, a trimethylsilyl azide, a triethyl silyl azide, a ******** pill silyl azide, a triisopropyl silyl azide, a tributyl silyl azide, a ******** butylsilyl azide, a **** sec-butylsilyl azide, a **** tert-butylsilyl azide, tert-butyldimethylsilyl azide, a dimethyl ******** silyl azide, etc. are mentioned. Lewis acid ****** -- a zinc chloride, a zinc bromide, and a titanium tetrachloride -- titanium, an aluminum chloride, the aluminium bromide, tetraisopropoxy titanium, ******** propoxy aluminum, 2 tin chloride, and a tin etc. tetrachloride are mentioned 4 bromuration a low-grade trialkylsilyl azide -- a compound (3) -- receiving -- 1-1.2 a twice mol and a Lewis acid -- a compound (3) -- receiving -- 5 - 20 mol % -- using is desirable 10 - 30 hours of reaction time are [reaction temperature / 50-100 **, especially 60-80 degrees C] desirable. A silica gel column chromatography etc. can perform refining.

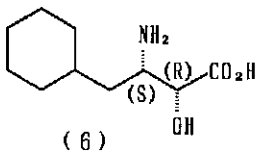
[0029] An optical-activity (2S and 3S)-cyclohexyl ************ derivative (5) is obtained by hydrocracking a compound (4) to a compound (4) using the catalyst of 1 - 10% of the weight of 5 - 10% palladium-carbon etc. As for reaction temperature, it is preferably good to perform 10-30 degrees C and hydrogen pressure, and to perform [0-50-degree C] reaction time at 15 - 25atm preferably one to 30 atm in 10 - 40 hours. Although especially the amount of solvents is not limited, its thing of a compound (4) used an amount (capacity) 3- 5 times is desirable. Here, although the low-grade trialkylsilyl group of the 2nd place changes to a hydroxy group when alcohol is used as a solvent, when a tetrahydrofuran etc. is used, it does not change. Refining removes the catalyst after a reaction, and after it distills off a solvent, a silica gel column chromatography etc. can perform it.

[0030] Thus, the configuration inversion to obtained (2R and 3S)-cyclohexyl ************ (6) from an optical-activity (2S and 3S)-cyclohexyl ************ derivative (5) is well-known technique (J.Am.Chem.Soc., 1949, 71 volumes, and 110 pages) shown by the following reaction formula. It can carry out.

[0031]

[Formula 22]





[0032] (Among a formula, R6 shows the phenyl group which may have the low-grade alkyl group or the substituent, and R1 and R2 show the same thing as the above)

[0033] A compound (14) is obtained by making an acyl-chloride compound react to a compound (5) under presence of a base. As an acyl-chloride compound, an acetyl chloride, a chlorination propionyl, the chlorination butyryl, a benzoyl chloride, a chlorination 2-methyl benzoyl, a chlorination 3-methyl benzoyl, a chlorination 4-methyl benzoyl, a chlorination 2-methoxy benzoyl, a chlorination 3-methoxy benzoyl, a chlorination 4-methoxy benzoyl, a chlorination 2-****** benzoyl, a chlorination 3-****** benzoyl, a chlorination 4-****** benzoyl, etc. are mentioned. As a base, a trimethylamine, a triethylamine, a diisopropyl ethylamine, a pyridine, 4-dimethylamino pyridine, etc. are mentioned. moreover, a base -- a compound (5) -- receiving -- 1-1.2 twice -- it is as good as the ** **** A reaction is -20 degrees C - 30 degrees C in temperature, and is performed by making it react for 6 to 20 hours. Although especially the amount of solvents is not limited, it is desirable to use an amount (capacity) 3- 5 times to a compound (5). After it processes refining with an after [reaction] 1N-hydrochloric acid and it distills off a solvent, a silica gel column chromatography etc. can perform it.
[0034] A compound (15) is obtained by making the thionyl chloride of a mol react a compound (14), its 1, - 3 times. A reaction is -20 degrees C - 50 degrees C in temperature, and is performed by making it react for 1 to 3 hours. Although especially the amount of solvents is not limited, it is desirable to use an amount (capacity) 1- 3 times to a compound (14). After a reaction, if a solvent is distilled off, a compound (15) will be obtained. A compound (15) is obtained as a hydrochloride here, when a thionyl chloride is used.
[0035] A compound (6) melts a compound (15) to a hydrochloric acid 20 of an amount (capacity), - 25% the 5 - 10 times, and is obtained by making it react in reaction temperature 80-100 **, the reaction time 5, - 20 hours. A compound (6) is obtained by condensing a reaction solution. In addition, when a compound (15) is used with a hydrochloride, a compound (6) is obtained as a hydrochloride.
[0036] Thus, what is necessary is to melt into xeransis hydrochloric-acid-gas-alcoholic mixed liquor, to be the temperature of 70 - 100 **, to make it react for 1 to 5 hours, to perform an esterification, and just to neutralize further, in order to acquire the ester field (7) from the obtained compound (6).
[0037] As alcohol used here, a methanol, ethanol, propanol, an isopropanol, a butanol, an isobutanol, sec-butyl alcohol, tert-butyl alcohol, etc. are mentioned. A xeransis hydrochloric-acid-gas-alcoholic mixed solution has the desirable thing of a compound (6) used an amount (capacity) 3- 5 times. After distilling off a reaction solution, saturation can melt the residue in the solution of an amount (capacity) the three to 5 times, can add the aqueous solution of the base of a molar quantity there about one to 3 times, and can be performed by making it react at the temperature of -20 degrees C - 30 degrees C. As a solvent to use, toluene, a tetrahydrofuran, ethyl acetate, chloroform, a methylene chloride, etc. are mentioned. As a base to use, a sodium carbonate, a sodium hydrogencarbonate, potassium carbonate, a potassium hydrogencarbonate, etc. are mentioned. After a saturation operation end, refining performs liquid separation operation and is performed by condensing and recrystallizing an organic layer.
[0038]
[Effect of the Invention] Like a ** top, this invention technique is technique advantageous to the industrial target which can manufacture the optical-activity cyclohexyl ********** derivative with high optical purity with sufficient yield safely.
[0039]

[Example] Hereafter, although an example explains this invention still in detail, this invention is not limited to these examples. Especially measurement in an example was performed under the following instrument for analysis and conditions, unless it limited.
1. Gas-Chromatography Machine Vessel:Shimazu GC-9A (Shimadzu Make)
Column: OV-101 Silica capillary-tube phi 0.25mm x 25m (GL Sciences, Inc. make)
Measurement Temperature: It is a temperature-up injection temperature:200 degree-C2. high-performance-chromatography machine at a part for 10 degrees-C/in 100-250 degree C. Vessel:********** 500 (product made from **********)
Detector: UV detector ********** 484 (product made from **********)
3. NMR Machine Vessel:AM-400 Type Equipment 400MHz (Product made from **********)
Internal-standard Matter: Tetramethylsilane 4. angle-of-rotation machine Vessel:DIP-4 type equipment (day duty light industrial incorporated company make)
5. Elemental-Analysis Device:CHN-2400 (Product made from Par **********)
6. Mass-Analysis Device:M80B (Hitachi Make)
[0040] Example 1(2SR)-******-4-cyclohexyl -(3R)- It reaches 23.25g (0.1 mols) of the synthetic :2-******-4-cyclohexyl-3-oxo methyl butyrates which are a hydroxybutyric acid methyl. Ru2Cl42((+)-BINAP) NEt3 169mg (0.1mmol) It melted to methanol 15ml and the mixed solution of 105ml of methylene chlorides, and taught the 500ml autoclave, and the reaction was performed at hydrogen pressure 100atm and 20 degrees C for 20 hours. a reaction solution is condensed and a silica gel column chromatography refines (2SR) - ******-4-cyclohexyl-(3R)-hydroxybutyric acid methyl 23.30g (99% of yield) was obtained Analysis of a gas chromatography showed that the Singh field was 65% and the anti field was 35%.
Optical purity Singh field 92%ee (96:4)
Anti field 82%ee (91:9)
the decision of optical purity -- (2 SR)-******-4-cyclohexyl-(3R)-hydroxybutyric acid methyl 47mg (0.2mmol) and (R)-alpha-methoxy-alpha-truffe ****** methylphenyl acetic-acid chloride 51mg (0.2mmol) -- pyridine 1ml -- it was made to react in inside for 5 hours, and HPLC analysis determined by considering as the ester compound of a (R)-alpha-methoxy-alpha-truffe ****** methylphenyl acetic acid Hereafter, the analysis condition is shown.
Column: YMC-PAK A-003-3phi 4.6x250mm (product made from , Inc. wye ********)
Eluate:Hexane:tetrahydrofuran =99:1 style a part for **:1ml/-- detection wavelength: -- again, the ratio of the thing of - field and the thing of the (R and 32S)-field is 96:4 among the Singh fields (2S and 3R), and 254nm was understood that the ratio of the thing of - field and the thing of the (2S and 3S)-field is 91:9 among the anti fields (2R and 3R This was deduced from the data of the compound guided after this example.
The 1H-NMR:(CDCl3 and deltappm) Singh field 0.84-1.85 (m, 13H, CH), 2.43 (s, 1H, OH), 3.82 (s, 1H, OH), 3.82 (s, 3H, OCH3), 4.08-4.16 (m, 1H, CHO), the 4.20 (d, 1H, J= 6.50Hz, CHCl) anti field 0.82-1.86 (m, 13H, CH), 2.38 (br s, 1H, OH), 3.82 (s, 3H, OCH3), 4.18-4.23 (m, 1H, CHO), and 4.30 (d, 1H, J= 3.98Hz, CHCl)
[0041] Example 24-cyclohexyl -(2S and 3R)- 85g [of methanol solutions (0.441 mols)], and methanol 100ml of the synthetic :28%-sodium methylate of an epoxy methyl butyrate It put into the reactor and cooled to 5 degrees C in the ice bath. it compounded in the example 1 there (2SR) - ******-4-cyclohexyl-(3R)-hydroxybutyric acid methyl 100g (0.426 mols) Methanol 200ml The melted solution was dropped under cooling. It agitated at 5 degrees C after instillation for 2 hours. Then, after adding a reaction mixture into 0.1M phosphate buffer solution * (pH=7) 500ml cooled at 0 degree C, reduced pressure distilling off of the methanol was carried out. After ethyl acetate's extracting a residue and distilling off a solvent, a rough product is distilled simply (102-110 degrees C / 0.1mmHg), and it is 4-cyclohexyl. -(2S and 3R)- 56.91g (75%

of yield) of epoxy methyl butyrates was obtained.
*0. Composition:phosphoric-acid 1 sodium of 1M phosphate buffer solution (NaH2PO4.2H2O) 5.55g phosphoric-acid disodium (Na2HPO4.12H2O) 21.5g water 1000mlGLC It turns out that the ****:transformer ratio of the epoxy compound obtained by analysis is 5:95.
1H-NMR:(CDCl3 and deltappm)0.84-1.84 (m, 13H, CH), 3.15-3.19 (m, 2H, CH), and 3.78(s, 3H, CH3) [alpha] D+30.60 degree (C= 2.25 and methanol) elemental analysis C11H18O3 It carries out.

	C	H
理論値 (%)	66.64	9.15
実測値 (%)	66.39	8.91

[0042] Example 3(3S)-azide-4-cyclohexyl [1.0g (73mmol) of and zinc chlorides It put into the reactor and agitated at 70 degrees C for 20 hours.] -(2S)-4-cyclohexyl obtained in the synthetic : example 2 of a trimethylsiloxy methyl butyrate -(2S and 3R)- 14.43g [of epoxy methyl butyrates] (72.9mmol), and trimethylsilyl azide 8.4g (73mmol) A silica gel column chromatography (hexane:ethyl-acetate =9:1 (capacity factor)) refines after a reaction, and it is (3S)-azide-4-cyclohexyl. -(2S)- 20.29g (91% of yield) of trimethylsiloxy methyl butyrates It obtained.
1H-NMR:(CDCl3 and deltappm)0.14-0.18 (m, 9H, SiCH3), 0.76-1.82 (m, 13H, CH), 3.49-3.53 (m, 1H, CHN3), 3.75 (s, 3H, OCH3), 4.34 (d, 1H, J= 3.97Hz, CHO) elemental analysis As C14H27N3O3Si

	C	H	N
計算値 (%)	53.64	8.68	13.40
実測値 (%)	53.41	8.84	13.62

[0043] Example 4(3S)-amino-4-cyclohexyl -(2S)- - (3S) azide-4-cyclohexyl obtained in the synthetic : example 3 of a trimethylsiloxy methyl butyrate -(2S)- 50.0g (159.5mmol) of trimethylsiloxy methyl butyrates, 2.5g [of 2% of the weight of the 5% palladium-carbon] and xeransis tetrahydrofuran 200ml of the amount (capacity) of 4 times was put into the 500ml autoclave, and it was made to react at hydrogen pressure 25atm and a room temperature for 48 hours. After checking that the raw material had disappeared by TLC (benzene:ethyl-acetate =8:2 (capacity factor)), the catalyst was removed using cerite. A solvent is distilled off and it is (3S)-amino-4-cyclohexyl. -(2S)- 36.7g (80% of yield) of trimethylsiloxy methyl butyrates was obtained. Elemental analysis C14H29NO3Si It carries out.

	C	H	N
計算値 (%)	58.49	10.17	4.87
実測値 (%)	58.72	10.52	5.18

[0044] Example 5(3S)-bends amino-4-cyclohexyl [It put into the reactor, and considered as 0 degree C of inside **s in the ice bath, and 4.89g (34.8mmol) of benzoyl chlorides was dropped slowly.] -(2S)- - (3S) amino-4-cyclohexyl obtained in the synthetic : example 4 of a hydroxybutyric acid methyl -(2S)- Xeransis tetrahydrofuran 100ml of 10.0g (34.8mmol) of a trimethylsiloxy methyl butyrate, and its amount (capacity It agitated for 16 hours, after returning to a room temperature. 10ml of 5%-hydrochloric-acid aqueous solutions was added to the reaction mixture, and the reaction was stopped. Ethyl acetate extracts, after distilling off a solvent, a silica gel column chromatography (benzene:ethyl-acetate =10:1-5:1 (capacity factor)) refines, and it is (3S)-bends amino-4-cyclohexyl. -(2S)- Hydroxybutyric acid methyl 10.3g (92% of yield) was obtained.
1H-NMR:(CDCl3 and deltappm)0.78-1.94 (m, 13H, CH), 3.82 (s, 3H, OCH3), 4.43 (d, 1H, J= 2.95Hz, CHO), 4.62- 4.71 (m, 1H, CHN), 6.31 (d, 1H, J= 9.06Hz, NH), and

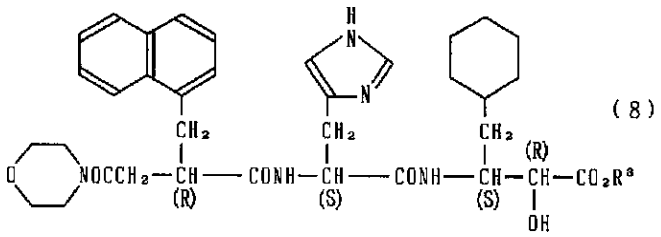
7.40 -7.80 (m, 5H, ArH) elemental analysis C18H25NO4 ******

	C	H	N
計算値 (%)	67.69	7.89	4.39
実測値 (%)	67.38	8.23	4.66

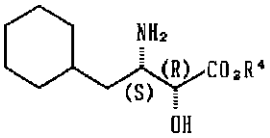
MS m/e:320(M+1)+ [0045] Example 6(3S)-amino-4-cyclohexyl -(2R)- - (3S) bends amino-4-cyclohexyl obtained in the synthetic : example 5 of a hydroxybutyric acid hydrochloride -(2S)- hydroxybutyric acid methyl 10.0g (31.3mmol) It melts to toluene 30ml of an amount (capacity) the 3 times, and is 9.3g (78.3mmol) of thionyl chlorides at 5 degrees C under ice-cooling. After dropping, it agitated as 30 degrees C for 2.5 hours. the residue obtained after collecting solvents -- 100ml of the 6N-hydrochloric acids of the amount (capacity) of 10 times adding -- warming (90 degrees C of inside **s) -- it agitated the bottom for 16 hours It washes with toluene, after removing a benzoic acid, a water layer is condensed, and it is (3S)-amino-4-cyclohexyl. -(2R)- 6.37g (85% of yield) of hydroxybutyric acid hydrochlorides was obtained.
1H-NMR:(D2O, deltappm)0.90-1.81 (m, 13H, CH), 3.72-3.78 (m, 1H, CHN), 4.44(d, 1H, J= 3.53Hz, CHO) [0046] Example 7(3S)-amino-4-cyclohexyl [It melted in 42ml of the solutions of the isopropanol-hydrochloric acid gas of the amount (capacity) of 10 times, and agitated at 80 degrees C for 3 hours.] -(2R)- - (3S) amino-4-cyclohexyl obtained in the synthetic : example 6 of a hydroxybutyric acid isopropyl -(2R)- 4.2g (14.6mmol) of hydroxybutyric acid hydrochlorides Solvents were collected, chloroform and the saturation sodium-hydrogencarbonate aqueous solution were added to the obtained residue, and liquid separation operation was performed. 4.1g (95% of yield) of rough products was obtained by condensing the obtained organic layer under reduced pressure. The obtained rough product was melted to the diisopropyl ether, the hexane was added, and the recrystallization was performed. The separated white needle crystal is filtered, and it dries, and is (3S)-amino-4-cyclohexyl. -(2R)- Hydroxybutyric acid isopropyl 3.36g (82% of yield) was obtained. The gas chromatography showed that it was the 98% of the degrees of chemical pure.
m.p. 85.5-86 degree-C[alpha]24D-21.50 **(C= 1.03 and CHCl3) 1H-NMR:(CDCl3 and deltappm)0.82-1.82 (m, 13H, CH), 1.29 (d, J= 6.26Hz, 6H, CH3), 3.20-3.90 (m, 1H, CHN), 3.97 (d, J= 2.38Hz, CHO), 5.08-5.19 (m, 1H, OCH)

Field

[Field of the Invention] Homo-sapiens renin (Human renin) inhibitory action is shown, and this invention is the useful following formula (8) as a hypertension treatment agent.
[0002]
[Formula 15]



[0003] The peptide compound (JP,62-234071,A) expressed with (R3 shows the alkyl group of carbon numbers 1-7 among a formula) is constituted, and it is the following formula (9) especially important as the dissymmetry component.
[0004]
[Formula 16]



(9)

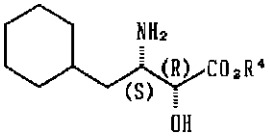
[0005] It is related with the new manufacturing method of optical-activity (2R and 3S)-cyclohexyl ************s expressed with (R4 shows a hydrogen atom or the alkyl group of carbon numbers 1-7 among a formula), and a cyclohexyl butyric-acid derivative useful as intermediate field of this manufacturing method.

Technique

[Description of the Prior Art] The configuration of a peptide compound expressed with the above-mentioned general formula (8) affects activity, and it is checked that it is desirable that especially two asymmetrical carbons by the side of a carboxylate are (2R and 3S)-arrangement. Therefore, the following formula which constitutes the important dissymmetry fraction of the above-mentioned peptide compound (9)

[0007]

[Formula 17]



(9)

[0008] The method of manufacturing industrially advantageously optical-activity (2R and 3S)-cyclohexyl ************s expressed with (R4 shows the same thing as the above among a formula) was desired.

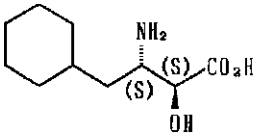
[0009] As technique of manufacturing (R and 32S)-cyclohexyl ************, conventionally J. Chem.Soc., Chem.Commun., 1989, and 1678 pages, Chem.Lett., 1990, 723 pages, J.Med.Chem., 1990, and 2707 pages, And it oxidizes, the technique of using a phenylalanine as a raw material, i.e., the alcohol guided from now on, is made into an aldehyde, and the technique of carrying out adding hydrocyanic acid gas etc. and making two optical-activity points is reported to JP,1-172365,A. However, since it had the process which uses oxidation reaction and a detrimental cyanide compound by this technique, while there was a problem in industrialization, the aldehyde generated in the interval was very unstable, and it was very difficult to be easy to carry out racemization and to obtain what has high optical purity.

[0010] Moreover, although the technique of manufacturing from a 4-cyclohexyl methyl-2-azetidinone derivative was reported to JP,2-121963,A, this technique was not satisfactory in yield and optical purity, either.

[0011] On the other hand, it is the following formula (10).

[0012]

[Formula 18]



(10)

[0013] It comes out and the method (J.Med.Chem., 1990, and 2702 pages) of reversing the configuration, 2R and (3S)-field, of the 2nd place is learned as a

process of optical-activity (2S and 3S)-cyclohexyl ********** expressed.

Effect

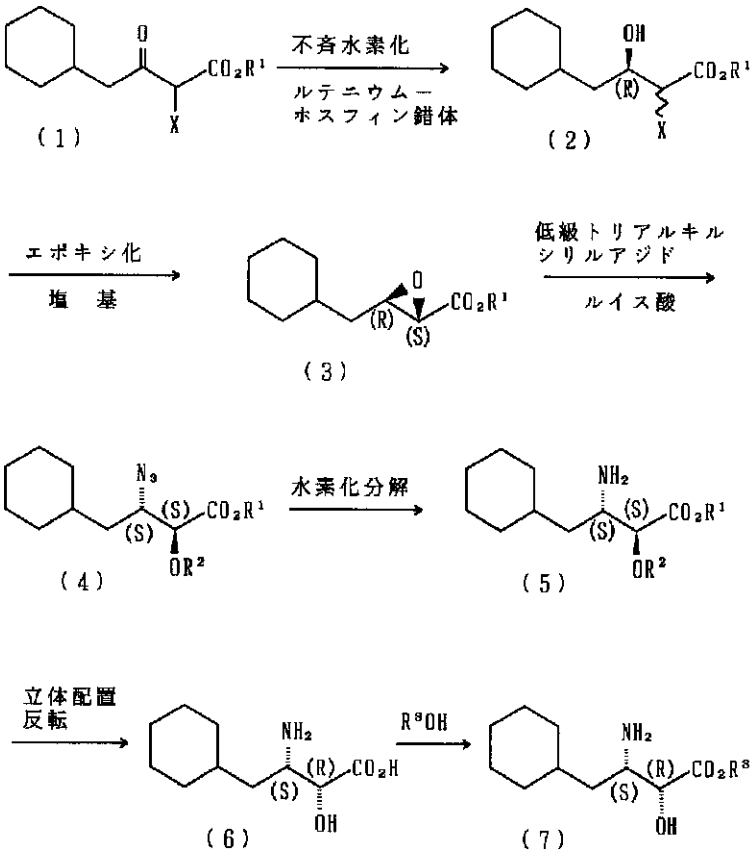
[Effect of the Invention] Like a ** top, this invention technique is technique advantageous to the industrial target which can manufacture the optical-activity cyclohexyl ********** derivative with high optical purity with sufficient yield safely.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] Therefore, this invention aims at offering the technique of being easy operation and manufacturing - cyclohexyl **********s with high (2R, 3S) optical purity in a safety and a high yield.

MEANS

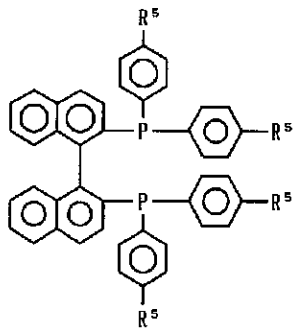
[Means for Solving the Problem] In such actual condition, as a result of inquiring zealously, this invention persons used 4-cyclohexyl-2-halogeno-3-oxo butylate as the start raw material, succeeded in manufacturing an optical-activity (2S, 3S)-cyclohexyl ********** derivative via a new cyclohexyl butyric-acid derivative, and completed this invention.
[0016] this invention technique is shown by the following reaction formula.
[0017]
[Formula 19]



[0018] (the inside of a formula, and R1 -- a low-grade alkyl group -- in R2, R3 shows the alkyl group of carbon numbers 1-7, X shows a halogen atom for a hydrogen atom or a low-grade trialkylsilyl group, and a wavy line means 2S-arrangement and/or 2R-arrangement)
[0019] Dissymmetry hydrogenation of the 4-cyclohexyl-2-halogeno-3-oxo butylate (1) is carried out under presence of a ruthenium-phosphine complex, and this invention technique is 4-cyclohexyl-2-halogeno. -(3R)- Hydroxybutyric acid ester (2) and nothing, Subsequently, a base carries out bottom epoxidation of presence of this, and it is 4-cyclohexyl. -(2S and 3R)- Epoxy butylate (3) and nothing, Furthermore, a low-grade-under presence of Lewis acid trialkylsilyl azide is made to react to this, and it is - (3S) azide-4-cyclohexyl. -(2S)- It is the technique of manufacturing substitute butylate (4).
[0020] Furthermore, this invention technique is (3S)-azide-4-cyclohexyl. -(2S)- Substitute butylate (4) is hydrocracked. - (2S and 3S) cyclohexyl ********** derivative (5) and nothing, The configuration of the 2nd place of this is reversed. Subsequently, - (2R and 3S) cyclohexyl ********** (6) Or they are the salt, and nothing and the method of making alcohol (R3OH) react to this by request further, and manufacturing - (2R and 3S) cyclohexyl ******** tin ester (7).
[0021] In this invention, as a low-grade alkyl group, the thing of carbon numbers 1-4 is usually shown, and a trimethylsilyl machine, a triethyl silyl machine, a ******** pill silyl machine, a triisopropyl silyl machine, a tributyl silyl machine, a ******** butylsilyl machine, a **** sec-butylsilyl machine, a **** tert-butylsilyl machine, tert-butyldimethylsilyl machine, a dimethyl ******** silyl machine, etc. are mentioned as a low-grade trialkylsilyl group.
[0022] The compound (1) of a start raw material is obtained by halogenating 4-cyclohexyl-3-oxo butylate (J.Org.Chem., 29, 1964, and 1956 pages).
[0023] 4-cyclohexyl-2-halogeno -(3R)- Hydroxybutyric acid ester (2) is obtained by hydrogenating a ruthenium-phosphine complex for a compound (1) stereoselectively as a catalyst. As a ruthenium-phosphine complex, the ruthenium-phosphine complex of a publication and the thing specifically expressed with the following general formula (11) and (12) are mentioned to JP,61-63690,A and JP,2-191289,A.
[0024]
[Formula 20]

$Ru_2X_4(R^5\text{-BINAP})(NEt_3)$ （１１）

〔式中、R^5-BINAPは一般式（１３）で表わされる三級ホスフィン



（１３）

を意味し、R^5は水素原子、メチル基、tert－ブチル基又はメトキシ基を示し、Etはエチル基を示し、Ｘはハロゲン原子を示す〕

[0025]

[Formula 21]
[RuX(Y)(R^5-BINAP)]X　　(12)

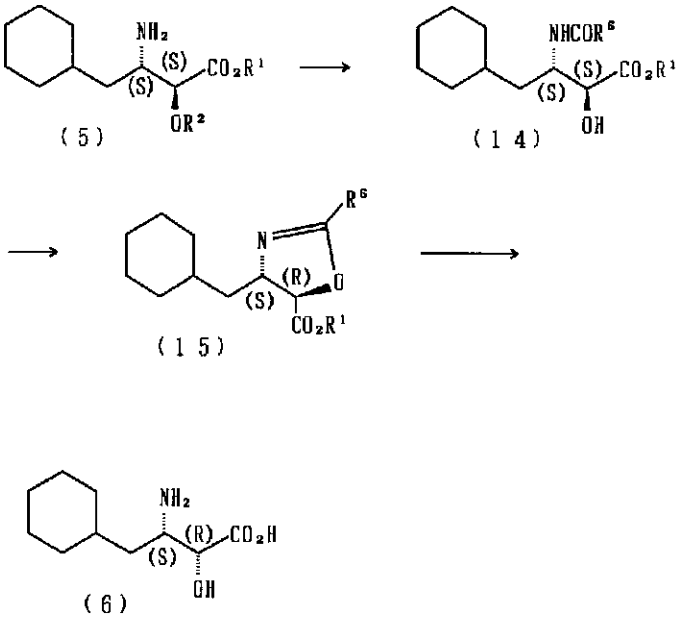
(式中、Y は置換基を有してもよいフェニル基を示し、R^5-BINAP及びX は前記と同じものを示す)

[0026] a ruthenium-phosphine complex -- a compound (1) -- receiving -- a 0.0002 - 0.01 times mol -- especially -- 0.001 - 0.005 time mol -- using is desirable As a solvent, the organic solvents usually used, such as a methanol, ethanol, propanol, an isopropanol, a butanol, tert-butyl alcohol, a methylene chloride, a tetrahydrofuran, and toluene, can be used. These solvents are similarly used in the following reactions. As for a solvent, in this reaction, it is desirable to use an amount (capacity) 2- 10 times to a compound (1). 0-50 degrees C of reaction temperature are 10-30 degrees C preferably, ten to 150 atm, hydrogen pressure is 50-100atm and it is preferably good to perform a reaction for 15 to 40 hours. For example, a silica gel column chromatography etc. can perform refining.
[0027] 4-cyclohexyl -(2S and 3R)- Epoxy butylate (3) is obtained by being -5 degrees C - 5 degrees C, and making a compound (2) and a base react preferably the reaction temperature of -20 degrees C - 30 degrees C in the reaction time 1 - 3 hours. As a base, alkali alkoxide, such as a sodium methylate, a sodium ethylate, sodium pro ********, sodium isopropylate, a sodium butyrate, a sodium tert-butyrate, a potassium methylate, potassium ethylate, potassium pro ********, potassium isopropylate, a potassium butyrate, and a potassium tert-butyrate, is mentioned. a solvent -- the amount (capacity) of 1 - 3 times of a compound (2) -- to use is good Refining is performed by distilling, after extracting by solvents, such as toluene, ethyl acetate, the ether, a methylene chloride, and chloroform, after adding a phosphate buffer solution (pH 7.0) for example, after a reaction and distilling off a solvent, and distilling off a solvent.
[0028] (3S)-azide-4-cyclohexyl -(2S)- Substitute butylate (4) is obtained by making a compound (3) and a low-grade trialkylsilyl azide react under presence of a Lewis acid. As a low-grade trialkylsilyl azide, a trimethylsilyl azide, a triethyl silyl azide, a ******** pill silyl azide, a triisopropyl silyl azide, a tributyl silyl azide, a ******** butylsilyl azide, a **** sec-butylsilyl azide, a **** tert-butylsilyl azide, tert-butyldimethylsilyl azide, a dimethyl ******** silyl azide, etc. are mentioned. Lewis acid ****** -- a zinc chloride, a zinc bromide, and a titanium tetrachloride -- titanium, an aluminum chloride, the aluminium bromide, tetraisopropoxy titanium, ******** propoxy aluminum, 2 tin chloride, and a tin etc. tetrachloride are mentioned 4 bromuration a low-grade trialkylsilyl azide -- a compound (3) -- receiving -- 1-1.2 a twice mol and a Lewis acid -- a compound (3) -- receiving -- 5 - 20 mol % -- using is desirable 10 - 30 hours of reaction time are [reaction temperature / 50-100 **, especially 60-80 degrees C] desirable. A silica gel column chromatography etc. can perform refining.
[0029] An optical-activity (2S and 3S)-cyclohexyl ********** derivative (5) is obtained by hydrocracking a compound (4) to a compound (4) using the catalyst of 1 - 10% of the weight of 5 - 10% palladium-carbon etc. As for reaction temperature, it is preferably good to perform 10-30 degrees C and hydrogen pressure, and to perform [0-50-degree C] reaction time at 15 - 25atm preferably one to 30 atm in 10 - 40 hours. Although especially the amount of solvents is not limited, its thing of a compound (4) used an amount (capacity) 3- 5 times is desirable. Here, although the low-grade trialkylsilyl group of the 2nd place changes to a hydroxy group when alcohol is used as a solvent, when a tetrahydrofuran etc. is used, it does not change. Refining removes the catalyst after a reaction, and after it distills off a solvent, a silica gel column chromatography etc. can perform it.
[0030] Thus, the configuration inversion to obtained (2R and 3S)-cyclohexyl ********** (6) from an optical-activity (2S and 3S)-cyclohexyl **********

derivative (5) is well-known technique (J.Am.Chem.Soc., 1949, 71 volumes, and 110 pages) shown by the following reaction formula. It can carry out.

[0031]

[Formula 22]



[0032] (Among a formula, R6 shows the phenyl group which may have the low-grade alkyl group or the substituent, and R1 and R2 show the same thing as the above)

[0033] A compound (14) is obtained by making an acyl-chloride compound react to a compound (5) under presence of a base. As an acyl-chloride compound, an acetyl chloride, a chlorination propionyl, the chlorination butyryl, a benzoyl chloride, a chlorination 2-methyl benzoyl, a chlorination 3-methyl benzoyl, a chlorination 4-methyl benzoyl, a chlorination 2-methoxy benzoyl, a chlorination 3-methoxy benzoyl, a chlorination 4-methoxy benzoyl, a chlorination 2-****** benzoyl, a chlorination 3-****** benzoyl, a chlorination 4-****** benzoyl, etc. are mentioned. As a base, a trimethylamine, a triethylamine, a diisopropyl ethylamine, a pyridine, 4-dimethylamino pyridine, etc. are mentioned. moreover, a base -- a compound (5) -- receiving -- 1-1.2 twice -- it is as good as the ** **** A reaction is -20 degrees C - 30 degrees C in temperature, and is performed by making it react for 6 to 20 hours. Although especially the amount of solvents is not limited, it is desirable to use an amount (capacity) 3- 5 times to a compound (5). After it processes refining with an after [reaction] 1N-hydrochloric acid and it distills off a solvent, a silica gel column chromatography etc. can perform it.

[0034] A compound (15) is obtained by making the thionyl chloride of a mol react a compound (14), its 1, - 3 times. A reaction is -20 degrees C - 50 degrees C in temperature, and is performed by making it react for 1 to 3 hours. Although especially the amount of solvents is not limited, it is desirable to use an amount (capacity) 1- 3 times to a compound (14). After a reaction, if a solvent is distilled off, a compound (15) will be obtained. A compound (15) is obtained as a hydrochloride here, when a thionyl chloride is used.

[0035] A compound (6) melts a compound (15) to a hydrochloric acid 20 of an amount (capacity), - 25% the 5 - 10 times, and is obtained by making it react in reaction temperature 80-100 **, the reaction time 5, - 20 hours. A compound (6) is obtained by condensing a reaction solution. In addition, when a compound (15) is used with a hydrochloride, a compound (6) is obtained as a hydrochloride.

[0036] Thus, what is necessary is to melt into xeransis

hydrochloric-acid-gas-alcoholic mixed liquor, to be the temperature of 70 - 100 **, to make it react for 1 to 5 hours, to perform an esterification, and just to neutralize further, in order to acquire the ester field (7) from the obtained compound (6).
[0037] As alcohol used here, a methanol, ethanol, propanol, an isopropanol, a butanol, an isobutanol, sec-butyl alcohol, tert-butyl alcohol, etc. are mentioned. A xeransis hydrochloric-acid-gas-alcoholic mixed solution has the desirable thing of a compound (6) used an amount (capacity) 3- 5 times. After distilling off a reaction solution, saturation can melt the residue in the solution of an amount (capacity) the three to 5 times, can add the aqueous solution of the base of a molar quantity there about one to 3 times, and can be performed by making it react at the temperature of -20 degrees C - 30 degrees C. As a solvent to use, toluene, a tetrahydrofuran, ethyl acetate, chloroform, a methylene chloride, etc. are mentioned. As a base to use, a sodium carbonate, a sodium hydrogencarbonate, potassium carbonate, a potassium hydrogencarbonate, etc. are mentioned. After a saturation operation end, refining performs liquid separation operation and is performed by condensing and recrystallizing an organic layer.

EXAMPLE

[Example] Hereafter, although an example explains this invention still in detail, this invention is not limited to these examples. Especially measurement in an example was performed under the following instrument for analysis and conditions, unless it limited.
1. Gas-Chromatography Machine Vessel:Shimazu GC-9A (Shimadzu Make)
Column: OV-101 Silica capillary-tube phi 0.25mm x 25m (GL Sciences, Inc. make)
Measurement Temperature: It is a temperature-up injection temperature:200 degree-C2. high-performance-chromatography machine at a part for 10 degrees-C/in 100-250 degree C. Vessel:********** 500 (product made from **********)
Detector: UV detector ********** 484 (product made from **********)
3. NMR Machine Vessel:AM-400 Type Equipment 400MHz (Product made from **********)
Internal-standard Matter: Tetramethylsilane 4. angle-of-rotation machine Vessel:DIP-4 type equipment (day duty light industrial incorporated company make)
5. Elemental-Analysis Device:CHN-2400 (Product made from Par **********)
6. Mass-Analysis Device:M80B (Hitachi Make)
[0040] Example 1(2SR)-******-4-cyclohexyl -(3R)- It reaches 23.25g (0.1 mols) of the synthetic :2-******-4-cyclohexyl-3-oxo methyl butyrates which are a hydroxybutyric acid methyl. Ru2Cl42((+)-BINAP) NEt3 169mg (0.1mmol) It melted to methanol 15ml and the mixed solution of 105ml of methylene chlorides, and taught the 500ml autoclave, and the reaction was performed at hydrogen pressure 100atm and 20 degrees C for 20 hours. a reaction solution is condensed and a silica gel column chromatography refines (2SR) - ******-4-cyclohexyl-(3R)-hydroxybutyric acid methyl 23.30g (99% of yield) was obtained Analysis of a gas chromatography showed that the Singh field was 65% and the anti field was 35%.
Optical purity Singh field 92%ee (96:4)
Anti field 82%ee (91:9)
the decision of optical purity -- (2 SR)-******-4-cyclohexyl-(3R)-hydroxybutyric acid methyl 47mg (0.2mmol) and (R)-alpha-methoxy-alpha-truffe ****** methylphenyl acetic-acid chloride 51mg (0.2mmol) -- pyridine 1ml -- it was made to react in inside for 5 hours, and HPLC analysis determined by considering as the ester compound of a (R)-alpha-methoxy-alpha-truffe ****** methylphenyl acetic acid Hereafter, the analysis condition is shown.

Column: YMC-PAK A-003-3phi 4.6x250mm (product made from , Inc. wye ********)
Eluate:Hexane:tetrahydrofuran =99:1 style a part for **:1ml/-- detection wavelength: -- again, the ratio of the thing of - field and the thing of the (R and 32S)-field is 96:4 among the Singh fields (2S and 3R), and 254nm was understood that the ratio of the thing of - field and the thing of the (2S and 3S)-field is 91:9 among the anti fields (2R and 3R This was deduced from the data of the compound guided after this example.
The 1H-NMR:(CDCl3 and deltappm) Singh field 0.84-1.85 (m, 13H, CH), 2.43 (s, 1H, OH), 3.82 (s, 1H, OH), 3.82 (s, 3H, OCH3), 4.08-4.16 (m, 1H, CHO), the 4.20 (d, 1H, J= 6.50Hz, CHCl) anti field 0.82-1.86 (m, 13H, CH), 2.38 (br s, 1H, OH), 3.82 (s, 3H, OCH3), 4.18-4.23 (m, 1H, CHO), and 4.30 (d, 1H, J= 3.98Hz, CHCl)
[0041] Example 24-cyclohexyl -(2S and 3R)- 85g [of methanol solutions (0.441 mols)], and methanol 100ml of the synthetic :28%-sodium methylate of an epoxy methyl butyrate It put into the reactor and cooled to 5 degrees C in the ice bath. it compounded in the example 1 there (2SR) - ******-4-cyclohexyl-(3R)-hydroxybutyric acid methyl 100g (0.426 mols) Methanol 200ml The melted solution was dropped under cooling. It agitated at 5 degrees C after instillation for 2 hours. Then, after adding a reaction mixture into 0.1M phosphate buffer solution * (pH=7) 500ml cooled at 0 degree C, reduced pressure distilling off of the methanol was carried out. After ethyl acetate's extracting a residue and distilling off a solvent, a rough product is distilled simply (102-110 degrees C / 0.1mmHg), and it is 4-cyclohexyl. -(2S and 3R)- 56.91g (75% of yield) of epoxy methyl butyrates was obtained.
*0. Composition:phosphoric-acid 1 sodium of 1M phosphate buffer solution (NaH2PO4.2H2O) 5.55g phosphoric-acid disodium (Na2HPO4.12H2O) 21.5g water 1000mlGLC It turns out that the ****:transformer ratio of the epoxy compound obtained by analysis is 5:95.
1H-NMR:(CDCl3 and deltappm)0.84-1.84 (m, 13H, CH), 3.15-3.19 (m, 2H, CH), and 3.78(s, 3H, CH3) [alpha] D+30.60 degree (C= 2.25 and methanol) elemental analysis C11H18O3 It carries out.

	C	H
理論値 (%)	66.64	9.15
実測値 (%)	66.39	8.91

[0042] Example 3(3S)-azide-4-cyclohexyl [1.0g (73mmol) of and zinc chlorides It put into the reactor and agitated at 70 degrees C for 20 hours.] -(2S)-4-cyclohexyl obtained in the synthetic : example 2 of a trimethylsiloxy methyl butyrate -(2S and 3R)- 14.43g [of epoxy methyl butyrates] (72.9mmol), and trimethylsilyl azide 8.4g (73mmol) A silica gel column chromatography (hexane:ethyl-acetate =9:1 (capacity factor)) refines after a reaction, and it is (3S)-azide-4-cyclohexyl. -(2S)- 20.29g (91% of yield) of trimethylsiloxy methyl butyrates It obtained.
1H-NMR:(CDCl3 and deltappm)0.14-0.18 (m, 9H, SiCH3), 0.76-1.82 (m, 13H, CH), 3.49-3.53 (m, 1H, CHN3), 3.75 (s, 3H, OCH3), 4.34 (d, 1H, J= 3.97Hz, CHO) elemental analysis As C14H27N3O3Si

	C	H	N
計算値 (%)	53.64	8.68	13.40
実測値 (%)	53.41	8.84	13.62

[0043] Example 4(3S)-amino-4-cyclohexyl -(2S)- - (3S) azide-4-cyclohexyl obtained in the synthetic : example 3 of a trimethylsiloxy methyl butyrate -(2S)- 50.0g (159.5mmol) of trimethylsiloxy methyl butyrates, 2.5g [of 2% of the weight of the 5% palladium-carbon] and xeransis tetrahydrofuran 200ml of the amount (capacity) of 4 times was put into the 500ml autoclave, and it was made to react at hydrogen pressure 25atm and a room temperature for 48 hours. After checking that the raw material had disappeared by TLC (benzene:ethyl-acetate =8:2

(capacity factor)), the catalyst was removed using cerite. A solvent is distilled off and it is (3S)-amino-4-cyclohexyl. -(2S)- 36.7g (80% of yield) of trimethylsiloxy methyl butyrates was obtained. Elemental analysis C14H29NO3Si It carries out.

	C	H	N
計算値 (%)	58.49	10.17	4.87
実測値 (%)	58.72	10.52	5.18

[0044] Example 5(3S)-bends amino-4-cyclohexyl [It put into the reactor, and considered as 0 degree C of inside **s in the ice bath, and 4.89g (34.8mmol) of benzoyl chlorides was dropped slowly.] -(2S)- - (3S) amino-4-cyclohexyl obtained in the synthetic : example 4 of a hydroxybutyric acid methyl -(2S)- Xeransis tetrahydrofuran 100ml of 10.0g (34.8mmol) of a trimethylsiloxy methyl butyrate, and its amount (capacity It agitated for 16 hours, after returning to a room temperature. 10ml of 5%-hydrochloric-acid aqueous solutions was added to the reaction mixture, and the reaction was stopped. Ethyl acetate extracts, after distilling off a solvent, a silica gel column chromatography (benzene:ethyl-acetate =10:1-5:1 (capacity factor)) refines, and it is (3S)-bends amino-4-cyclohexyl. -(2S)- Hydroxybutyric acid methyl 10.3g (92% of yield) was obtained.
1H-NMR:(CDCl3 and deltappm)0.78-1.94 (m, 13H, CH), 3.82 (s, 3H, OCH3), 4.43 (d, 1H, J= 2.95Hz, CHO), 4.62- 4.71 (m, 1H, CHN), 6.31 (d, 1H, J= 9.06Hz, NH), and 7.40 -7.80 (m, 5H, ArH) elemental analysis C18H25NO4 ******

	C	H	N
計算値 (%)	67.69	7.89	4.39
実測値 (%)	67.38	8.23	4.66

MS m/e:320(M+1)+ [0045] Example 6(3S)-amino-4-cyclohexyl -(2R)- - (3S) bends amino-4-cyclohexyl obtained in the synthetic : example 5 of a hydroxybutyric acid hydrochloride -(2S)- hydroxybutyric acid methyl 10.0g (31.3mmol) It melts to toluene 30ml of an amount (capacity) the 3 times, and is 9.3g (78.3mmol) of thionyl chlorides at 5 degrees C under ice-cooling. After dropping, it agitated as 30 degrees C for 2.5 hours. the residue obtained after collecting solvents -- 100ml of the 6N-hydrochloric acids of the amount (capacity) of 10 times adding -- warming (90 degrees C of inside **s) -- it agitated the bottom for 16 hours It washes with toluene, after removing a benzoic acid, a water layer is condensed, and it is (3S)-amino-4-cyclohexyl. -(2R)- 6.37g (85% of yield) of hydroxybutyric acid hydrochlorides was obtained.
1H-NMR:(D2O, deltappm)0.90-1.81 (m, 13H, CH), 3.72-3.78 (m, 1H, CHN), 4.44(d, 1H, J= 3.53Hz, CHO) [0046] Example 7(3S)-amino-4-cyclohexyl [It melted in 42ml of the solutions of the isopropanol-hydrochloric acid gas of the amount (capacity) of 10 times, and agitated at 80 degrees C for 3 hours.] -(2R)- - (3S) amino-4-cyclohexyl obtained in the synthetic : example 6 of a hydroxybutyric acid isopropyl -(2R)- 4.2g (14.6mmol) of hydroxybutyric acid hydrochlorides Solvents were collected, chloroform and the saturation sodium-hydrogencarbonate aqueous solution were added to the obtained residue, and liquid separation operation was performed. 4.1g (95% of yield) of rough products was obtained by condensing the obtained organic layer under reduced pressure. The obtained rough product was melted to the diisopropyl ether, the hexane was added, and the recrystallization was performed. The separated white needle crystal is filtered, and it dries, and is (3S)-amino-4-cyclohexyl. -(2R)- Hydroxybutyric acid isopropyl 3.36g (82% of yield) was obtained. The gas chromatography showed that it was the 98% of the degrees of chemical pure.
m.p. 85.5-86 degree-C[alpha]24D-21.50 **(C= 1.03 and CHCl3) 1H-NMR:(CDCl3 and deltappm)0.82-1.82 (m, 13H, CH), 1.29 (d, J= 6.26Hz, 6H, CH3), 3.20-3.90 (m, 1H, CHN), 3.97 (d, J= 2.38Hz, CHO), 5.08-5.19 (m, 1H, OCH)