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(54) Title: METHOD FOR THE PREPARATION OF CHIRAL HYDROXY ESTERS BY ENZYME/METAL MULTI-CATALYSIS

(57) Abstract: The invention provides a process for preparing a chiral hydroxy ester by reacting a compound having botha ketone group and an acyloxy group in a molecule with a hydrogen donor which reduces the ketone group into an hydroxyl group; a metal complex, which catalyzes both the reduction of the ketone and racemization reaction of produced hydroxy group; and an enzyme, which catalyzes enantioselective acyl transfer in anorganic solvent.

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METHOD FOR THE PREPARATION OF CHIRAL HYDROXY ESTERS BY ENZYME/METAL MULTI-CATALYSIS

Technical Field

The invention relates to a method for preparing chiral hydroxy esters, particularly, to a process for preparing chiral hydroxy esters with high optical purities by combining an enzyme and a metal catalyst in a single reaction chamber and inducing multi-step catalytic reactions.

Background Art

Much effort was focused on the developing new methods for stereoselective synthesis of optically active compounds with high optical purities. Among them, two methods are well studied and applied; one is kinetic resolution, utilizing an enzyme catalyst and the other is asymmetric synthesis, utilizing a metal catalyst. (Wong, C. H.; Whitesides, G. M. Enzymes in Synthetic Organic Chemistry; Pergamon: Oxford, U. K., 1994; Noyori, R., Asymmetric Catalysts in Organic Synthesis; Wiley: New York, 1994).

The kinetic resolution has some advantages - high optical purity of the end product, low unit cost of the enzyme catalyst, and simple reaction condition - and one apparent disadvantage that the yield is less than 50%. On the other hand, the asymmetric synthesis leads high optical purity and yield, but causes the increase of production cost due to the use of expensive chiral reagents. Also, the reaction conditions are complicated.

Recently, a new method that combines an enzyme catalyst and a metal catalyst, has been introduced. (Persson, B. A.; Larsson, A. L. E.; Ray, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* 1999, *121*, 1645.; Lee, D. H.; Huh, E. A.; Kim, M. -J.; Jung, H. M.; Koh, J. H.; Park, J., *Org. Lett.* 2000, *2*, 2377) for the dynamic kinetic resolution of racemic alcohols. According to dynamic kinetic resolution, an enzyme, as an enantioselective acylation catalyst is used with a metal catalyst as a racemization catalyst to produce single enantiomer from a racemic mixture. The yields of the products by this method are higher than those by optical resolution that uses enzyme catalysts only. Furthermore, this method is cost effective compared to the asymmetric synthesis that uses expensive chiral reagents.

It was also reported that ketones were successfully transformed to optically

pure esters by the combination of an enzyme and a metal catalyst. (Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J., *Org. Lett.* 2000, *2*, 409; Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J., *Org. Lett.* 2000, *2*, 2487). In this reaction, an excessive amount of acyl donor is used to increase yields. However, the excessive use of acyl donor increases the production cost and makes the separation of required product difficult because the acyl donor remains unreacted in a large portion and has similar polarity with that of product.

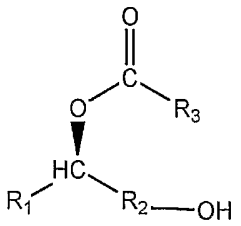
Disclosure of Invention

The invention provides a process for synthesizing chiral hydroxy esters with high optical purity and high yield from ketones by the combination of an enzyme catalyst and a metal catalyst without additional acyl donors, thereby resolving the problem caused by the use of excessive acyl donors.

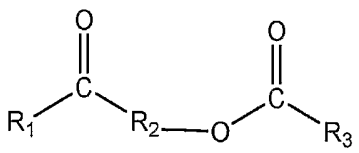
In detail, the invention provides a process for preparing chiral hydroxy esters by reacting a compound having both a ketone group and an acyloxy group in a molecule; a hydrogen donor which reduces the ketone into a hydroxy group; a metal complex, which catalyzes both the reduction of the ketone group and racemization of produced hydroxy group; and an enzyme, which catalyzes enantioselective acyl transfer in a suitable organic solvent.

Formula 1 represents the chiral hydroxy ester. Formula 2 represents the substrate compound having both a ketone and an acyloxy group.

[Formula 1]



[Formula 2]



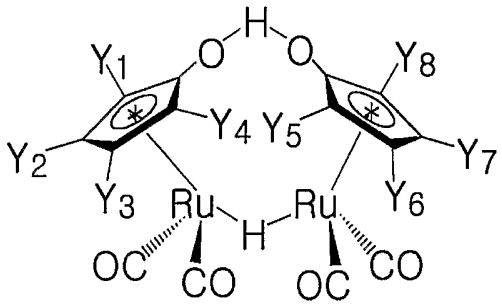
wherein R_1 and R_3 independently represent substituted or unsubstituted C_{1-15} alkyl

group, substituted or unsubstituted C_{1-15} akenyl group, substituted or unsubstituted C_{1-15} alkynyl group, substituted or unsubstituted C_{6-15} aryl group, substituted or unsubstituted C_{1-15} heteroaryl group, substituted or unsubstituted C_{4-15} cycloalkyl group, substituted or unsubstituted C_{4-15} heterocycloalkyl group or substituted or unsubstituted C_{2-15} heteroarylalkyl group.

R_2 represents substituted or unsubstituted C_{1-15} alkylene group, substituted or unsubstituted C_{6-15} arylene group, substituted or unsubstituted C_{4-15} heteroarylene group, substituted or unsubstituted C_{4-15} cycloalkylene group, substituted or unsubstituted C_{4-15} heterocycloalkylene group, or substituted or unsubstituted C_{2-15} heteroarylalkylene group. R_1 and R_2, R_2 and R_3, R_1 and R_3 may be linked to each other.

In one embodiment, the metal complex is a ruthenium complex represented by Formula 3.

[Formula 3]



wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7 and Y_8 each independently represent substituted or unsubstituted C_{1-10} alkyl group, substituted or unsubstituted C_{6-15} aryl group, substituted or unsubstituted C_{1-15} heteroaryl group.

Best mode for carrying out the Invention

The above and other features and advantages of the present invention will become more apparent by describing in detail exemplary embodiments thereof.

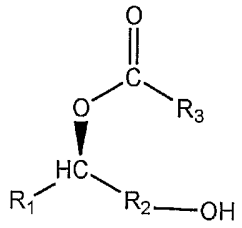
In the present invention, a chiral hydroxy ester is prepared by multi-step catalytic reactions in which an enzyme and a metal complex are used to induce asymmetrical reduction and transformation reaction.

Specifically, the following are mixed to form a substrate: a substrate having both ketone group and acyloxy group as represented by Formula 2; a ruthenium complex as represented by Formula 3, which reduces the ketone group and catalyzes the racemization of hydroxyl group; a hydrogen donor to reduce the ketone group; and an

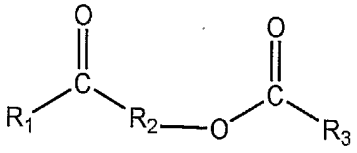
enzyme that catalyzes enantioselective acylation of one enantiomer of the racemic alcohols obtained by the racemization of hydroxyl group.

Then, the mixture is soaked in a solvent, deoxygenated by purging with inert gas, and agitated at 0 to 100° C to complete the reaction. The reacted mixture is worked-up and purification process provides optically pure hydroxy ester of Formula 1.

[Formula 1]



[Formula 2]

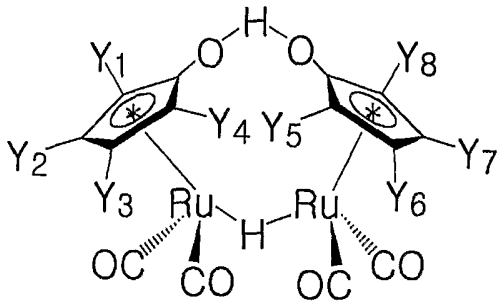


wherein R_1 and R_3 are independently selected from the group consisting of substituted or unsubstituted C_{1-15} alkyl group, substituted or unsubstituted C_{1-15} akenyl group, substituted or unsubstituted C_{1-15} alkynyl group, substituted or unsubstituted C_{6-15} aryl group, substituted or unsubstituted C_{4-15} heteroaryl group, substituted or unsubstituted C_{4-15} cycloalkyl group, substituted or unsubstituted C_{4-15} heterocycloalkyl group and substituted or unsubstituted C_{2-15} heteroarylalkyl group.

R_2 is selected from the group consisting of substituted or unsubstituted C_{1-15} alkylene group, substituted or unsubstituted C_{6-15} arylene group, substituted or unsubstituted C_{1-15} heteroarylene group, substituted or unsubstituted C_{4-15} cycloalkylene group, substituted or unsubstituted C_{4-15} heterocycloalkylene group, and substituted or unsubstituted C_{1-15} heteroarylalkylene group.

R_1 and R_2, R_2 and R_3, and R_1 and R_3 may be linked to each other. Examples of linking formation are substituted or unsubstituted fused ring of 7-20 carbon atoms or substituted or unsubstituted hetero fused ring of 5-20 carbon atoms.

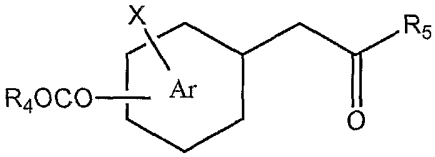
[Formula 3]



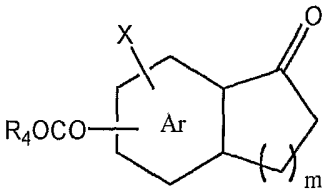
wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7 and Y_8 each independently represent substituted or unsubstituted alkyl group with 1 to 10 carbon atoms, substituted or unsubstituted C_{6-15} aryl group, substituted or unsubstituted C_{1-15} heteroaryl group.

The chemical compound of Formula 2 has both ketone and acyloxy groups and is preferably represented by Formulas 4 or 5.

[Formula 4]



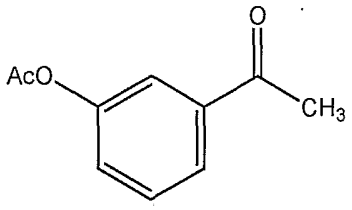
[Formula 5]



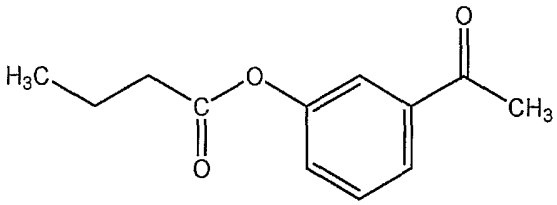
wherein R_4 represents an C_{1-10} alkyl group or an alkyl group with substituted heteroatoms, R_5 represents C_{1-5} alkyl group, C_{2-5} alkenyl group, or C_{2-5} alkynyl group, m represents an integer between 1 to 6, X represents halogen atom, C_{1-5} alkyl group, C_{2-5} alkenyl group, C_{1-5} alkoxy group, nitro group, amide group, sulfonyl group or more than one thioalkoxy group. Further,  represents C_{6-10} aryl group or C_{1-10} heteroaryl group.

Examples of Formulas 4 and 5 include Formulas 4a through 4d or Formulas 5a through 5d.

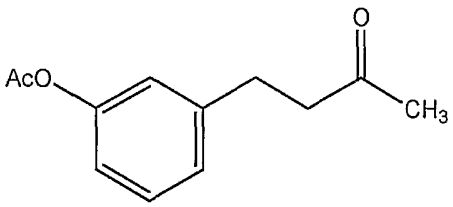
[Formula 4a]



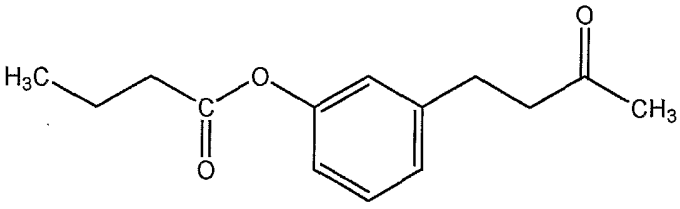
[Formula 4b]



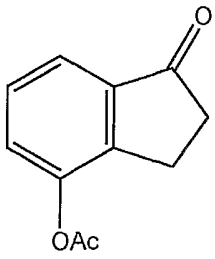
[Formula 4c]



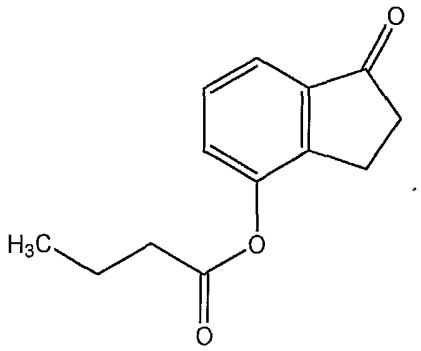
[Formula 4d]



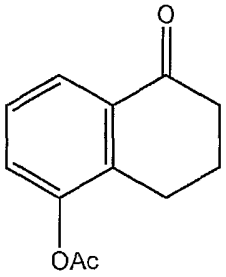
[Formula 5a]



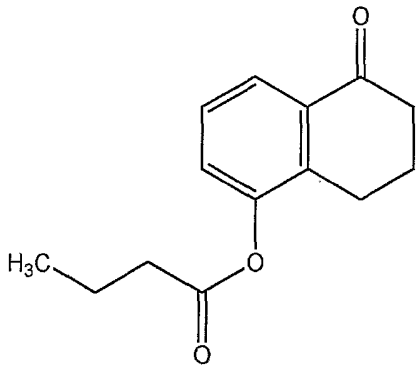
[Formula 5b]



[Formula 5c]



[Formula 5d]



The definitions and examples of the terminology used in this invention are described herein below:

Examples of unsubstituted C_{1-15} alkyl group include methyl, ethyl, propyl, isobutyl, sec-butyl, pentyl, iso-amil and hexyl. More than one hydrogen atom in such alkyl group may be substituted with halogen atom, halide, hydroxy group, nitro group, cyano group, amino group, amidino group, hydrazine, hydrazone, carboxyl group, sulfonic acid group, phosphoric acid group, lower alkyl group with 1 to 15 carbon atoms, and lower alkoxy group with 1 to 15 carbon atoms.

The unsubstituted C_{1-15} alkenyl or unsubstituted C_{1-15} alkynyl group refers to an alkyl group containing double or triple carbon bonding in the middle or at the end of the chain. Examples thereof include ethylene, propylene, butylene, hexylene and acetylene. More than one hydrogen atom in such alkenyl or alkynyl groups may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

Examples of the unsubstituted C_{1-15} alkylene group include methylene, ethylene, propylene, isobutylene, sec-butylene, pentylene, iso-amilene and hexylene. More than one hydrogen atom in the alkylene group may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

The aryl group refers to C_{6-30} carbocycle aromatic system in one or more ring structure, which may be used solely or in a combination. These rings may be held together by pendant method or fused together. Examples of aryl include phenyl, naphtyl, tetrahydronaphtyl, indenyl and biphenyl. More than one hydrogen atom in these aryl groups may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

The arylalkyl group is formed when one or more of the hydrogen atoms of the aryl group are substituted with lower alkyl radicals, such as methyl, ethyl or propyl radicals. Examples include benzil and phenylethyl. More than one hydrogen atom in the arylalkyl group may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

The heteroaryl group refers to a mono- or bicyclic aromatic group which includes 1, 2, 3 or 4 heteroatoms chosen from N, O, P and S. Also, the heteroaryl group refers to a mono- or bicyclic aromatic group in which heteroatom is oxidized or alkylated to form an oxide such as N-oxide or a quaternary amine salt. Examples thereof include thienyl, benzothienyl, pyridyl, pyrazinyl, pyramidinyl, pyridazinyl, quinolinyl, quinoxalinyl, imidazolyl, furanyl, benzofuranyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pirazolyl, pyrolyl, indolyl, 2-pyridonyl, 4-pyridonyl, N-alkyl-2-pyridonyl, pyrazinonyl, pyridazinonyl, pyrimidinonyl, oxazolonyl, corresponding N-oxides (for example, pyridyl N-oxide and quinolinyl N-oxide) and quaternary salts thereof but are not limited only to the ones specified. More than one hydrogen atom in the heteroaryl group may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

The heteroarylalkyl group refers to a heteroaryl group in which hydrogen atoms are partially substituted with alkyl groups. More than one hydrogen atom in the

heteroarylalkyl group may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

The cycloalkyl group refers to a monocyclic group including 4 to 15 carbon atoms. More than one hydrogen atom in the cycloalkyl group may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

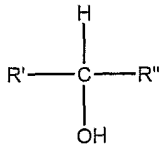
The heterocycloalkyl group refers to a monocyclic aromatic group, which includes 1, 2, 3 or 4 heteroatoms chosen from N, O, P or S. More than one hydrogen atom in the heterocycloalkyl group may be substituted with the same substituents as listed for the C_{1-15} alkyl group.

Preferably, the ruthenium complex of the Formula 3 reduces ketone group of the Formula 2 and simultaneously catalyzes the racemization reaction of hydroxyl obtained from the reduction. The complex preferably has a phenyl group or a methyl group in all Y_1 to Y_8 groups. Also, the amount of the ruthenium complex per 1 mole of the compound of Formula 2 is preferably 0.01 to 0.05 mol. More preferably 0.02 to 0.04 mol. When the amount is less than 0.01 mol, the reaction is excessively slow, and when the amount is greater than 0.05 mol, the production cost of chiral ester is high.

A enzyme, which catalyzes the acyl transfer reaction, is used, and more specifically, lipase is used. Lipase is an enzyme that hydrolizes ester, and selectively acylates one of the enantiomers of the racemic alcohol to produce chiral ester with high optical purity. Examples of such lipase are *Pseudomonas cepacia* lipase(LPS), *Candida antarctica* lipase(CAL) and *Candida rugosa* lipase(CRL). Immobilized LPS and immobilized CAL B are preferable. The amount of the immobilized lipase is 0.5 to 20 mg per 1 mmol of the substrate, but preferably 1 to 10 mg.

Hydrogen donor reduces the ketone group of Formula 2 to hydroxyl group in the presence of the catalyst of the ruthenium complex of Formula 3. One or more of such hydrogen donor is selected from the group consisting of hydrogen, formic acid, and alcohol of Formula 6.

[Formula 6]



wherein R' and R"each independently represent straight-chained, or branched C_{1-10} alkyl

group, C_{6-15} aryl group, or C_{1-15} heteroaryl group.

Preferably, the alcohol of Formula 6 has alkyl side-chain not to be affected by enzyme. Examples thereof are 2,4-dimethyl-3-pentanol and 2,6-dimethyl-4-heptanol.

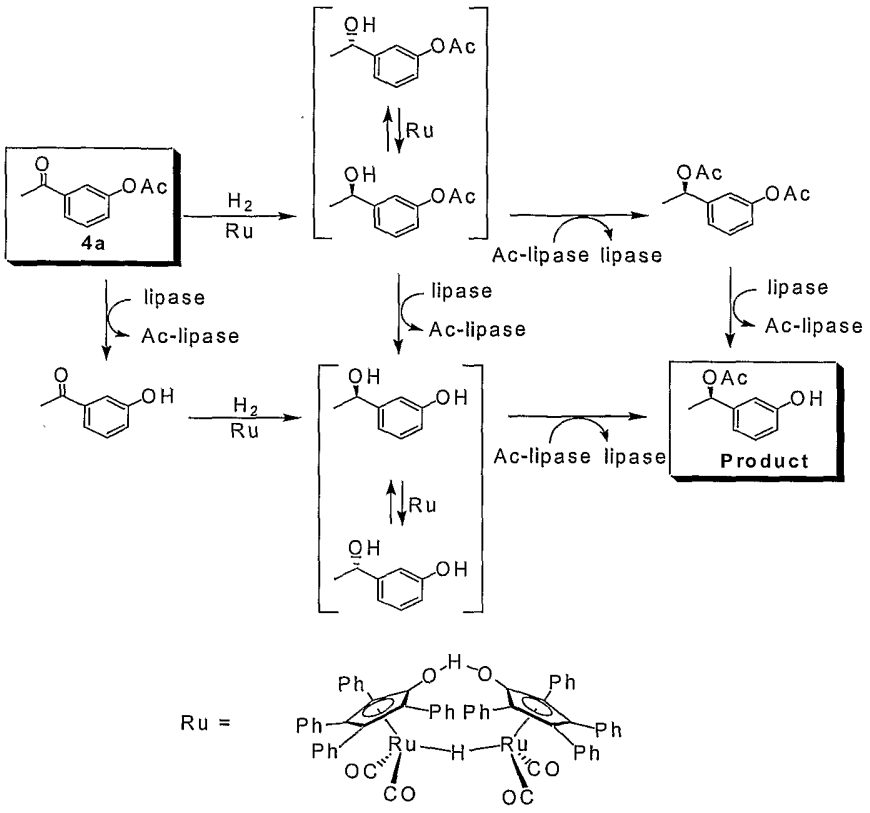
Preferably, hydrogen under the atmospheric pressure is used as the hydrogen donor because of easiness in removal after reaction. The amount of hydrogen donor is preferably 1 to 50 mol per 1 mol of the compound of Formula 2.

It is not necessary to use a particular type of solvent. However, because the yield and enatioselectivity of the product are affected in lipase-catalyzed reaction by solvent, it is preferable to use aprotonic solvent such as benzene, toluene, hexane, tetrahydrofuran, dioxan, C_{2-10} dialkyl ether (e.g., diethyl ether), C_{3-10} alkylacetate (e.g., ethyl acetate), acetonitrile, acetone, dicloromethane, cloroform, and carbon tetrachloride. The suitable amount of the solvent is controlled between 0.2 to 0.4 M based on the substrate used.

Although appropriate temperature of the reaction varies depending on the ruthenium catalyst, preferably, the temperature is 50 to 100° C and more preferably 70 to 80° C. At temperature below 50° C, the racemization reaction is slow, but at temperature above 100° C, the enzyme rapidly loses its activity.

Equation 1 illustrates the multi-step reaction of one of the representative examples.

[Equation 1]



The product of the above Equation 1 is useful as an intermediate for chiral medicines such as rivastigmine.

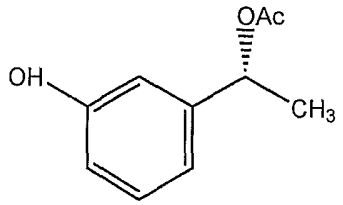
EXAMPLES

The following examples are intended to exemplify the claimed invention, and should not be construed as limiting the scope of the claimed invention.

[Example 1]

6mmol of compound of Formula 4, 0.012 mmol of ruthenium complex of Formula 3 (Both Y_1 and Y are phenyl), and 5 mg of immobilized lipase were mixed with 1.5 ml of toluene. The reaction vessel was deoxygenated and filled with hydrogen gas at atmospheric pressure. The resulting mixture was agitated for 72 hours at room temperature. After the complete reaction, optically pure hydroxy ester of Formula 1a was obtained by column chromatography.

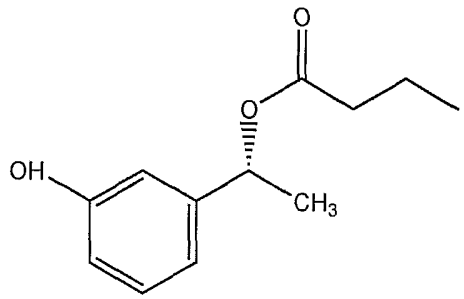
[Formula 1a]



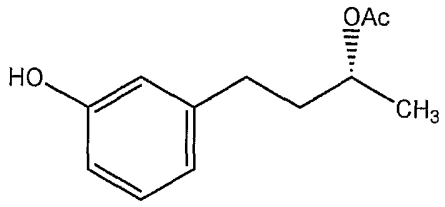
[Examples 2 to 8]

Using the same method as Example 1, but instead of using the compound of Formula 4, the compounds of Formula 4b to 4d and 5a to 5d, were used to obtain chiral hydroxy esters of Formulas 1b to 1h below, respectively.

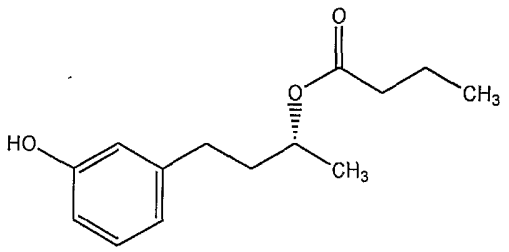
[Formula 1b]



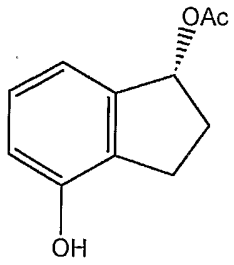
[Formula 1c]



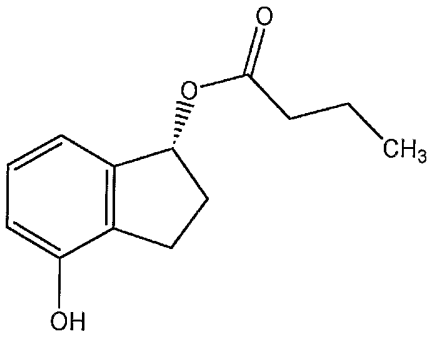
[Formula 1d]



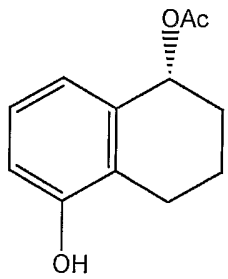
[Formula 1e]



[Formula 1f]



[Formula 1g]



[Formula 1h]

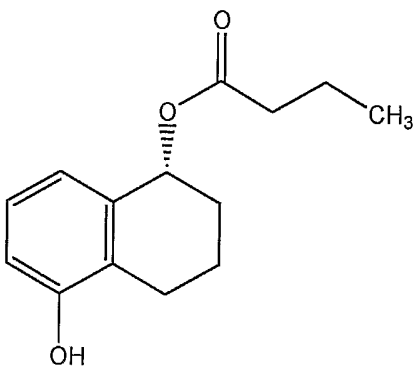


Table 1 shows the yield and optical purity of chiral esters prepared according to Experiments 1 to 8. The yield was determined by H-NMR and the optical purity was analyzed by High Performance Liquid Chromatography (HPLC) equipped with chiral column.

[Table 1]

	Substrate	Product	Yield (%)	Optical Purity (%)
Example 1	4a	1a	91	99
Example 2	4b	1b	90	98
Example 3	4c	1c	92	95
Example 4	4d	1d	90	98
Example 5	5a	1e	94	93
Example 6	5b	1f	93	97
Example 7	5c	1g	88	89
Example 8	5d	1h	87	99

According to Examples 1 through 8, as Table 1 depicts, the compounds having both ketone and acyloxy groups in a molecule were successfully transformed to optically pure hydroxyl esters in the presence of a ruthenium complex as a reduction and racemization catalyst, lipase as an acyl transfer catalyst, hydrogen gas as a hydrogen donor by multi-step catalytic reactions.

Industrial Applicability

According to the invention, chiral hydroxy esters are obtained with high optical purities and yields from substrates with various structures, all having both ketone and acyloxy groups in a molecule. The invention demonstrates that the synthesis of chiral compound by enzyme/metal catalyzed multi-step reaction can be executed in single reaction chamber. The chiral hydroxy ester prepared by the invention is useful as an intermediate compound in production of agricultural chemicals, medicines and natural chemical compounds. In particular, the chiral hydroxy ester of Formula 1a, prepared by the method according to the invention, is exceptionally useful as an intermediate compound in preparing a medicine such as rivastigmine.

What is claimed is:

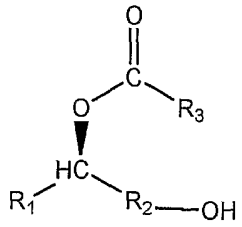
1. A process for preparing a chiral hydroxy ester comprising:

mixing a substrate compound having both a ketone group and an acyloxy group in a molecule with a hydrogen donor which reduces the ketone group into an hydroxy group, a metal complex which catalyzes both the reduction of the ketone into the hydroxy group and the racemization of produced hydroxy group, and an enzyme which catalyzes enantioselective acyl transfer in an organic solvent; and

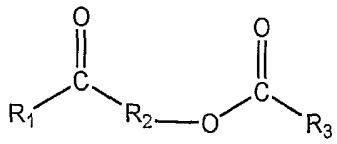
reacting the mixture.

2. The process of claim 1, wherein the chemical compound having both the ketone and the acyloxy group is represented by Formula 2 and the chiral hydroxy ester is represented by Formula 1

[Formula 1]



[Formula 2]



wherein R_1 and R_3 independently represent substituted or unsubstituted C_{1-15} alkyl group, substituted or unsubstituted C_{1-15} akenyl group, substituted or unsubstituted C_{1-15} alkynyl group, substituted or unsubstituted C_{6-15} aryl group, substituted or unsubstituted C_{1-15} heteroaryl group, substituted or unsubstituted C_{4-15} cycloalkyl group, substituted or unsubstituted C_{4-15} heterocycloalkyl group, or substituted or unsubstituted C_{2-15}

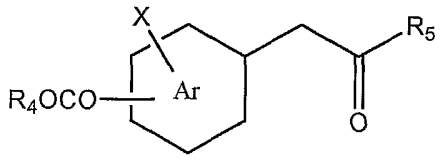
heteroarylalkyl group;

R_2 represents substituted or unsubstituted C_{1-15} alkylene group, substituted or unsubstituted C_{6-15} arylene group, substituted or unsubstituted C_{4-15} heteroarylene group, substituted or unsubstituted C_{4-15} cycloalkylene group, substituted or unsubstituted C_{4-15} heterocycloalkylene group, or substituted or unsubstituted C_{2-15} heteroarylalkylene group; and

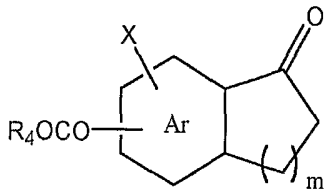
R_1 and R_2, R_2 and R_3, R_1 and R3 may be linked to each other.

3. The process of claim of 2, wherein the compound of the Chemical Formula 2 is represented by Formula 4 or 5

[Formula 4]



[Formula 5]



wherein R_4 represents an C_{1-10} alkyl group or an alkyl group substituted with heteroatoms;

R_5 represents C_{1-5} alkyl group, C_{2-5} alkenyl group, C_{2-5} alkynyl group;

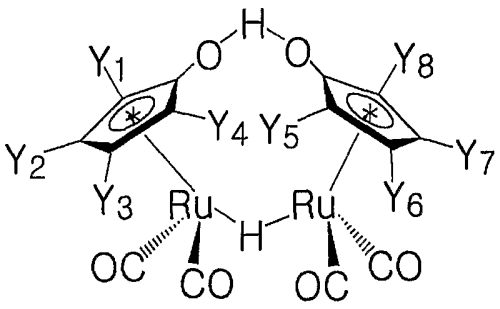
m represents an integer between 1 to 6;

X represents halogen atom, C_{1-5} alkyl group, C_{2-5} alkenyl group, C_{1-5} alkoxy group, nitro group, amide group, sulfonyl group or more than one thioalkoxy group; and

represents C_{6-10} aryl group or C_{1-10} heteroaryl group.

4. The process of claim 1, wherein the metal complex is a ruthenium complex as represented by Formula 3.

[Formula 3]



wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7 and Y_8 each independently represent substituted or unsubstituted C_{1-10} alkyl group, substituted or unsubstituted C_{6-15} aryl group, substituted or unsubstituted C_{1-15} heteroaryl group.

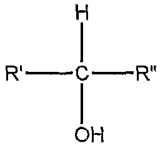
5. The process of claim 4, wherein Y_1 to Y_8 of the ruthenium complex are all phenyl or methyl group.

6. The process of claim 1, wherein the amount of the metal complex represented by the Formula 3 is 0.01 to 0.05 mol per 1 mol of the substrate used.

7. The process of claim 1, wherein the reaction of the mixture is carried out at a temperature of 0 to 100°. .

8. The process claim of 1, wherein the hydrogen donor is selected from the group consisting of hydrogen, formic acid and alcohol of Formula 6

[Formula 6]



wherein R' and R" each independently represent straight-chained, or branched C_{1-10} alkyl group, C_{6-15} aryl group, or C_{1-15} heteroaryl group.

9. The process of claim 8, wherein the hydrogen donor is supplied at atmospheric pressure.

10. The process of claim 1, wherein the enzyme is a lipase selected from the group consisting of *Pseudomonas cepacia* lipase (LPS), *Candida antarctica* lipase (CAL) and *Candida rugosa* lipase (CRL).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/01437

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C12P 41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C12P 41/00, A61K 31/365, C08G 63/06, C07D 317/62, C07C 205/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
KIPASS, Delphion, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5886213 A (Gilead Sciences, Inc.) Mar. 23, 1999 see the whole document	1 - 10
A	US 2002/0156300 A1 (Gilead Sciences, Inc.) Oct. 24, 2002 see the whole document	1 - 10
A	US 5625030 A (Metabolix, Inc.) Apr. 29, 1997 see the whole document	1 - 10
A	US 5216015 A (Rhone-Poulenc Rorer et al.) Jun. 1, 1993 see the whole document	1 - 10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 OCTOBER 2003 (10.10.2003)	13 OCTOBER 2003 (13.10.2003)

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Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5594

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/01437

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US5886213A	23.03.1999	US5886213A	23.03.1999
US2002/0156300A1	24.10.2002	US6518438BB	11.02.2003
US5625030A	29.04.1997	US5625030A	29.04.1997
US5216015A	01.06.1993	US5216015A	01.06.1993