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(54) Title: ASCORBIC ACID DERIVATIVES HAVING ALPHA-LIPOYL GROUPS AND PROCESS FOR PREPARING THE SAME

(57) Abstract: The present invention provides an ascorbic acid derivative having an α-lipoyl group and a process for preparing the same. The ascorbic acid derivative of the present invention has excellent stability in an aqueous medium, and thus can minimize denaturation caused by environmental factors such as temperature, light, oxygen, and water, even when being stored in an aqueous composition for a long eriod of time.

【DESCRIPTION】

【Invention Title】

ASCORBIC ACID DERIVATIVES HAVING ALPHA-LIPOYL GROUPS AND PROCESS FOR PREPARING THE SAME

【TECHNICAL FIELD】

The present invention relates to an ascorbic acid derivative having an α-lipoyl group and a process for preparing the same.

【BACKGROUND ART】

Pharmaceutical compositions and/or cosmetic compositions include various antioxidants. A variety of compounds such as α-lipoic acid, coenzyme Q10, α-tocopherol, retinol, glutathione, ascorbic acid, butylated hydroxy toluene, genistein, quercetin, propyl gallate, epigallocatechin gallate, gallocatechin gallate, sylibin, diosmetin, kaempferol, epicatechin, and galangin are known as antioxidants.

Ascorbic acid which is widely used as an antioxidant has a structure similar to that of Y-lactone. Due to its structure, ascorbic acid sensitively reacts with environmental factors such as air, particularly oxygen, heat, and light to be easily decomposed. In order to improve stability of ascorbic acid, a method of adding an anti-oxidizing agent, a method of stabilizing ascorbic acid in a multi-lamellar emulsion, a method of stabilizing ascorbic acid in an oil in water type emulsion, and

a method of inhibiting oxidization of ascorbic acid using zinc sulfate and L-tyrosine have been reported (U.S. Patent No. 4,938,969, European Patent Publication No. 533,667 B1, etc.). Furthermore, in order to improve stability of ascorbic acid, ascorbic acid is chemically modified into a derivative such as sodium ascorbylphosphate, magnesium ascorbyl phosphate, calcium ascorbylphosphate, ascorbic acid polypeptide, ethyl ascorbyl ether, ascorbyl dipalmitate, ascorbyl palmitate, ascorbyl glucoside, and ascorbyl ethylsilanol pectinate. However, even though the chemical structure of ascorbic acid is modified as described above, stability of ascorbic acid is not satisfactory when ascorbic acid is exposed to water, light, or air, particularly in an aqueous medium.

Alpha-lipoic acid, which has various pharmacological effects such as improving immune function, reducing blood sugar level, and suppressing appetite in human body, is readily reduced to dihydrolipoic acid which has unpleasant odor. Although a method of encapsulating α-lipoic acid using liposome has been introduced in order to overcome this problem, it is difficult to encapsulate a large amount of α-lipoic acid.

Therefore, there is a need to develop a method of improving stabilities of ascorbic acid and α-lipoic acid, in addition to preventing ascorbic acid and α-lipoic acid from unpleasant odor formation and/or discoloration.

[DETAILED DESCRIPTION OF THE INVENTION]

[TECHNICAL PROBLEM]

The present inventors conducted various researches in order to develop methods for improving stability of α-lipoic acid and ascorbic acid, particularly in an aqueous medium. As a result, the present inventors found that, when ascorbic acid modified into ascorbic acid derivatives having α-lipoic acid, the obtained ascorbic acid derivatives have excellent stability; and unpleasant odor formation and discoloration of each of ascorbic acid and α-lipoic acid can be significantly prevented. Furthermore, since the ascorbic acid derivatives can be dissociated into ascorbic acid and α-lipoic acid in vivo environment, for example, in stomach with acidic environment or in skin tissue, it has been found that synergistic pharmacological effects such as whitening, anti-aging, skin care, anti-wrinkle, and moisturizing can be expected through the two types of antioxidants.

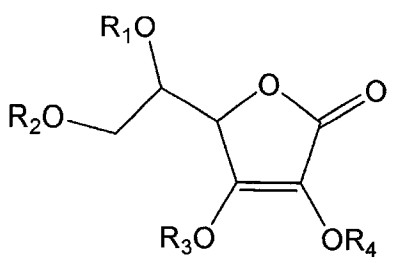
Thus, the present invention provides an ascorbic acid derivative having α-lipoic acid.

The present invention also provides a process for preparing the ascorbic acid derivative.

【TECHNICAL SOLUTION】

According to an aspect of the present invention, there is provided an ascorbic acid derivative represented by the following Formula 1:

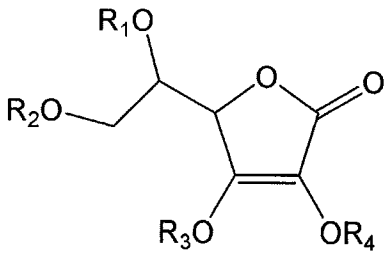
Formula 1



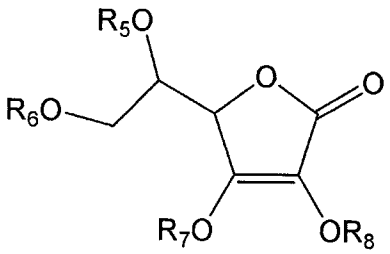
wherein one of the substituents R_1 to R_4 is an α-lipoyl group; one or two of the remaining substituents are, each independently, an α-lipoyl group, a C_1-C_4 alkyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a C_8-C_{18} acyl group; and the remaining substituents are hydrogen atoms.

According to another aspect of the present invention, there is provided a process for preparing an ascorbic acid derivative of Formula 1, the method comprising (a) reacting a compound of Formula 2 with a compound of Formula 3 and (b) deprotecting the product obtained in Step (a):

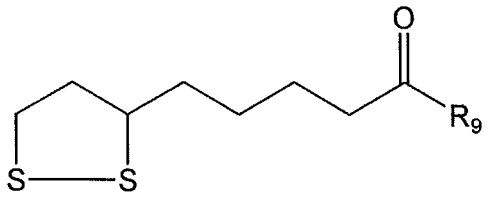
Formula 1



Formula 2



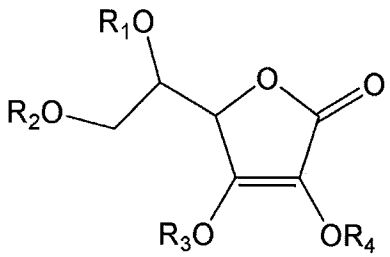
Formula 3



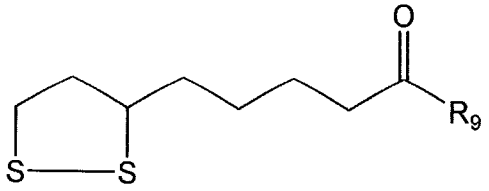
wherein R_1, R_2, R_3, and R_4 are the same as defined in the above; two or three of the substituents R_5 to R_8 are hydrogen atoms, and the remaining substituents are hydroxy protecting groups; and R_9 is a hydroxy group, a carbodiimidyl group, a halogen atom, a C_1-C_4 alkoxy group, a hydroxysuccinimidyl group, an ethylcarbonyloxy group, an ethoxycarbonyloxy group, or an imidazolyl group.

According to still another aspect of the present invention, there is provided a process for preparing an ascorbic acid derivative of Formula 1, the method comprising reacting a compound of Formula 4 with a compound of Formula 3:

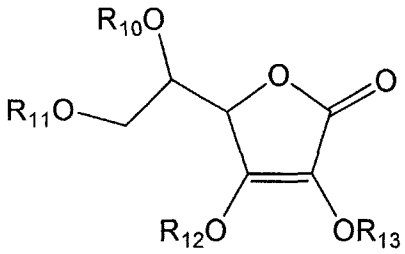
Formula 1



Formula 3



Formula 4



wherein R_1, R_2, R_3, and R_4 are the same as defined in the above; R_9 is a hydroxy group, a carbodiimidyl group, a halogen atom, a C_1-C_4 alkoxy group, a hydroxysuccinimidyl group, an ethylcarbonyloxy group, an ethoxycarbonyloxy group, or an imidazolyl group; and one or two of the substituents R_{10} to R_{13} are, each independently, an α-lipoyl group, a C_1-C_4 alkyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a C_8-C_{18} acyl group, and the remaining substituents are hydrogen atoms.

The reacting a compound of Formula 3 with a compound of Formula 4 may be performed in the presence of one or more coupling agent selected from the group consisting of 3-dimethyl-aminopropyl-N-ethyl carbodiimide, dicyclohexyl carbodiimide, diisopropyl carbodiimide, and ethoxy carbonyl chloride; and in the presence of one or more base selected from the group consisting of dimethylaminopyridine, imidazole, pyridine, diisopropylethylamine, and triethylamine.

【ADVANTAGEOUS EFFECTS】

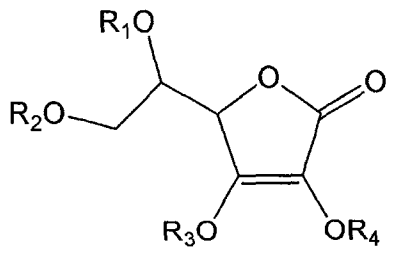
The ascorbic acid derivative according to the present invention contains two types of substituents including α-lipoic acid in its structure. The ascorbic acid derivative has excellent stability in an aqueous medium, and thus can minimize

denaturation caused by environmental factors such as temperature, light, oxygen, and water, even when being stored in an aqueous composition for a long period of time. In particular, odor caused by denaturation of α-lipoic acid, e.g., reduction of α-lipoic acid, can be significantly prevented. In addition, since the ascorbic acid derivatives can be dissociated into ascorbic acid and α-lipoic acid in vivo environment, for example, in stomach with acidic environment or in skin tissue, synergistic pharmacological effects such as whitening, anti-aging, skin care, anti-wrinkle, and moisturizing can be expected through the two types of antioxidants. Therefore, the ascorbic acid derivative according to the present invention can be usefully applied to pharmaceutical compositions and cosmetic compositions, particularly to aqueous pharmaceutical compositions and cosmetic compositions.

[BEST MODE FOR CARRYING OUT THE INVENTION]

The present invention provides an ascorbic acid derivative represented by the following Formula 1:

Formula 1



wherein one of the substituents R_1 to R_4 is an α-lipoyl group; one or two of the remaining substituents are, each independently, an α-lipoyl group, a C_1-C_4 alkyl

group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a C_8-C_{18} acyl group; and the remaining substituents are hydrogen atoms.

Among the ascorbic acid derivative according to the present invention, preferred are those wherein: two of the substituents R_1 to R_4 are hydrogen atoms; one of the remaining substituents is an α-lipoyl group; and the remaining substituent is an α-lipoyl group, an ethyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a palmitoyl group. Among the substituents, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45) refers to a polyethylene glycol group, and preferably a polyethylene glycol group having an average molecular weight of about 300 to about 2000, and preferably about 1000.

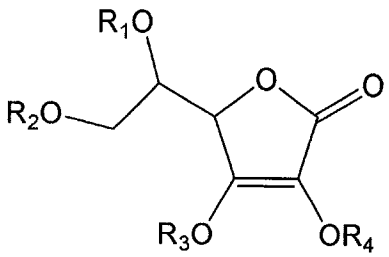
More preferred ascorbic acid derivative of the present invention are: L-5,6-di-α-lipoyl-ascorbic acid; L-2,3-di-α-lipoyl-ascorbic acid; L-2,6-di-α-lipoyl ascorbic acid; L-6-α-lipoyl-2-glucosyl-ascorbic acid; L-6-α-lipoyl-3-polyethylene glycol-ascorbic acid; L-6-α-lipoyl-2-ethyl-ascorbic acid; L-6-α-lipoyl-3-ethyl-ascorbic acid; L-6-palmitoyl-2-α-lipoyl-ascorbic acid; L-2-α-lipoyl-3-polyethylene glycol-ascorbic acid; L-2-α-lipoyl-3-ethyl-ascorbic acid.

The ascorbic acid derivative according to the present invention contains two types of substituents including α-lipoic acid in its structure. The ascorbic acid derivative has excellent stability in an aqueous medium, and thus can minimize denaturation caused by environmental factors such as temperature, light, oxygen, and water, even when being stored in an aqueous composition for a long period of time. In particular, odor caused by denaturation of α-lipoic acid, e.g., reduction of α-lipoic acid, can be significantly prevented. In addition, since the ascorbic acid

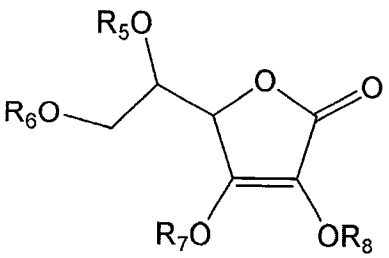
derivatives can be dissociated into ascorbic acid and α-lipoic acid in vivo environment, for example, in stomach with acidic environment or in skin tissue, synergistic pharmacological effects such as whitening, anti-aging, skin care, anti-wrinkle, and moisturizing can be expected through the two types of antioxidants. Therefore, the ascorbic acid derivative according to the present invention can be usefully applied to pharmaceutical compositions and cosmetic compositions, particularly to aqueous pharmaceutical compositions and cosmetic compositions.

The present invention also provides a process for preparing an ascorbic acid derivative of Formula 1, the method comprising (a) reacting a compound of Formula 2 with a compound of Formula 3 and (b) deprotecting the product obtained in Step (a):

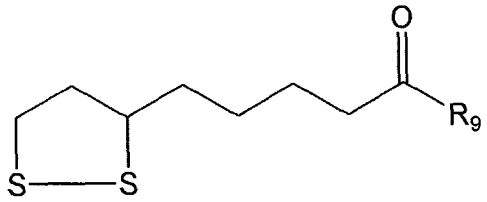
Formula 1



Formula 2



Formula 3



wherein R_1, R_2, R_3, and R_4 are the same as defined in the above; two or three of the substituents R_5 to R_8 are hydrogen atoms, and the remaining substituents are hydroxy protecting groups; and R_9 is a hydroxy group, a carbodiimidyl group, a halogen atom, a C_1-C_4 alkoxy group, a hydroxysuccinimidyl group, an ethylcarbonyloxy group, an ethoxycarbonyloxy group, or an imidazolyl group.

Among the compound of Formula 2, preferred are those wherein: both R_5 and R_6 are hydrogen atoms and both R_7 and R_8 are hydroxy protecting groups; both R_7 and R_8 are hydrogen atoms and both R_5 and R_6 are hydroxy protecting groups; or both R_5 and R_8 are hydrogen atoms and both R_6 and R_7 are hydroxy protecting groups.

The compound of Formula 2 may be prepared by introducing a hydroxy protecting group into a desired position in ascorbic acid using a conventional method. For example, a hydroxy protecting group may be selectively introduced into a hydroxy group of position 2, position 3, or positions 5 and 6 of ascorbic acid according to Journal of Organic Chemistry 69, pp 7026, 2004 and Journal of the American Chemical Society, 102, pp 6304, 1980. The hydroxy protecting group may be selected from the group consisting of a benzyl group, an isopropylidenyl group, a benzoyl group, a benzyloxycarbonyl group, an acetyl group, and a silyl group.

As the compound of Formula 3, α-lipoic acid (i.e., R_9 is a hydroxy group) may be directly used. Alternatively, in order to easily remove byproducts, a group activating the carboxyl group of α-lipoic acid such as a carboimidyl group, a halogen atom, a C_1- C_4 alkoxy group, a hydroxysuccinimidyl group, an ethylcarbonyloxy group, or an imidazolyl group may be introduced into α-lipoic acid and then used in the reaction.

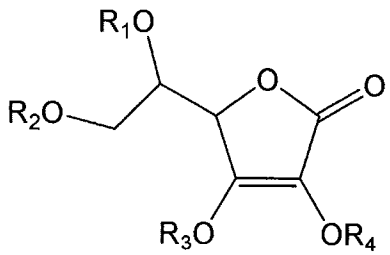
The reaction between the compound of Formula 2 and the compound of Formula 3 may be performed in the presence of a coupling agent, such as 3-dimethyl-aminopropyl-N-ethyl carbodiimide, dicyclohexyl carbodiimide, diisopropyl carbodiimide, and ethoxy carbonyl chloride; and in the presence of a base, such as dimethylaminopyridine, imidazole pyridine, diisopropylethylamine, and triethylamine. The reaction may be performed in a solvent, such as dichloromethane, ethyl acetate, diethylformamide, tetrahydrofuran (THF), chloroform, and dimethyl sulfone imide, at room temperature (at about 25℃) at atmospheric pressure. The ratio of the compound of Formula 2 to the compound of Formula 3 may be 1 : 1-1.5 equivalence ratio, and preferably 1 : 1.1-1.3 equivalence ratio, but is not limited thereto. When the reaction is performed in the range described above, purification of the ascorbic acid derivative may be facilitated since un-reacted ascorbic acid is not remained. The product prepared according to the reaction above, i.e., the compound having an α-lipoyl group and a hydroxy protecting group, may be isolated by removing the solvent using a conventional method, for example, distillation under reduced pressure.

Deprotection of the product prepared by the reaction between the compound of Formula 2 and the compound of Formula 3, i.e., a reaction for removing the hydroxy protecting group, may be conducted using a conventional

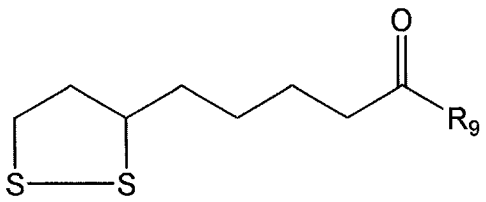
method for removing a hydroxy protecting group. For example, when a benzyl group is used as the hydroxy protecting group, the hydroxy protecting group may be removed by dissolving the product obtained from the reaction of the compound of Formula 2 and the compound of Formula 3 in methanol, tetrahydrofuran, or a mixture thereof, and hydrogenising the resultant using palladium/carbon (Pd/C). When an isopropylidenyl group is used as the hydroxy protecting group, the hydroxy protecting group may be removed by stirring the product obtained from the reaction of the compound of Formula 2 and the compound of Formula 3 in hydrochloric acid and methanol. The obtained product may be isolated using a conventional method, e.g., concentration under reduced pressure and, if desired, a filtering process may be further included.

The compound of Formula 1 according to the present invention may also be prepared by reacting a compound having a single substituent, e.g., α-lipoic acid, with α-lipoic acid or its activated derivative. That is, the present invention provides a process for preparing an ascorbic acid derivative of Formula 1, the method comprising reacting a compound of Formula 4 with a compound of Formula 3:

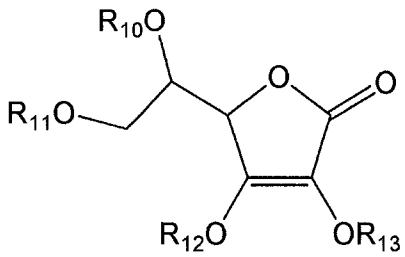
Formula 1



Formula 3



Formula 4



wherein R_1, R_2, R_3, and R_4 are the same as defined in the above; R_9 is a hydroxy group, a carbodiimidyl group, a halogen atom, a C_1-C_4 alkoxy group, a hydroxysuccinimidyl group, an ethylcarbonyloxy group, an ethoxycarbonyloxy group, or an imidazolyl group; and one or two of the substituents R_{10} to R_{13} are, each independently, an α-lipoyl group, a C_1-C_4 alkyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a C_8-C_{18} acyl group, and the remaining substituents are hydrogen atoms.

Among the compound of Formula 4, preferred are those wherein: R_{11} is an α-lipoyl group and R_{10}, R_{12}, and R_{13} are hydrogen atoms; or one of the substituents R_{10} to R_{13} is an ethyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a palmitoyl group and the remaining substituents are hydrogen atoms. The compound of Formula 4 may be prepared by introducing an α-lipoyl group into position 2, 3, 5, and/or 6 of ascorbic acid according to Journal of Organic Chemistry, V69, pp 7026-7032, 2004.

The reaction between the compound of Formula 3 and the compound of Formula 4 may be performed in the presence of a coupling agent, such as 3-dimethyl-aminopropyl-N-ethyl carbodiimide, dicyclohexyl carbodiimide, diisopropyl carbodiimide, and ethoxy carbonyl chloride; and in the presence of a base, such as dimethylaminopyridine, imidazole pyridine, diisopropylethylamine, and triethylamine. The reaction may be performed in a solvent, such as dichloromethane, ethyl acetate, diethylformamide, tetrahydrofuran, chloroform, and dimethyl sulfone imide, at room temperature (at about 25℃) at atmospheric pressure. The ratio of the compound of Formula 4 to the compound of Formula 3 may be 1 : 1-1.5 equivalence ratio, and preferably 1 : 1.1-1.3 equivalence ratio, but is not limited thereto. When the reaction is performed in the range described above, purification of the ascorbic acid derivative may be facilitated since un-reacted ascorbic acid is not remained. The product prepared according to the reaction above may be isolated by removing the solvent using a conventional method, for example, distillation under reduced pressure.

Hereinafter, the present invention will be described more specifically with reference to the following examples. The following examples are only for illustrative purposes and are not intended to limit the scope of the invention.

Preparation Example 1: Preparation of L-5,6-O-isopropylidin-ascorbic acid

L-5,6-O-isopropylidin-ascorbic acid was prepared according to a method disclosed in Journal of the American Chemical Society, Vol. 102, No. 20, pp 6304, 1980. That is, 100 g of ascorbic acid was added to 50 ml of acetone. While the reaction mixture was stirred at room temperature, 10 ml of acetyl chloride was

added to the mixture, which was then stirred for 3 hours. The mixture was cooled in ice bath and filtered to isolate a precipitate. The precipitate was washed with 500 ml of cold acetone and dried under reduced pressure to obtain 105 g of L-5,6-O-isopropylidin-ascorbic acid (yield: 86%, mp: 206-208 ℃).

^{1}H NMR (400MHz, CDCL3), Chemical shift; 5.50 (1H, d), 5.18 (1H, m), 4.20(2H, t), 2.52(2H, m), 2.51 (4H, t), 2.25-1.55 (12H, m)

Preparation Example 2: Preparation of 2,3-dibenzyl-ascorbic acid

50 g of L-5,6-O-isopropylidin-ascorbic acid prepared in Preparation Example 1 was added to 70 ml of dimethylformamide. 64 g of calcium carbonate was added to the reaction mixture, which was then stirred for 30 minutes. 60 ml of benzyl bromide was gradually added to the reaction mixture, which was then stirred overnight at room temperature. The reaction mixture was distilled under reduced pressure to remove the solvent, and 300 ml of dichloromethane was added thereto. The reaction mixture was washed with water and further distilled under reduced pressure to obtain a brown solid. The obtained brown solid was added to methanol to remove un-reacted reactants and byproducts (i.e., a compound having a single benzyl group). The obtained reaction mixture was dried to obtain 65 g of L-5,6-O-isopropylidin-2,3-dibenzyl-ascorbic acid (yield: 71%).

50 g of L-5,6-O-isopropylidin-2,3-dibenzyl-ascorbic acid obtained in the above was added to a mixed solvent of 20 ml of tetrahydrofuran (THF) and 20 ml of 1.5 N hydrochloric acid, stirred at 50℃ for 5 hours, and then distilled under reduced pressure. 300 ml of ethyl acetate was added to the obtained residue. The

resultant reaction mixture was washed with water and then dried under reduced pressure to obtain 43 g of 2,3-dibenzyl-ascorbic acid (yield: 95%).

^{1}H NMR (400MHz, CDCL3), Chemical shift; 4.99 (1H, d), 3.81 (2H, d), 3.93 (1H, m), 2.52(2H, m), 2.61 (4H, t), 1.73 (4H, m), 2.23-1.55 (12H, m)

Example 1: Preparation of L-5,6-di-α-lipoyl-ascorbic acid

5 g L-2,3-dibenzyl-ascorbic acid prepared obtained in Preparation Example 2 and 7.3 g of α-lipoic acid were added to 100 ml of dichloromethane. While stirring the reaction mixture, 6.76 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide was gradually added to the reaction mixture over the period of 30 minutes. 500 mg of N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred overnight at room temperature. The reaction mixture was distilled under reduced pressure and 100 ml of ethyl acetate was added to the resulting residue. Then, the resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 8.5 g of L-5,6-di-α-lipoyl-2,3-dibenzyl-ascorbic acid as a solid (yield: 78%).

5 g of L-5,6-di-α-lipoyl-2,3-dibenzyl-ascorbic acid was dissolved in 50 ml of a mixture of methanol and tetrahydrofuran (THF) (1:1, v/v), and 1 g of 5% active palladium/carbon was added to the reaction mixture, which was then stirred under a hydrogen pressure for 5 hours. The reaction mixture was filtered and the obtained filtrate was dried under reduced pressure to obtain 3.65 g of L-5,6-di-α-lipoyl-ascorbic acid (yield: 95%).

^{1}H NMR (400MHz, CDCL3), Chemical shift ; 5.50 (1H, d), 5.18 (1H, m), 4.20(2H, t), 2.52(2H, m), 2.51 (4H, t), 2.25-1.55 (12H, m)

Example 2: Preparation of L-2,3-di-α-lipoyl-ascorbic acid

3 g of L-5,6-O-isopropylidin-ascorbic acid prepared in Preparation Example 1 and 6.01 g of α-lipoic acid were added to 100 ml of dichloromethane. While stirring the reaction mixture, 5.59 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide was gradually added to the reaction mixture over the period of 30 minutes. 500 mg of N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred overnight at room temperature. The reaction mixture was distilled under reduced pressure and 100 ml of ethyl acetate was added to the resulting residue. Then, the resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 6.25 g of L-5,6-O-isopropylidin-2,3-di-α-lipoyl-ascorbic acid as a solid (yield: 76 %).

3 g of L-5,6-O-isopropylidin-2,3-di-α-lipoyl-ascorbic acid was added to 5 ml of 1 N HCl and 50 ml of methanol was added to the reaction mixture, which was then stirred at room temperature for 6 hours. The reaction mixture was distilled under reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 2.38 g of L-2,3-di-α-lipoyl-ascorbic acid as a solid (yield: 85%).

^{1}H NMR (400MHz, CDCL3), Chemical shift ; 4.99 (1H, d), 3.81 (2H, d), 3.93 (1H, m), 2.52(2H, m), 2.61 (4H, t), 1.73 (4H, m), 2.23-1.55 (12H, m)

Example 3: Preparation of L-2,6-di-α-lipoyl ascorbic acid

3 g of L-6-α-lipoyl-ascorbic acid obtained in Comparative Example 1 described below and 2.04 g of α-lipoic acid were added to 100 ml of dichloromethane. While stirring the reaction mixture, 1.89 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide was gradually added to the reaction mixture over the period of 30 minutes. 500 mg of N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred at room temperature overnight. The reaction mixture was distilled under reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 3.73 g of L-2,6-di-α-lipoyl-ascorbic acid as a solid (yield: 82%).

^{1}H NMR (400MHz, CDCL3), Chemical shift; 5.2 (1H, d), 4.44 (1H, m), 4.23 (2H, dd), 2.52(2H, m), 2.51-2.61 (4H, m), 1.84 (4H, m), 1.29-2.25 (12H, m)

Example 4: Preparation of L-6-α-lipoyl-2-glucosyl-ascorbic acid

5.0 g of L-ascorbic acid and 5.11 g of glucose were added to 50 ml of a mixed solvent of chloroform and dimethylformamide (2:1, v/v). While stirring the reaction mixture, 6.12 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide was gradually added to the mixture over the period of 30 minute. 500 mg of N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred at room temperature overnight. The reaction mixture was distilled under reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 5.95 g of L-2-glucosyl-ascorbic acid as a solid (yield: 62%).

3.0 g of L-2-glucosyl-ascorbic acid and 2.01 g of α-lipoic acid were added to 100 ml of a mixed solvent of chloroform and methylene chloride (2:1, v/v). While stirring the reaction mixture, 1.87 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide was gradually added to the reaction mixture over the period of 30 minutes. 500 mg of N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred at room temperature overnight. 150 ml of water was slowly added to the reaction mixture, which was then extracted with 300 ml of ethyl acetate. The obtained organic layer was washed three times with water, dried over sodium sulfate, and then concentrated under reduced pressure. 300 ml of n-hexane was added to the resulting residue, and the resultant was filtered to isolate crystal. The obtained crystal was dried to obtain 3.84 g of L-6-α-lipoyl-2-glucosyl-ascorbic acid (yield: 82%).

m.p.: 63-67 ℃

^{1}H NMR (400MHz, CDCl3), 9.72(1H, s), 5.01 (1H, d), 4.24-3.99(2H, d), 4.18-4.14(1H, q), 3.95-3.87(1H, m), 3.81-3.56(2H, d), 3.63-3.57(2H, m), 3.41-3.33(1H, m), 2.61-2.51(2H, m), 2.54-2.50(1H, m), 2.26-2.24(2H, t), 1.98-1.73(2H, m), 1.68-1.29(6H, m)

Example 5: Preparation of L-6-α-lipoyl-3-polyethylene glycol-ascorbic acid

Step 1. Preparation of L-3-polyethylene glycol-ascorbic acid

5.0 g of polyethylene glycol bromide (PEG-Br) having a molecular weight of 1000 and 0.97 g of ascorbic acid were added to 30 ml of dimethylformamide. 0.98 g of potassium carbonate was added to the reaction mixture, which was then stirred at room temperature overnight. The reaction mixture was distilled under

reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 4.59 g of L-3-polyethylene glycol-ascorbic acid as a solid (yield: 78%).

Step 2. Preparation of L-6-α-lipoyl-3-polyethylene glycol-ascorbic acid

3.0 g of L-3-polyethylene glycol-ascorbic acid and 0.58 g of α-lipoic acid were added to 50 ml of a mixed solvent of chloroform and methylene chloride (2:1, v/v). While stirring the reaction mixture, 0.54 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide was gradually added to the reaction mixture over the period of 30 minutes. 300 mg of N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred at 50℃ overnight. The resultant was distilled under reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 2.24 g of L-6-α-lipoyl-3-polyethylene glycol-ascorbic acid as a solid (yield: 74%).

m.p.: 53-57 ℃

^{1}H NMR (400MHz, acetone-d_6), 4.96 (1H, d), 4.42-4.38(2H, q), 3.90 (1H, t), 4.13-3.54(polyethylene glycol, m)3.71-3.56(3H, m), 2.60-2.55(2H, t), 2.50-2.42(1H, m), 2.02-2.01(2H, m), 1.94-1.86(1H, m), 1.78-1.65(4H, m), 1.62-1.47(2H, m).

Example 6: Preparation of L-6-α-lipoyl-2-ethyl-ascorbic acid

7.68 g of L-2-ethyl-ascorbic acid (yield: 82 %) was prepared in the same manner as in Step 1 of Example 5, except that 5.00 g of bromo ethane was used

instead of polyethylene glycol bromide and the reaction was performed at about -10℃ instead of room temperature. Furthermore, 6.06 g of L-6-α-lipoyl-2-ethyl-ascorbic acid (yield: 63 %) was prepared in the same manner as in Step 2 of Example 5, except that 5.0 g of L-2-ethyl-ascorbic acid was used instead of L-3-polyethylene glycol-ascorbic acid.

^{1}H NMR (400MHz, acetone-d_6), 4.97 (1H, d), 4.43-4.39(2H, q), 3.92 (1H, t), 3.73-3.58(3H, m), 3.25-3.14(2H, m), 2.62-2.56(2H, t), 2.51-2.43(1H, m), 2.01-2.00(2H, m), 1.95-1.85(1H, m), 1.78-1.64(4H, m), 1.61-1.49(2H, m), 1.34-1.28(3H, t)

Example 7: Preparation of L-6-α-lipoyl-3-ethyl-ascorbic acid

8.15 g of L-3-ethyl-ascorbic acid (yield: 87 %) was prepared in the same manner as in Step 1 of Example 5, except that 5.00 g of bromo ethane was used instead of polyethylene glycol bromide. Furthermore, 6.63 g of L-6-α-lipoyl-3-ethyl-ascorbic acid (yield: 69 %) was prepared in the same manner as in Step 2 of Example 5, except that 5.0 g of L-3-ethyl-ascorbic acid was used instead of L-3-polyethylene glycol-ascorbic acid.

^{1}H NMR (400MHz, acetone-d_6), 4.96 (1H, d), 4.42-4.38(2H, q), 3.94 (1H, t), 3.75-3.59(3H, m), 3.24-3.12(2H, m), 2.62-2.57(2H, t), 2.53-2.46(1H, m), 2.04-2.01(2H, m), 1.96-1.85(1H, m), 1.77-1.63(4H, m), 1.63-1.51(2H, m), 1.35-1.29(3H, t)

Example 8: Preparation of L-6-palmitoyl-2-α-lipoyl-ascorbic acid

5.0 g of α-lipoic acid and 3.18 g of triethylamine were dissolved in 80 ml of methylene chloride. The reaction mixture was cooled to about -15℃ and then

3.16 g of ethyl chloroformate was gradually added thereto. The reaction mixture was stirred for 1 hour while the temperature was maintained and then further stirred at room temperature for 1 hour. The reaction mixture was cooled again to about -15℃. A solution of 12.05 g of L-6-palmitoyl-ascorbic acid and 3.18 g of triethylamine in 100 ml of methylene chloride was rapidly added to the reaction mixture, which was then stirred for 2 hours while gradually increasing the temperature to room temperature. The resultant was concentrated under reduced pressure. 100 ml of a mixed solvent of n-hexane and methylene chloride (2:1, v/v) was added to the obtained obtained oily residue. The reaction mixture was cooled to -5℃ and then filtered. The obtained crystal was dried to obtain 10.37 g of L-6-palmitoyl-2-α-lipoyl-ascorbic acid (yield: 71%).

m.p.: 129-132℃

^{1}H NMR (400MHz, $CDCl_3$), 4.89 (1H, s), 4.42-4.38(1H, q), 4.36-4.22 (2H, m), 3.62-3.55(1H, m), 3.23-3.10(2H, m), 2.65-2.61(2H, t), 2.52-2.44(1H, m), 2.39-2.35(2H, t), 1.97-1.89(1H, m), 1.79-1.43(8H, m), 1.35-1.04(24H, m), 0.90-0.88(3H, t)

Example 9: Preparation of L-2-α-lipoyl-3-polyethylene glycol-ascorbic acid

3.0 g of L-3-polyethylene glycol-ascorbic acid prepared according to Step 1 of Example 5 and 0.58 g of α-lipoic acid were added to 50 ml of a mixed solvent of chloroform and methylene chloride (2:1, v/v). While stirring the reaction mixture, 0.54 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide was gradually added to the reaction mixture over the period of 30 minutes. 300 mg of

N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred at room temperature (about 25℃) overnight. The resultant was distilled under reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 3.84 g of L-6-α-lipoyl-3-polyethylene glycol-ascorbic acid as a solid (yield: 76%).

m.p.: 55-59℃

^{1}H NMR (400MHz, acetone-d_6), 4.97 (1H, d), 4.41-4.37(2H, q), 3.89 (1H, t), 4.11-3.53(polyethylene, m)3.76-3.57(3H, m), 2.61-2.54(2H, t), 2.49-2.39(1H, m), 2.04-2.00(2H, m), 1.93-1.85(1H, m), 1.77-1.68(4H, m), 1.59-1.45(2H, m).

Example 10: Preparation of L-2-α-lipoyl-3-ethyl-ascorbic acid

Step 1. Preparation of L-3-polyethylene glycol-ascorbic acid

5.0 g of bromo ethane and 0.97 g of ascorbic acid were added to 30 ml of dimethylformamide. 0.98 g of potassium carbonate was added to the reaction mixture, which was then stirred at room temperature overnight. The resultant was distilled under reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 4.06 g of L-3-ethyl-ascorbic acid (yield: 69%).

Step 2. Preparation of L-2-α-lipoyl-3-ethyl-ascorbic acid

3.0 g of L-3-ethyl-ascorbic acid and 0.58 g of α-lipoic acid were added to 50 ml of a mixed solvent of chloroform and methylene chloride (2:1, v/v). While stirring the reaction mixture, 0.54 g of 3-dimethyl-aminopropyl-N-ethyl carbodiimide

was gradually added to the reaction mixture over the period of 30 minutes. 300 mg of N,N'-dimethylaminopyridine was added to the reaction mixture, which was then stirred at room temperature (about 25℃) overnight. The resultant was distilled under reduced pressure, and 100 ml of ethyl acetate was added to the resulting residue. The resultant was washed three times with 1 N hydrochloric acid and water. The resultant was distilled under reduced pressure to remove the solvent and dried in vacuo to obtain 8.84 g of L-2-α-lipoyl-3-ethyl-ascorbic acid as a solid (yield: 92%).

^{1}H NMR (400MHz, acetone-d_6), 4.96 (1H, d), 4.42-4.38(2H, q), 3.90 (1H, t), 3.71-3.56(3H, m), 3.21-3.06(2H, m), 2.60-2.55(2H, t), 2.50-2.42(1H, m), 2.02-2.01(2H, m), 1.94-1.86(1H, m), 1.78-1.65(4H, m), 1.62-1.47(2H, m), 1.36-1.30(3H, t)

Comparative Example 1: Preparation of L-6-α-lipoyl-ascorbic acid

L-6-α-lipoyl-ascorbic acid was prepared according to a method disclosed in Journal of the American Chemical Society, 54, pp 308, 1977. That is, 1.76 g of ascorbic acid and 2.47 g of α-lipoic acid were added to 10 ml of anhydrous hydrogen sulfate. The reaction mixture was stirred for 30 hours, and then 250 ml of water was added thereto. The resultant was extracted by adding 300 ml of ethyl acetate thereto. The obtained organic layer was washed three times with water, dried over sodium sulfate. The resultant was concentrated under reduced pressure. 300 ml of hexane was added to the resulting residue, and the resultant was filtered. The obtained crystal was dried to obtain 2.5 g of L-6-α-lipoyl-ascorbic acid (yield: 68%).

m.p.: 45-47℃

^{1}H NMR (400MHz, CDCL3), Chemical shift; 4.9 (1H, d), 4.44 (1H, m), 4.32 (2H, dd), 2.52(1H, m), 2.54 (2H, t), 1.85 (2H, m), 1.29-2.25 (6H, m)

Comparative Example 2: Preparation of L-2-α-lipoyl-ascorbic acid

18.8 g of L-5,6-O-isopropylidin-ascorbic acid prepared in Preparation Example 1 and 20 g of α-lipoic acid were added to 200 ml of pyridine. While stirring the reaction mixture, a solution of 24 g of dicyclohexyl carbodiimide in 50 ml of dichloromethane was gradually added to the reaction mixture, which was then stirred at room temperature overnight. The resultant was distilled under reduced pressure, and then extracted by adding 200 ml of ethyl acetate thereto. The obtained organic layer was washed three times with a saturated aqueous solution of sodium carbonate. The resultant was concentrated under reduced pressure, and 300 ml of a mixed solvent of ether and hexane (1:1, v/v) was added thereto. The resultant was cooled to -10℃ and then filtered. The filtrate was dried to obtain 32 g of L-5,6-O-isopropylidin-2-α-lipoyl-ascorbic acid (yield: 92%).

3 g of L-5,6-O-isopropylidin-2-α-lipoyl-ascorbic acid obtained in the above was added to 20 ml of a mixed solvent of dichloromethane and methanol (1:1, v/v). While stirring the reaction mixture, 300 mg of p-toluenesulfonic acid was added to the reaction mixture, which was then stirred at 40℃ for 12 hours. The resultant was concentrated under reduced pressure and then extracted by adding 100 ml of ethyl acetate thereto. The obtained organic layer was washed three times with brine and dried under reduced pressure to obtain 2 g of L-2-α-lipoyl-ascorbic acid (yield: 74%).

^{1}H NMR (400MHz, CDCL3), Chemical shift; 5.1 (1H, d), 4.43 (1H, m), 4.28 (2H, dd), 2.49(1H, m), 2.53 (2H, t), 1.81 (2H, m), 1.31-2.22 (6H, m)

Experimental Example: Chemical stability test and sensory test

3.0 g of each of ascorbic acid derivatives prepared according to Examples 1 to 10 and Comparative Examples 1 and 2 was completely dissolved in 100 ml of a mixed solvent of distilled water and acetone (1:1 v/v) to prepare a clear solution. The solution was stirred at 40℃ for 30 minutes to evaporate acetone to prepare a micelle solution. 10 ml of each of the micelle solutions was respectively stored at 45℃ for one week, two weeks, three weeks, and four weeks to measure the amount of the remaining antioxidant and to perform sensory tests.

In order to identify stability of the ascorbic acid derivatives, the amount of ascorbic acid in each of the micelle solutions was measured three times using high performance liquid chromatography to calculate the mean values. Conditions for the high performance liquid chromatography are as follows: column - ACE 5-C18 (4.6*150mm, 5 ㎛), mobile phase - a mixture of acetonitrile and 0.1% phosphoric acid solution (80:20), wavelength of detector - UV 224 nm, flow rate - 1 ml/min, and amount of injection - 2 ㎕.

Sensory tests were performed as follows: 10 healthy women in late twenties estimated odor intensity of samples to calculate the mean values of average odor intensity. The odor intensity is established as in the following Table 1.

Table 1

Odor Intensity	Description
0	No odor
1	Detectable odor

2	Normal odor
3	Strong odor
4	Very strong odor
5	Unendurable odor

The results of stability test (measurement of the remaining antioxidant amount) and sensory test are shown in Tables 2 and 3.

Table 2

Derivatives (Example)	Period (week)	Amount of antioxidant (%)			Sensory Test
		Theoretical amount (%)	Measured amount (%)	Remaining ratio (Measured amount / Theoretical amount) (%)	
Example 1	0	6	6.0	100	0
	1	6	5.9	98.3	0
	2	6	5.8	96.7	0
	3	6	5.6	93.3	0.5
	4	6	5.6	93.3	0.5
Example 2	0	6	6.0	100	0
	1	6	6.0	100	0
	2	6	5.8	96.7	0
	3	6	5.7	95.0	0.2
	4	6	5.6	93.3	0.3
Example 3	0	6	6.0	100	0
	1	6	5.8	96.7	0
	2	6	5.8	96.7	0
	3	6	5.7	95.0	0.1
	4	6	5.7	95.0	0.3
Comparative Example 1	0	6	6.0	100	0
	1	6	5.7	95.0	0.3
	2	6	5.2	86.7	1.4
	3	6	4.3	71.7	2.2
	4	6	3.2	53.3	2.8
Comparative	0	6	6.0	100	0

Example 2	1	6	5.6	93.3	0.6
	2	6	4.1	68.3	2.1
	3	6	3.6	60.0	2.5
	4	6	2.3	38.3	2.7

Table 3

Derivatives (Example)	Period (week)	Amount of antioxidant (%)			Sensory Test
		Theoretical amount (%)	Measured amount (%)	Remaining ratio (Measured amount / Theoretical amount) (%)	
Example 4	0	5	5.00	100	0
	1	5	4.89	97.8	0.2
	2	5	4.76	95.2	0.4
	3	5	4.71	94.2	0.5
	4	5	4.69	93.8	0.8
Example 5	0	5	5.00	100	0
	1	5	4.91	98.2	0.1
	2	5	4.87	97.4	0.2
	3	5	4.78	95.6	0.2
	4	5	4.72	94.4	0.7
Example 6	0	5	5.00	100	0
	1	5	4.94	98.8	0.2
	2	5	4.87	97.4	0.2
	3	5	4.76	95.2	0.6
	4	5	4.71	94.2	0.6
Example 7	0	5	5.00	100	0
	1	5	4.92	98.4	0.1
	2	5	4.78	95.6	0.4
	3	5	4.73	94.6	0.4
	4	5	4.68	93.6	0.9
Example 8	0	5	5.00	100	0
	1	5	4.94	98.8	0.1

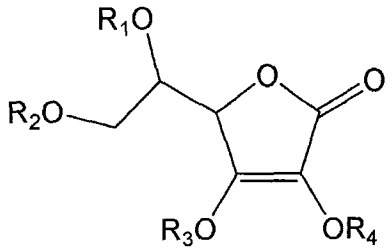
	2	5	4.89	97.8	0.4
	3	5	4.76	95.2	0.6
	4	5	4.70	94.0	0.7
Example 9	0	5	5.00	100	0
	1	5	4.83	96.6	0.4
	2	5	4.77	95.4	0.6
	3	5	4.71	94.2	0.6
	4	5	4.64	92.8	0.7
Example 10	0	5	5.00	100	0
	1	5	4.92	98.4	0.2
	2	5	4.88	97.6	0.5
	3	5	4.79	95.8	0.6
	4	5	4.72	94.4	0.8

Referring to Tables 2 and 3, when ascorbic acid and α-lipoic acid having discoloration and odor problems are made into the derivatives according to the present invention, the derivatives show at least 90% of remaining amount in an aqueous medium, thereby increasing stability thereof; and significantly reduce unpleasant odor problems.

[CLAIMS]

1. An ascorbic acid derivative represented by the following Formula 1:

Formula 1

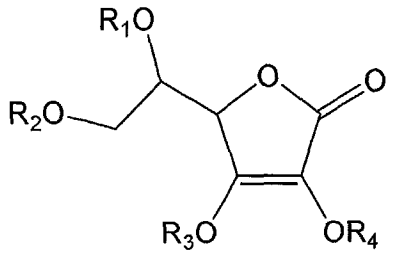


wherein one of the substituents R_1 to R_4 is an α-lipoyl group; one or two of the remaining substituents are, each independently, an α-lipoyl group, a C_1-C_4 alkyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a C_8-C_{18} acyl group; and the remaining substituents are hydrogen atoms.

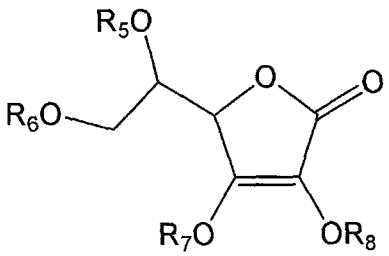
2. The ascorbic acid derivative of claim 1, which is selected from the group consisting of L-5,6-di-α-lipoyl-ascorbic acid; L-2,3-di-α-lipoyl-ascorbic acid; L-2,6-di-α-lipoyl ascorbic acid; L-6-α-lipoyl-2-glucosyl-ascorbic acid; L-6-α-lipoyl-3-polyethylene glycol-ascorbic acid; L-6-α-lipoyl-2-ethyl-ascorbic acid; L-6-α-lipoyl-3-ethyl-ascorbic acid; L-6-palmitoyl-2-α-lipoyl-ascorbic acid; L-2-α-lipoyl-3-polyethylene glycol-ascorbic acid; and L-2-α-lipoyl-3-ethyl-ascorbic acid.

3. A process for preparing an ascorbic acid derivative of Formula 1, the method comprising (a) reacting a compound of Formula 2 with a compound of Formula 3 and (b) deprotecting the product obtained in Step (a):

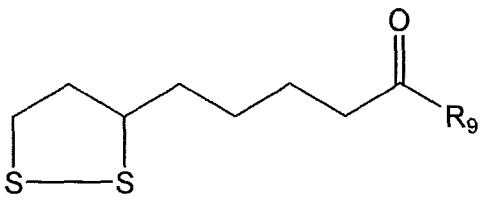
Formula 1



Formula 2



Formula 3



wherein R_1, R_2, R_3, and R_4 are the same as defined in Claim 1;

two or three of the substituents R_5 to R_8 are hydrogen atoms, and the remaining substituents are hydroxy protecting groups; and

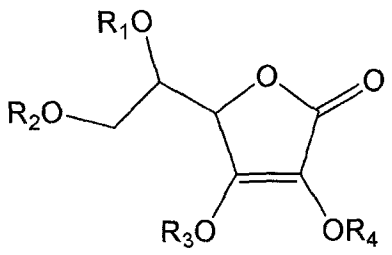
R_9 is a hydroxy group, a carbodiimidyl group, a halogen atom, a C_1-C_4 alkoxy group, a hydroxysuccinimidyl group, an ethylcarbonyloxy group, an ethoxycarbonyloxy group, or an imidazolyl group.

4. The process of claim 3, wherein both R_5 and R_6 are hydrogen atoms and both R_7 and R_8 are hydroxy protecting groups; both R_7 and R_8 are hydrogen atoms and both R_5 and R_6 are hydroxy protecting groups; or both R_5 and R_8 are hydrogen atoms and both R_6 and R_7 are hydroxy protecting groups.

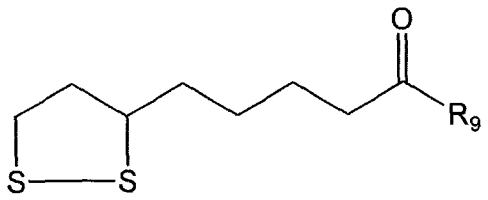
5. The process of claim 3 or 4, wherein the hydroxy protecting group is selected from the group consisting of a benzyl group, an isopropylidenyl group, a benzoyl group, a benzyloxycarbonyl group, an acetyl group, and a silyl group.

6. A process for preparing an ascorbic acid derivative of Formula 1, the method comprising reacting a compound of Formula 4 with a compound of Formula 3:

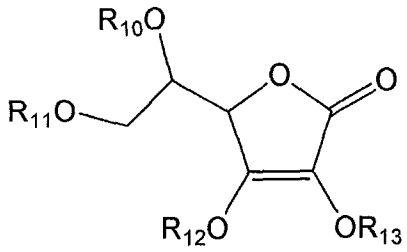
Formula 1



Formula 3



Formula 4



wherein R_1, R_2, R_3, and R_4 are the same as defined in Claim 1;

R_9 is a hydroxy group, a carbodiimidyl group, a halogen atom, a C_1-C_4 alkoxy group, a hydroxysuccinimidyl group, an ethylcarbonyloxy group, an ethoxycarbonyloxy group, or an imidazolyl group; and

one or two of the substituents R_{10} to R_{13} are, each independently, an α-lipoyl group, a C_1-C_4 alkyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a glucosyl group, or a C_8-C_{18} acyl group, and the remaining substituents are hydrogen atoms.

7. The process of claim 6, wherein R_{11} is an α-lipoyl group; and R_{10}, R_{12}, and R_{13} are hydrogen atoms.

8. The process of claim 6, wherein one of the substituents R_{10} to R_{13} is an ethyl group, CH_3CH_2O-$(CH_2CH_2O)_m$-CH_2CH_2- (wherein m is an integer of 7 to 45), a

glucosyl group, or a palmitoyl group; and the remaining substituents are hydrogen atoms.

9. The process of any one of claims 6 to 8, wherein the reacting a compound of Formula 3 with a compound of Formula 4 is performed in the presence of one or more coupling agent selected from the group consisting of 3-dimethyl-aminopropyl-N-ethyl carbodiimide, dicyclohexyl carbodiimide, diisopropyl carbodiimide, and ethoxy carbonyl chloride.

10. The process of any one of claims 6 to 8, wherein the reacting a compound of Formula 3 with a compound of Formula 4 is performed in the presence of one or more base selected from the group consisting of dimethylaminopyridine, imidazole, pyridine, diisopropylethylamine, and triethylamine.