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WO 2006/009338 A1

(54) Title: PROCESS FOR PREPARING CHIRAL SUBSTITUTED CARBOXYLIC ACID

(57) Abstract: The present invention relates to a new process for preparing optically active carboxylic acid derivatives by use of enzyme.

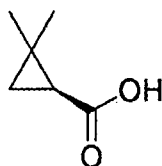
PROCESS FOR PREPARING CHIRAL SUBSTITUTED CARBOXYLIC ACID**Technical Field**

5 The present invention relates to a process for preparing optically active cyclopropanecarboxylic acid derivatives by use of enzyme.

Background Art

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Substituted cyclopropanecarboxylic acid, particularly dimethylcyclopropanecarboxylic acid is an industrially valuable chiral building block of the following formula, which is used in various applications, such as a dihydropeptidase I inhibitor, a raw material for the synthesis of insecticides of pyrethrin type (GB-A 1,269,847), an intermediate for the synthesis of enzyme inhibitor cilastatin (European Patent Publication No. 48,301), and an optical resolution agent:



20

Prior processes for preparing this compound are broadly divided into two processes. One is a process of preparing the compound by preparation of an ester from actively active amine, L-menthol or (S)-mandelic acid ester and then repeated

recrystallization of the ester. The other is a process of preparing the compound in the S-form by fermentation processes. However, these processes may be said to have industrial limitations, since they involves some of various shortcomings, including a low optical purity and yield of products, the use of optical resolution reagents, and a need for repeated recrystallization.

In detailed examples of each of these processes, JP-A 80-051023 discloses a process of preparing (S)-dimethylcyclopropanecarboxylic acid using quinine by an optical resolution method. This process has shortcomings in that the quinine is highly expensive and not available stably, and the yield is low. Also, GB-A 1,260,847 discloses a process of performing optical resolution using D- or L-phenethylamine, but has the problem of insufficient industrial utility since this process yields (S)-dimethylcyclopropanecarboxylic acid with a optical purity of only 49% at low yield.

US-B 4,487,956 discloses an optical resolution method using L-menthol. This method is useful in view of high yield and high optical purity but has problems in that a post-treatment process is very complicated, and the use of highly expensive L-menthol is required. Also, US-B 4,542,235 discloses the use of optically active diphenylethylamine substituted for the preparation of chiral (S)-dimethylcyclopropanecarboxylic acid. However, this patent has problems in that the chiral diphenylethylamine, an

expensive reagent which is not easily available, causes a great increase in production costs, recrystallization must be performed at least two times, and the use of excessive solvent upon recrystallization is required. Furthermore, US-B 5,166,417
5 discloses a process comprising formation of diastereomers with optically active L-(3-methoxyphenyl)ethylamine and optical resolution of the diastereomers by recrystallization. However, this process has the problem of insufficient industrial utility in that the used chiral amine is highly expensive, the yield is
10 as low as 21%, and the optical purity of the resulting (S)-dimethylcyclopropanecarboxylic acid is only 93%.

Moreover, US Patent No. 5,243,070 discloses a process for preparing (S)-dimethylcyclopropanecarboxylic acid, comprising esterifying dimethylcyclopropanecarboxylic acid with chiral
15 mandelic acid methyl ester, to form esters; fractionating crystallizing the formed esters to separate at least one of the formed diastereomeric esters; and subsequently hydrolyzing at least one of the separated esters. This process has problems in that the (S)-mandelic acid methyl ester used in the process is
20 an expensive reagent, and recrystallization must be repeated at least three times in order to increase the optical purity of the product. In recently published processes, US-B 5,273,903 and 5,360,731 disclose microbiological processes for the preparation of (S)-dimethylcyclopropanecarboxamide by selective
25 decomposition of racemic dimethylcyclopropanecarboxamide with

various microorganisms. These processes have the problem of insufficient commercial utility in that it takes as long as two days to preculture microorganisms, a reaction step and a separation step are complicated, and the concentration of a reaction substrate is about 2%.

Meanwhile, PCT Publication WO 2004/5241 discloses a process of preparing (S)-dimethylcyclopropanecarboxylic acid by optical resolution with esterase. However, enzymatic optical resolution is generally made only by a specific enzyme other than that all enzymes have no optical resolution effect for compounds of certain structures, and furthermore, even lipases which are used in optical resolution have, depending on the source thereof, a difference in the kinds of compounds and optical isomers on which the lipases act, as well as in enzymatic reactivity. On the basis of such facts, the above-mentioned PCT publication hardly seems to disclose the optical resolution of (S)-dimethylcyclopropanecarboxylic acid by the substantial use of enzyme, since it incorrectly describes esterase as belonging to the class of microorganisms, and esterase used in Examples of the specification is not concretely specified.

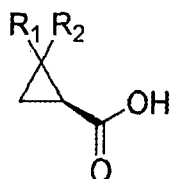
Disclosure of Invention

The present inventors have surprisingly found that, only when racemic cyclopropanecarboxylic acid ester is reacted with a

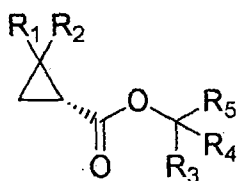
Candida antarctica-derived lipase in an aqueous solution, only (S)-substituted cyclopropanecarboxylic acid ester of the following formula (3) will be specifically hydrolyzed so that (S)-substituted cyclopropanecarboxylic acid and (R)-substituted cyclopropanecarboxylic acid ester will remain in the reaction solution. Accordingly, it is an object of the present invention to provide a new, industrially economical process for preparing (S)-cyclopropanecarboxylic acid derivatives with high optical purity at high yield, by reacting a high concentration of a substrate with a hydrolytic enzyme without using either the prior expensive resolving agents, such as optically active amine or L-menthol, or complex fermentation processes.

The present invention provides a new process for preparing a chiral-substituted cyclopropanecarboxylic acid by use of enzyme. More specifically, the present invention provides a new process for preparing an optically active cyclopropanecarboxylic acid and an optically active cyclopropanecarboxylic acid ester, which comprises the steps of: (a) reacting racemic cyclopropanecarboxylic acid ester of the following formula (3) with a *Candida Antarctica*-derived lipase enzyme in an aqueous solution; and (b) separating an optically active (S)-cyclopropanecarboxylic acid compound of the following formula (1) and an optically active (R)-cyclopropanecarboxylic acid ester compound of the following formula (2):

(Formula 1)

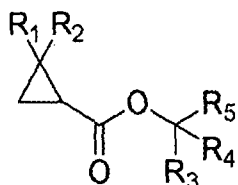


(Formula 2)



5

(Formula 3)



10 wherein R_1 and R_2 , which may be the same or different, are each independently selected from hydrogen, substituted or unsubstituted straight or branched C_{1-7} alkyl, substituted or unsubstituted straight or branched C_{1-7} alkenyl, benzyl, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or

15 unsubstituted arylalkyl, and substituted or unsubstituted heteroarylalkyl; R_3 and R_4 , which may be the same or different, are each independently selected from hydrogen, substituted or unsubstituted straight or branched C_{1-7} alkyl, substituted or unsubstituted straight or branched alkenyl, benzyl, substituted

or unsubstituted C₃₋₇ cycloalkyl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heteroarylalkyl; and R₅ is selected from straight or branched C₁₋₇ alkyl, halogen-substituted straight or branched C₁₋₇ alkyl, and straight or branched C₁₋₇ alkyl substituted with substituted or unsubstituted straight or branched C₁₋₇ alkoxy.

Hereinafter, the present invention will be described in detail.

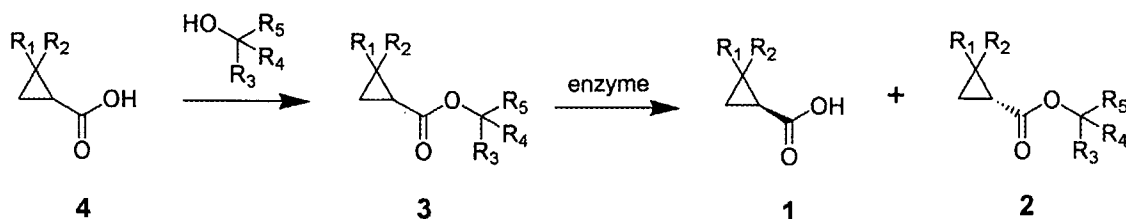
According to the present invention, when the racemic cyclopropanecarboxylic acid ester of formula 3 is reacted with a lipase enzyme in an aqueous solution while maintaining temperature and pH at constant levels, only (S)-substituted cyclopropanecarboxylic acid ester will be specifically hydrolyzed so that (S)-substituted cyclopropanecarboxylic acid and (R)-substituted cyclopropanecarboxylic acid ester will remain in the reaction solution. The (S)-substituted cyclopropanecarboxylic acid and the (R)-substituted cyclopropanecarboxylic acid ester can be separated by a simple separation step. This is because the *Candida Antarctica*-derived lipase specifically hydrolyzes the (S)-cyclopropanecarboxylic acid ester compound.

Lipase enzymes which are generally used in optical resolution are various, including lipases derived from *Candida cylindracea*, *Pseudomonas sp.*, *Candida rugosa* or *Candida antarctica*, and have, depending on the source thereof, a

difference in the kinds of compounds and optical isomers on which the lipases act, as well as in enzymatic reactivity. Most of the lipases are meaningless as enzymes for the use of optical resolution since they show no hydrolytic reaction, or even if they show some hydrolysis, they result in low optical purity. However, the present inventors have found that, in enzymatic resolution reaction, only the *Candida Antarctica*-derived lipase results in very high conversion and high optical purity.

The enzymatic optical resolution progresses as shown in the following reaction scheme 1:

(Reaction Scheme 1)



As can be seen in Reaction Scheme 1, the racemic cyclopropanecarboxylic acid ester (3) may be easily prepared by esterifying the racemic cyclopropanecarboxylic acid (4) with various alcohols.

According to conventional esterification, the racemic cyclopropanecarboxylic acid ester (3) may be prepared at a quantitative yield of more than 95% by a process in which thionyl chloride is added dropwise to the racemic cyclopropanecarboxylic acid (4) in an organic solvent to prepare

a compound substituted with a leaving group such as acyl halide, and alcohol derivatives are added to the reaction mixture. The produced racemic cyclopropanecarboxylic acid ester (3) is subjected to optical resolution with the *Candida Antarctica*-
5 derived lipase in an aqueous solution.

According to the present invention, optical resolution by specific enzymatic hydrolysis with the *Candida Antarctica*-derived lipase may be applied to all carboxylic acid esters having a cyclopropanecarboxylic acid lead structure. Position 2
10 of the cyclopropane of formula 2 may be substituted with any substituent. For the purpose of the inventive preparation process, however, R_1 and R_2 in the compound, which may be the same or different, are preferably selected from substituted or unsubstituted straight or branched C_1 - C_7 alkyl, substituted or
15 unsubstituted straight or branched C_1 - C_7 alkenyl, benzyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heteroalkyl. More preferably, R_1 and R_2 in the compound, which may be the same or different, are selected from methyl, ethyl,
20 n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, fluoromethyl, difluoromethyl, and trifluoromethyl. Most preferably, R_1 and R_2 are all methyl.

Furthermore, conversion and selectivity in the optical resolution by specific enzymatic hydrolysis with the *Candida*
25 *Antarctica*-derived lipase are most influenced by the kinds of R_3 ,

R₄ and R₅ substituents of the racemic cyclopropanecarboxylic acid ester. In ester substituents which can be subjected to the enzymatic reaction according to the present invention, R₃ and R₄ are preferably selected from hydrogen, substituted or unsubstituted C₁₋₇ alkyl, substituted or unsubstituted alkenyl, benzyl, substituted or unsubstituted C₃₋₇ cycloalkyl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heteroarylalkyl, and R₅ is preferably selected from straight or branched C₁₋₇ alkyls. Position 1 of the R₅ substituent is preferably substituted with an electron-rich atom in order to increase conversion and optical purity in the enzymatic reaction according to the present invention, and thus, R₅ is preferably selected from halogen-substituted straight or branched C₁₋₇ alkyl, and straight or branched C₁₋₇ alkyl substituted with a substituted or unsubstituted straight or branched C₁₋₇ alkoxy group. More preferably, R₃ and R₄ are all hydrogen, and R₅ is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, methoxymethyl and ethoxymethyl.

As the enzyme used in the optical resolution by the specific enzymatic hydrolysis, the *Candida Antarctica*-derived lipase as described above is commercially available. The concentration of the *Candida Antarctica*-derived lipase in the reaction system is preferably 1-30% by weight, and more preferably about 5% by weight, based on the weight of the

racemic cyclopropanecarboxylic acid ester as a substrate. The enzyme is immobilized for use in view of the convenience of reaction and economic efficiency.

According to present invention, optical resolution of
5 cyclopropanecarboxylic acid by specific hydrolysis with the *Candida Antarctica*-derived lipase is carried out while maintaining reaction temperature and pH at constant levels. The reaction temperature is preferably 10-80 °C, and more preferably 20-45 °C in view of conversion and optical purity.

10 Although the hydrolysis for optical resolution may be performed at a pH range of 6-9, the highest effect of the enzymatic reaction is shown at pH 7.0.

The concentration of the racemic cyclopropanecarboxylic acid ester which is used as a substrate in the enzymatic
15 resolution reaction is preferably 3-70%, and more preferably 5-40% in view of process efficiency.

In the inventive process, after the resolution reaction by specific enzymatic hydrolysis, the optically active cyclopropanecarboxylic acid and the optically active
20 cyclopropanecarboxylic acid ester can be separated by a simple post-treatment step.

Namely, the (R)-cyclopropanecarboxylic acid ester is extracted as an organic solvent layer by treatment with a suitable organic solvent such as ethyl acetate or
25 dichloromethane, and then, the pH of the remaining aqueous layer

is reduced to about 2, from which the (S)-cyclopropanecarboxylic acid is extracted with an organic solvent.

After completion of the enzymatic reaction, the enzyme used in the enzymatic reaction may be separated by means of a filter, etc., and then washed for reuse.

Best Mode for Carrying Out the Invention

The present invention will hereinafter be described in further detail by examples. It will however be obvious to a person skilled in the art that the present invention is not limited to or by the examples.

Preparation 1: Preparation of substituted cyclopropanecarboxylic acid 2-chloroethylester

500 ml of methylene chloride and 228 g of dimethylcyclopropanecarboxylic acid were placed in a reactor, and stirred well at ambient temperature, to which 236 g of thionyl chloride (SOCl_2) was then added dropwise at a constant temperature of 20 °C. At further stirring for 1 hour at ambient temperature, 190 g of 2-chloroethanol was added dropwise slowly, followed by further stirring for 2 hours at ambient temperature. The stirred solution was washed with a saturated sodium carbonate (Na_2CO_3) solution, dried with anhydrous sodium sulfate (Na_2SO_4), and distilled under reduced pressure to remove the organic solvent, thus obtaining 360 g of the title racemic

dimethylcyclopropanecarboxylic acid 2-chloroethylester.

Preparations 2 to 4: Preparation of racemic dimethylcyclopropanecarboxylic acid esters

Various racemic dimethylcyclopropanecarboxylic acid esters
5 were prepared in the same manner as in preparation 1 except that different kinds of alcohols (2,2,2-trifluoroethanol (Preparation 2), 2-methoxyethanol (Preparation 3) and 2-bromoethanol (Preparation 4)) were used. The results of Preparations 1 to 4 are shown in Table 1 below.

10

(Table 1)

Preparation No.	Used alcohol	Yield (%)
Preparation 1	2-chloroethanol	94%
Preparation 2	2,2,2-trifluoroethanol	95%
Preparation 3	2-methoxyethanol	98%
Preparation 4	2-bromoethanol	97%

Example 1

In 1 ml of 50 mM sodium phosphate (pH 7 buffer), 50 mg (5%)
15 of the racemic dimethylcyclopropanecarboxylic acid 2-chloroethylester prepared in Preparation 1 and 2.5 mg of *Candida Antarctica* type B lipase enzyme were allowed to react at 30 °C for 20 hours. Then, 0.2 ml of the reaction solution was taken and mixed well with 0.1 ml of 1N hydrochloric acid solution and
20 extracted with 1 ml of ethyl acetate.

The ethyl acetate extract was measured for optical purity by gas chromatography equipped with a chiral column.

Comparative Examples 1-15: Comparison of stereospecific hydrolysis between enzymes

5 For the comparison of the conversions and optical purities of (S)-dimethylcyclopropanecarboxylic acid optical isomers between the use of *Candida Antarctica* type B lipase in the preparation process of the present invention and the use of other enzymes, enzymatic reactions were performed under the same
10 conditions except that different kinds of enzymes.

The results of example 1 and comparative examples 1-15 are shown in Table 2 below were used.

(Table 2)

Example No.	Kind of enzyme	Optical purity of dimethylcyclopropane carboxylic acid (ee%)	Conversion (%)	Chiral form
Example 1	<i>Candida Antarctica</i> type B lipase	99	40.0	S form
Comp. Example 1	<i>Candida cylindracea</i> lipase	99	1.0	S form
Comp. Example 2	<i>Mucor miehei</i> lipase	0	0	
Comp. Example 3	<i>Candida rugosa</i> lipase	50	2.1	S form
Comp. Example 4	Porcine pancreatic lipase	0	0	
Comp. Example 5	<i>Thermomyces</i> lipase	0	0	
Comp. Example 6	<i>Achromobacter</i> lipase	0	0	
Comp. Example 7	<i>Alcaligenes</i> lipase	43	3.2	S form
Comp. Example 8	<i>Pseudomonas cepacia</i> lipase	21	1	S form

Comp. Example 9	<i>Pseudomonas stutzeri</i> lipase	0	0	
Comp. Example 10	<i>Rhizopus</i> lipase	0	0	
Comp. Example 11	<i>Bacillus licheniformis</i> protease	98	0.7	S form
Comp. Example 12	<i>Bacillus amyloliquefaciens</i> protease	0	0	
Comp. Example 13	<i>Aspergillus oryzae</i> protease	32	3.2	S form
Comp. Example 14	<i>Bacillus subtilis</i> protease	30	2.1	S form
Comp. Example 15	Porcine liver esterase	0	0	

As can be seen in Table 2 above, in the stereospecific hydrolysis of the racemic dimethylcyclopropanecarboxylic 2-chloromethylester as a substrate, only the *Candida Antarctica* type B lipase showed the production of (S)-dimethylcyclopropanecarboxylic acid optical isomers with high optical purity at a conversion of an industrially useful level, and other lipases, proteases and esterase showed no enzymatic reaction. This suggests that the *Candida Antarctica*-derived lipase enzyme used in the inventive preparation process has a remarkable effect as a hydrolytic enzyme.

Example 2

For the comparison of enzymatic reactions between substituted alcohols, an (S)-dimethylcyclopropanecarboxylic acid optical isomer was prepared in the same manner as in Example 1 except that the dimethylcyclopropanecarboxylic acid 2,2,2-trifluoroethylester prepared in Preparation 2 was used as a substrate.

Example 3

For the comparison of enzymatic reactions between substituted alcohols, an (S)-dimethylcyclopropanecarboxylic acid optical isomer was prepared in the same manner as in Example 1 except that the dimethylcyclopropanecarboxylic acid 2-methoxyethylester prepared in Preparation 3 was used as a substrate.

Example 4

For the comparison of enzymatic reactions between substituted alcohols, an (S)-dimethylcyclopropanecarboxylic acid optical isomer was prepared in the same manner as in Example 1 except that the dimethylcyclopropanecarboxylic acid 2-bromoethylester prepared in Preparation 4 was used as a substrate.

The results of the enzymatic reactions of Examples 2 to 4 using different kinds of substituted alcohols are shown in Table 3 below.

(Table 3)

	Used ester	Optical purity of (S)- dimethylcyclopropane carboxylic acid (ee%)	Conversion (%)
Example 2	Dimethylcyclopropanecarboxylic acid 2,2,2-trifluoroethylester	99%	48.5%
Example 3	Dimethylcyclopropanecarboxylic acid 2-methoxyethylester	98%	18.2%
Example 4	Dimethylcyclopropanecarboxylic acid 2-	98.7%	45%

	bromoethylester		
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Examples 5 to 8

Examples 5 to 8 were performed under the same reaction conditions as in Example 1 except that, in order to examine a change in conversion with a change in substrate concentration, the amount of the racemic dimethylcyclopropanecarboxylic acid 2-chloroethylester used as a substrate was increased to 100 mg (10%), 200 mg (20%), 400 mg (40%) and 600 mg (60%), and thus, the amount of the *Candida Antarctica* type B lipase was also increased to 5 mg, 10 mg, 20 mg and 30 mg. The results of Examples 5 to 8 are shown in Table 4 below.

(Table 4)

	Substrate concentration	Optical purity of (S)-dimethylcyclopropanecarboxylic acid (ee%)	Conversion (%)
Example 5	10%	99	33.5%
Example 6	20%	99	23%
Example 7	40%	99	14.4%
Example 8	60%	99	11%

From the results in Table 4, it could be found that the stereospecific hydrolysis well progressed even at an increased substrate concentration of 60%.

Industrial Applicability

As described above, the present invention provides the new, industrially economical process for preparing the (S)-
5 cyclopropanecarboxylic acid derivatives with high optical purity at high yield, by reacting a high concentration of the substrate with the hydrolytic enzyme without using either the prior expensive resolving agents, such as optically active amine or L-menthol, or complex fermentation processes.

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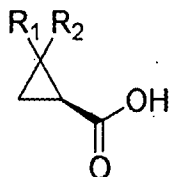
What Is Claimed Is:

1. A process for preparing an optically active cyclopropanecarboxylic acid and an optically active
5 cyclopropanecarboxylic acid ester, which comprises the steps of:

(a) reacting racemic cyclopropanecarboxylic acid ester of the following formula (3) with a *Candida Antarctica*-derived lipase enzyme in an aqueous solution; and

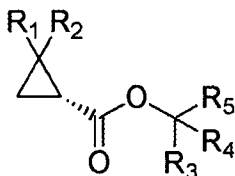
(b) separating an optically active (S)-
10 cyclopropanecarboxylic acid compound of the following formula (1) and an optically active (R)-cyclopropanecarboxylic acid ester compound of the following formula (2):

(Formula 1)

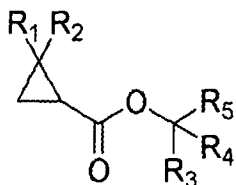


15

(Formula 2)



(Formula 3)



wherein R₁ and R₂, which may be the same or different, are each independently selected from hydrogen, substituted or
5 unsubstituted straight or branched C₁₋₇ alkyl, substituted or unsubstituted straight or branched C₁₋₇ alkenyl, benzyl, substituted or unsubstituted C₃₋₇ cycloalkyl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heteroarylalkyl; R₃ and R₄, which may be the same or different,
10 are each independently selected from hydrogen, substituted or unsubstituted straight or branched C₁₋₇ alkyl, substituted or unsubstituted straight or branched alkenyl, benzyl, substituted or unsubstituted C₃₋₇ cycloalkyl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heteroarylalkyl; and
15 R₅ is selected from straight or branched C₁₋₇ alkyl, halogen-substituted straight or branched C₁₋₇ alkyl, and straight or branched C₁₋₇ alkyl substituted with substituted or unsubstituted straight or branched C₁₋₇ alkoxy.

2. The process of Claim 1, wherein R₁ and R₂, which may be
20 the same or different, are each independently selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, n-pentyl, n-hexyl, fluoromethyl, difluoromethyl, and trifluoromethyl.

3. The process of Claim 1, wherein R_3 and R_4 are all hydrogen, and R_5 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, methoxymethyl and ethoxymethyl.

5

4. The process of Claim 2 or 3, wherein R_1 and R_2 are all methyl.

5. The process of Claim 1, wherein the reaction is carried
10 out at a temperature of 10-80 °C.

6. The process of Claim 5, wherein the reaction is carried
out at a temperature of 20-45 °C.

15 7. The process of Claim 1, wherein the concentration of the substituted racemic cyclopropanecarboxylic acid ester is 3-70%.

8. The process of Claim 7, wherein the concentration of the substituted racemic cyclopropanecarboxylic acid ester is 5-40%.

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9. The process of Claim 1, wherein the *Candida Antarctica*-derived lipase is a *Candida Antarctica* type B lipase.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/003019**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)

C12P, C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKIPASS**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/083126 A2 (Dow Global Technologies Inc.) 9 Oct. 2003 See Whole Document, especially Claims	1-9
Y	WO 98/29561 A1 (SMITHKLINE BEECHAM PLC) 9 Jul. 1998 See Whole Document, especially Claims	1-9
Y	KR 2001-27210 A (KIST) 6 Apr. 2001 See Whole Document	1-9
A	KR 2003-82730 A (POSTECH) 23 Oct. 2003 See Whole Document	1-9

 Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search

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