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(71) Applicant *(for all designated States except US)*: **ENZYTECH, LTD.** [KR/KR]; 217-2, Sinseong-dong, Yusoneg-gu, Daejeon 305-805 (KR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HWANG, Soon Ook** [KR/KR]; 217-2, Sinseong-dong, Yuseong-gu, Daejeon 305-805 (KR). **CHUNG, Sun Ho** [KR/KR]; 512-302 Cheongsol APT, Songgang-dong, Yuseong-gu, Daejeon 305-752 (KR).

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(54) Title: PROCESS FOR L-CARNITINE

(57) Abstract: The present invention relates to the process for the preparation of L-carnitine from racemic 3-acyloxy-gamma-butyrolactone or alkyl (R)-4-chloro-3-hydroxybutyrate. In more detail, this present invention relates to the process for the preparation of L-carnitine from (R)-3-hydroxy-gamma-butyrolactone, which was produced from racemic 3-acyloxy-gamma-butyrolactone by stereospecific hydrolysis using enzyme in the aqeous phase or organic phase including aqeous solvent or alkyl (R)-4-chloro-3-hydroxybutyrate, followed by a ring-opening reaction, epoxydation and a nucleophilic substitution by trimethylamine to prepare L-carnitine. The method of making L-carnitine is easier and more economical comparing to the con¬ ventional methods and L-carnitine produced has higher optical purity.

Description

PROCESS FOR L-CARNITINE

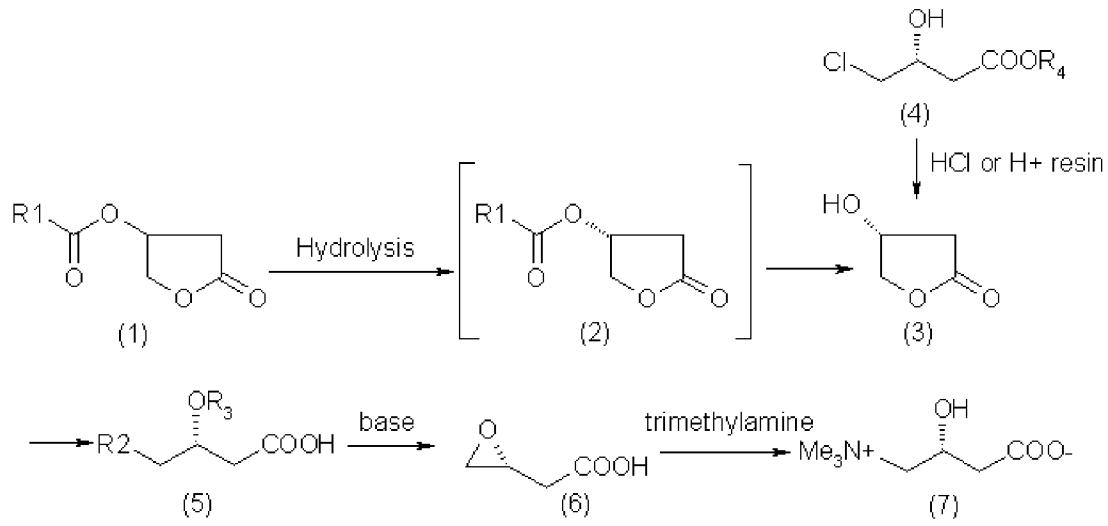
Technical Field

[1] The present invention relates to the process for the preparation of L-carnitine represented by the general formula 7 in scheme 1. In more detail,

[2] racemic 3-acyloxy-gamma-butyrolactone represented by the general formula 1 is hydrolyzed stereospecifically using enzymes in the aqueous phase or organic phase including aqueous solvent, based on the above reaction, (R)-3-acyloxy-gamma-butyrolactone represented by the general formula 2 is prepared therefrom, and (R)-3-hydroxy-gamma-butyrolactone is prepared by hydrolysis from either (R)-3-acyloxy-gamma-butyrolactone or (R)-4-chloro-3-hydroxybutyrate represented by the general fomula 4, followed by ring-opening reaction using both of halogen acid and carboxylic acid for the preparation of (R)-3-acyloxy-4-halobutyric acid represented by the general formula 5, epoxydation reaction for the preparation of (R)-3,4-epoxybutyric acid salt or (R)-3,4-epoxybutyric acid in the presence of a base consecutively. Then, L-carnitine is produced by well-known methods.

[3] [Scheme 1]

[4]



[5] In scheme 1, R_1 is selected from substituted or unsubstituted alkyl groups or alkenyl groups, wherein the alkyl contains from C_1 to C_8, benzyl groups, cycloalkyl groups comprising from C_3 to C_6, substituted or unsubstituted arylalkyl groups, and substituted or unsubstituted heteroarylalkyl groups. R_2 is halogen group such as F, Cl, Br, and I, R_3 is acyl group(COC_nH_{2n+1}, n=1~4) and R_4 is alkyl groups comprising from C_1 to C_8.

[6] Carnitine occurrs as two enantiomers, L-carnitine and D-carnitine. L-carnitime is normally present in the body, and plays a vital role in metabolism of the fatty acid and

carrying fatty acid through the mitochindria membrane. And L-carnitine is a natural substance used in energy metabolism and elevation of the heart faculty. L-carnitine and their derivatives are used as an anticonvulsant and blood product supplements.

[7] D,L-carnitine racemate has been used as a medicine or food additives, However D-carnitine has been reported to have a competitive interference effect against the physiological roles of L-carnitine in vivo. Therefore, a lot of research works have been peformed in preparing L-carnitine.

[8]

Background Art

[9] There are several methods to prepare L-carnitine.

[10] Optically resolving agent including L-tartaric acid(European Patent 157,315), dibenzoyl-D-tartaric acid(U.S. Pat. 4,933,490), dibenzoyl -L-tartaric acid(U.S. Pat. 4,610,828), D-mandelic acid(Japanese Unexamined Patent Publication Sho 59-231,048) and N-acetyl-D-glutamate(Japanese Unexamined Patent Publication Hei 1-131,143) were reacted with D,L-carnitine or the racemate of its derivatives. Then, L-carnitine was seperated using the difference of solubility in solvent. But the above method has some difficulties in recrystallization step.

[11] L-carnitine is produced by stereoselective hydroxylation of crotonobetain or gamma-butyrobetain using microorganisms or enzymes(U.S. Pat. 4,708,936, U.S. Pat. 4,371,618, U.S. Pat. 4,650,759).

[12] There is the method of obtaining L-carnitine from (R)-4-chloro-3-hydroxybutyrate which is produced by reduction of 4-chloro-3-oxobutyrate. Case by micro organisms(Journal of American Chemical Society, 1985, 107, 4028-4031). Another method of preparing L-carnitine from (R)-4-chloro-3-hydroxybutyrate derivatives produced by stereoselective reduction of 4-chloro-3-oxobutyrate derivative using catalyst were reported(U.S. Pat. 4,895,979, European Patent 339,764, Tetrahedron Letters, 1998, 29:1555). However, the above method also has disadvantages because of high cost of the catalyst and high hydrogen pressure during the reaction.

[13] There is the method of preparing L-carnitine using chiral materials from natural source. D-mannitol is employed(U.S. Pat. 4,413,142). However, the reaction steps are very complicated and heavy metal compounds such as tetraacetyl lead are employed. Furthermore, the process of preparing L-carnitine from D-(R)-tartaric acid(Tetraheron Letters, 31, 7323-7326, 1990) includes many complicated steps.

[14] There is a method for preparing L-carnitine from optically pure compounds. (S)-3-hydroxy-gamma-butyrolactone as starting material is subjected to ring-opening reaction and epoxydation with an inversion of the chiral center, and nucleophilic substitution by trimethylamine(Korean Patent 0255039). In another case, L-carnitine can

be prepared from (R)-epichlorohydrin by ring-opening reaction using trimethylamine and the reaction with acetonitrile and crown ether in acidic condition(Korean Patent 10-2005-0010203). But this method is unsuitable becase starting material is too expensive.

[15] As previously stated, a lot of methods of preparing L-carnitine were reported. But, these methods are not suitable for industrial use due to their disadvantages such as difficulties in the preparing compounds with high optically purity and many complicated manufacturing steps and high hydrogen pressure during the reaction.

[16]

Disclosure of Invention

Technical Problem

[17] In preparing L-carnitine, the method by ring-opening reaction and epoxydation from (S)-3-hydroxy-gamma-butyrolactone(Korean Patent 0255039) needs the inversion of the chiral center because raw material is (S)-isomer instead of (R)-isomer. So (S)-3-hydroxy-gamma-butyrolactone is subjected to activation of hydroxy group and ring-opening reaction in the presence of acid. Korean Patent (Registration Number 0332703) shows the method of preparing (S)-3,4-epoxybutyric aci salt from (S)-3-hydroxy-gamma-butyrolactone by ring-opening reaction and epoxydation. But, said compound is unsuitable for precursor of L-carnitine because it has opposite configuration of L-carnitine.

[18] With this in mind, the inventors herein attempted a method of preparing L-carnitine as follows;

[19] From racemic 3-acyloxy-gamma-butyrolactone, (R)-3-hydroxy-gamma-butyrolactone is prepared by hydrolysis using enzymes(Korea Patent Application # 10-2005-0089119), or alkyl (R)-4-chloro-3-hydroxybutyrate using acid(Liebigs Ann. IRecueil, 1877-1879, 1997) or resin catalyst(H+ resin, Korean Patent Application # 10-2005-0010927),

[20] Then, (R)-3-hydroxy-gamma-butyrolactone is subjected to ring-opening reaction using both of halogen acid and carboxylic acid to prepare (R)-3-acyloxy-4-halobutyric acid. (R)-3-acyloxy-4-halobutyric acid is subjected to epoxydation reaction to prepare (R)-3,4-epoxybutyric acid or it's salt. Then L-carnitine is produced via a well-known reaction(Journal of Organic Chemistry, 53, 104-107, 1988).

[21] In the method which includes the process for the preparation of (R)-3-hydroxy-gamma-butyrolactone, the epoxy compound can be produced easily from (R)-3-hydroxy-gamma-butyrolactone because the inversion step is not required. And optically pure compound(99 ee%) can be produced by hydrolysis using enzyme, so L-carnitine with high optical purity can be obtained.

[22] This invention does not include using expensive or unsafe agent. Low-price compounds are used compared to the traditional process. Based on these facts, the above method for preparing L-carnitine is expected to be economical in the industrial application.

[23]

Technical Solution

[24] This invention is explained in more detail as follows.
(R)-3-hydroxy-gamma-butyrolactone is prepared from racemic 3-acyloxy-gamma-butyrolactone by sterospecific hydrolysis using lipases in aqeous phase or organic phase including aqueous solvent, or by hydrolysis from (R)-3-acyloxy-gamma-butyrolactone. And (R)-3-hydroxy-gamma-butyrolactone can be produced from alkyl (4)-4-chloro-3-hydroxyburtrate. Then, L-carnitine is produced from the above compound by ring-opening reaction using both of halogen acid and alkyl carboxylic acid to prepare (R)-3-acyloxy-4-halobutyric acid, and epoxydation of (R)-3-acyloxy-4-halobutyric acid to prepare (R)-3,4-epoxybutyric acid salt or (R)-3,4-epoxybutyric acid consecutively.

[25] In the general formula 2, R_1 is selected from substited or unsubstited alkyl groups or alkenyl groups, wherein the alkyl contains from C_1 to C_8, benzyl groups, cycloalkyl groups comprising from C_3 to C_6, substited or unsubstited arylalkyl groups, and substited or unsubstited heteroarylalkyl groups. In the general formular 5, corresponding to (R)-3-acyloxy-4-halobutyric acid, R_2 is halogen group(F, Cl, Br, I), R_3 is acyl group(COC_nH_{2n+1}, n=1~4). And in the formula 4, R_4 is alkyl groups comprising from C_1 to C_8.

[26] In preparing optically active intermediate, CAL B(Novozyme 435, Novozyme) may be used for stereospecific hydrolysis. PS-D(Amano) or lipase producing microorganisms are also suitable as biocatalysts.

[27] For the ring-opening reaction, halogen acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, and hydroiodic acid and C_1~C_4 alkylcarboxyric acid such as acetic acid may be used. Epoxydation reaction is carried out in aqeous solution or mixture of aqeous phase and organic phase, wherein bases according to this invention include the following;

[28] Alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, and lithium hydroxide,

[29] Alkaline earth metal hydroxide such as magnesium hydroxide, calcium hydroxide and barium hydroxide,

[30] Alkali metal alkoxide such as sodium methoxide, sodium ethoxide, sodium t-butoxide,

[31] Alkylamine such as NHR_5R_6(wherein,R_5 and R_6 are alkyl groups of C2~7, respectively), and

[32] Quaternary ammonium hydroxide such as tetrabutyl ammonium hydroxide, benzylt rimethyl ammonium hydroxide.

[33] L-carnitine is prepared from (R)-3,4-epoxybutyric acid salt or (R)-3,4-epoxybutyric acid obtained from the above reaction by adding trimethylamine according to the general process.

[34] In this invention, the reactants and the products were confirmed by FT-NMR(Burker Inc., Model DPX300) and 3-hydroxy-gamma-butyrolactone, 3-acyloxy-gamma-butyrolactone, ethyl 4-chlro-3-hydroxybutyrate, 3-acetoxy-3-bromobutyric acid were analyzed by gas chromatography(Donam Instruments Inc., Model DS6200) eqipped with HP-FFAP(Agilent Inc., 30 m X 0.53 mm) column. Optical purity of (R)-3-hydroxy-gamma-butyrolactone and (R)-3-acyloxy-gamma-butyrolactone were detected by HPLC(LAB Alliance Inc., Model 201) eqipped with chiral column AD-H(Daicel Inc., 0.46cm X 25cm) using hexane and isopropyl alcohol mixture(90:10) as mobile phase. The absorbance was 220 nm and flow rate was 0.7 ml/min. Optical purity of L-carnitine are measured by polarimeter(ATAGO, Model AP-100).

[35] The following specific examples are intended to be illustrative of the invention and shoud not be construed as limiting the scope of the invention as defined by appended calims.

[36]

[37] Example 1. Preparation of racemic 3-butoxy-gamma-butylolactone(1)

[38]

[39] Pyridine(35 g) and butyryl chloride(47 g) were added to the chloroform (300 ml) containing racemic 3-hydroxy-gamma-butyrolactone(30 g) and stirred at 0℃ and then reacted at room temperature. The reaction mixture was extracted with organic solvent and concentrated by vacuum evaporation to afford 33g of 3-butoxy-gamma-butyrolactone, and this product was confirmed by nuclear magnetic resonance.

[40] ^{1}H-NMR(300 MHz, $CDCl_3$) : 0.9(t, 3H), 1.5-1.7(dd, 2H), 2.2-2.3(t, 2H), 2.5-2.9m, 2H), 4.3-4.5(m, 2H), 6.4(m, 1H) ppm

[41]

[42] Example 2. Preparation of (R)-3-hydroxy-gamma-butylolactone(3)

[43]

[44] 3-butoxy-gamma-butyrolactone(5 %, v/v) prepared from Example 1 was added to 0.2 M potassium phosphate buffer(pH 7.0) and the reaction was carried out at 30 ℃ using lipase CAL B(0.2 %). In this condition, high optically active

(R)-3-butyloxy-gamma-butyrolactone(99 ee%, 80 % converion) was obtained by solvent extraction. This material was converted to (R)-3-hydroxy-gamma-butyrolactone using sulfuric acid solution and enantiomeric excess of this product(99ee%) was confirmed by above-mentioned method.

[45]

[46] Example 3. Preparation of (R)-3-hydroxy-gamma-butyrolactone(3)

[47]

[48] Ethyl (R)-4-chloro-3-hydroxybutyrate(5 %, w/v) was added to the vial containing distilled water and Amberlite IR-120(5 %, w/v) and the reaction was carried out at 60 ℃. After 32 hours, (R)-3-hydroxy-gamma-butyrolactone was obtained from organic solvent. The conversion was 99 % and optical purity was maintained as before.

[49]

[50] Example 4. Preparation of (R)-3-acetoxy-4-bromobutyric acid(5)

[51]

[52] (R)-3-hydroxy-gamma-butyrolactone(6.6 g) was stirred with 20 ml of 30% hydrogen bromide in acetic acid at 60 ℃ for 4 hours. Product(7.8 g) was obtained by distillation under reduced pressure and solvent extraction and confirmed by 1H-NMR.

[53] 1H-NMR(300MHz, CDCl3) : 2.08(m, 3H), 2.83(m, 2H), 3.53-3.74(dd, 2H), 5.35(m, 1H)

[54]

[55] Example 5. Preparation of (R)-3,4-epoxybutyric acid(6)

[56]

[57] (R)-3,4-epoxybutyrate sodium salt was prepared by addition of the aqueous solution of 3N NaOH to (R)-3-acetoxy-4-bromo butyric acid which was prepared from Example 4. Then the solution was acidified to pH 3-4 and extracted with ethyl ether. The combined organic extracts were distilled under reduced pressure to (R)-3,4-epoxybutyric acid and was confirmed 1H-NMR.

[58] 1H-NMR(300 MHz, CDCL3) : 2.3-2.8(m, 2H), 2.6-2.9(m, 2H), 3.3-3.4(m, 1H)

[59]

[60] Example 6. Preparation of L-carnitine(7)

[61]

[62] Trimethylamine solution(2 eq.) was added to aqueous solution containing (R)-3,4-epoxybutyrate sodium salt or (R)-3,4-epoxybutyric acid prepared from Example 5 and stirred at 45 ℃, for 2 hours . After purification of this solution using cation exchange resin(Amberite IR-120), L-carnitine was obtained. The optical purity was analyzed by polarimeter(ATAGO Inc., Model AP-100).

[63] $[\alpha]^{2}_{D}$ = -30 (C=1, $H_2$0)

[64]

[65]

[66]

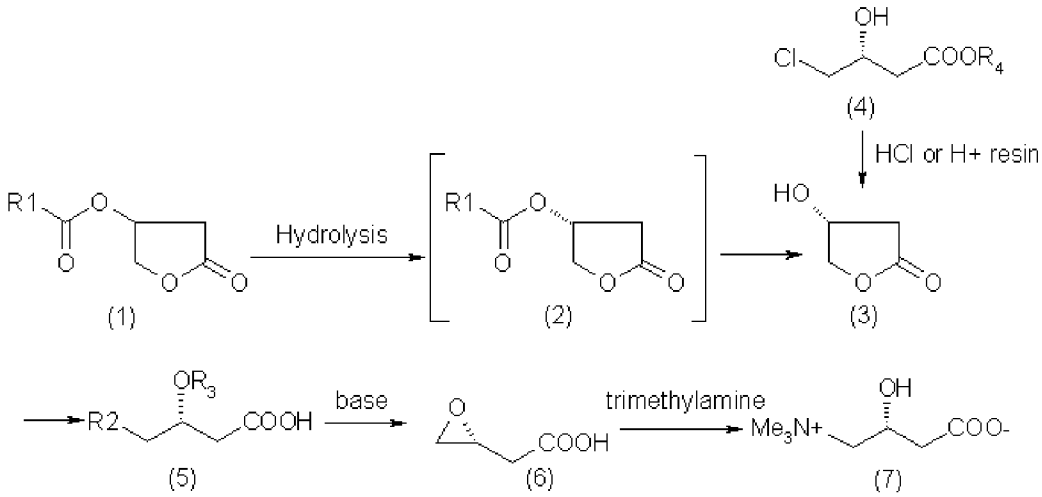
Industrial Applicability

[67] As aforesaid, under the process for the prepaing L-carnitine according to this invention, racemic 3-acyloxy-gamma-butyrolactone as a raw materal is hydrolyzed stereospecifically using enzymatic method or (R)-4-chloro-3-hydroxybutyrate is hydrolyzed to (R)-3-hydroxy-gamma-butyrolactone, followed by the ring-opening reaction, epoxydation, and nucleophilic substitution consecutively. Furthermore, low-price compounds such as sulfuric acid, sodium hydroxide and trimethylamine are used. Therefore, this method is an economically useful process on the industrial scale.

[68]

Claims

[1] A process for preparing (R)-3,4-epoxybytyric acid and the salt thereof, wherein (R)-3-hydroxy-gamma-butyrolactone repesented by the general formula 3 in scheme 1 is subjected to ring-opening reaction using both of halogen acid and carboxylic acid, (R)-3-acyloxy-4-halobutyic acid represented by the general formula 5 is prepared therefrom, and
(R)-3-acyloxy-4-halobutyic acid is subjected to epoxydation reaction in the presence of a base in order to preapare (R)-3,4-epoxybytyric acid and the salt thereof
[scheme 1]



In scheme 1, R_1 is selected from substituted or unsubstituted alkyl groups or alkenyl groups, wherein the alkyl contains from C_1 to C_8, benzyl groups, cycloalkyl groups comprising from C_3 to C_6, substituted or unsubstituted arylalkyl groups, and substituted or unsubstituted heteroarylalkyl groups. R_2 is halogen compound such as F, Cl, Br, and I, R_3 is acyl group(COC_nH_{2n+1}, n=1~4) and R_4 is alkyl groups comprising from C_1 to C_8.

[2] A process of preparing L-carnitine, wherein
racemic 3-acyloxy-gamma-butyrolactone repesented by the general formula 1 is hydrolyzed stereospecifically using enzymes in the aqeous phase or organic phase including aqeous solvent and (R)-3-acyloxy-gamma-butyrolactone repesented by the general formula 2 is hydrolyzed for the preparation of (R)-3-hydroxy-gamma-butyrolactone repesented by the general formula 3.
(R)-3-hydroxy-gamma-butyrolactone is subjected to ring-opening reaction with both of halogen acid and carboxylic acid for the preparation of (R)-3-acyloxy-4-halobutyric acid repesented by the general formula 5,
(R)-3-acyloxy-4-halobutyric acid is subjected to epoxydation reaction in order to

prepare 3,4-epoxybutyric acid or the salt thereof, and 3,4-epoxybutyric acid or the salt thereof undergoes nucleophilic substitution by trimethylamine to prepare L-carnitine.

[3] A process of preparing L-carnitine, wherein
alkyl (R)-4-chloro-3-hydroxybutyrate repesented by the general formula 4 in scheme 1 is subjected to hydrolysis using acid catalyst or cation exchange resin for the preparation of (R)-3-hydroxy-gamma-butyrolactone,
(R)-3-hydroxy-gamma-butyrolactone is subjected to ring-opening reaction with both of halogen acid and carboxylic acid for the preparation of (R)-3-acyloxy-4-halobutyric acid repesented by the general formula 5,
(R)-3-acyloxy-4-halobutyric acid is subjected to epoxydation reaction in the presence of a base in order to prepare 3,4-epoxybutyric acid and the salt thereof, and
3,4-epoxybutyric acid or the salt thereof undergoes nucleophilic substitution by trimethylamine to prepare L-carnitine.

[4] A process for preparing (R)-3-acyloxy-4-halobutyric acid repesented by the general formula 5 according to claim 1, claim 2 and claim 3, wherein said ring-opening reaction is carried out using halogen acid such as hydrofluoric acid, hydrochloric acid, bromic acid, and iodic acid and carboxylic acid such as alkyl-carboxylic acid having carbon atomes of 1~4 including acetic acid.

[5] A process for preparing (R)-3,4-epoxybutyric acid salt or (R)-3,4-epoxybutyric acid according to claim 1, claim 2 and claim 3, wherein a base used for said epoxydation is selected from the group consisting of alkali metal hydroxide, alkaline earth metal hydroxide, alkali metal alkoxide, alkylamine and quarternary amine hydroxide in the presence of water as single solvent or co-solvent containing an organic solvent with water.

[6] A process for preparing (R)-3,4-epoxybutyric acid salt or (R)-3,4-epoxybutyric acid according to claim 5,wherein said alkali metal hydroxide is selected from the group consisting of sodium hydroxide, sodium potassium and lithium hydroxide; said alkaline earth metal hydroxide is selected from the group consisting of magnesium hydroxide, calcium hydroxide and barium hydroxide; said alkali metal alkoxide is selected from the group consisting of sodium methoxide, sodium ethoxide and potassium t-buthoxide; said alkylamine is selected from the group consisting of NHR_5R_6 (hence, R_5 and R_6, respectively, is an alkyl group having carbon atoms of 2~7) and NH_2R_7 (R_7 is an alkyl group having carbon atoms of 3~9); said quarternary amine hydroxide is selected from the group consisting of tetrabutylammonium hydroxide and benzyltrimethylammonium hydroxide.

[7] A process for preparing L-carnitine according to calim 2 and claim 3, wherein (R)-3-hydroxy-gamma-butyrolactone repesented by the general formula 3 in schem 1 is subjected to ring-opening reaction using both of bromic acid and acetic acid for preparing (R)-3-acetoxy-4-bromobutyric acid repesented by the general formula 5, and then said derivative is subjected to epoxidation in the presence of sodium hydroxide and water as single solvent or co-solvent containing an organic solvent with water. (R)-3,4-epoxybutyric acid salt and (R)-3,4-epoxybutyric acid as a result of this, undergoes nucleophilic substitution by trimethylamine to prepare L-carnitine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2006/002003

A. CLASSIFICATION OF SUBJECT MATTER

C07D 303/40(2006.01)i

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)

IPC 8 C07D 303/40

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

Korean Patents and applications for inventions since 1975

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

PUB MED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6342034 B1 (Byun, Il Suk et al) 29 Jan. 2002 See abstract, example 1-10, claims 1-19	1-7
A	US 6284902 B1 (Byun, Il Suk et al) 4 Sep. 2001 See abstract, example 1-9, claims 1-5	1-7

☐ 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	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2006/002003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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