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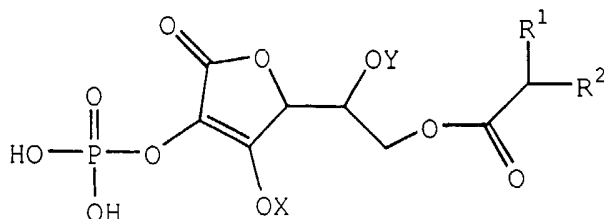
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(54) Title: STABILIZED ASCORBIC ACID DERIVATIVES



(1)

(57) Abstract: An ascorbic acid derivative, which is a compound represented by the following general formula (1) or a salt thereof: [Chemical Formula 11] (1)(wherein X and Y each represents H or a protective group for OH, R₁ and R₂ each represents an alkyl group having from 1 to 19 carbon atoms, which may be linear or branched, and the total number of carbon atoms in R₁ and R₂ is an integer of 5 to 22).



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DESCRIPTION

STABILIZED ASCORBIC ACID DERIVATIVES

5 This Application claims the priority of an application based on U.S. Provisional Application Serial No. 60/373609 (filed on April 19, 2002).

Technical Field

10 The present invention relates to a novel ascorbic acid derivative. More specifically, the present invention relates to an ascorbic acid derivative which is a stable compound, and a process for producing the same. The present invention also relates to various forms or
15 embodiments containing such an ascorbic acid derivative, such as vitamin C preparations or agents, collagen production accelerators, whitening agents, skin agent for external use or application, medical or pharmaceutical preparations, agricultural chemical preparations, animal
20 or veterinary drug preparations, food additives and additives for animal feeding stuff, each containing an ascorbic acid derivative).

Background Art

25 Ascorbic acid has activities such as inhibition of lipid peroxide production, acceleration of collagen production, retardation of melanin formation and enhancement of immune functions or performances. For these purposes, ascorbic acid has heretofore been used in
30 the fields of medical or pharmaceutical preparations, agricultural chemical preparations, animal or veterinary drug preparations, foods, animal feeding stuff, cosmetic preparations, etc. However, ascorbic acid has poor stability with the elapse of time and poor lipid
35 solubility. Accordingly, the amount of ascorbic acid which has permeated through the cell membrane and has cumulated in cells is rather limited, and the

physiological actions of vitamin C cannot necessarily be achieved to a satisfactory extent, if the ascorbic acid per se is used. In order to improve the stability of ascorbic acid, various derivatives thereof have been proposed, such as one wherein the hydroxyl group present in the enediol portion at the 2-or 3-position, which is susceptible to oxidation, is converted into a phosphoric acid ester as described in, e.g., JP-B (examined Japanese patent publication) 52-1819 (Patent Document 1), and JP-A (unexamined published Japanese patent application) 02-279690 (Patent Document 2), or one wherein the acylation thereof is effected with a fatty acid so as to improve the lipid solubility, as described in, e.g., JP-A-59-170085 (Patent Document 3). However, there are very few derivatives which have been improved both in stability and in lipid solubility.

As for the ascorbic acid which has been improved both in stability and in lipid solubility, JP-A-61-152613 (Patent Document 4) describes a cosmetic composition containing a 6-O-higher-acyl ascorbic acid-2-phosphoric acid ester salt. However, in this patent publication, a process for producing a sulfuric acid ester (but not a phosphoric acid ester) thereof is described, a process for producing a phosphoric acid ester thereof is not described, and the ascorbic acid derivative, the provision of which is described in this publication, is not identified. From these points, it is difficult to recognize that the 6-O-higher-acyl ascorbic acid-2-phosphoric acid ester is disclosed in this publication so as enable the practice thereof.

JP-A-10-298174 (Patent Document 5) describes a process for producing 6-O-higher-acyl ascorbic acid-2-phosphoric acid ester and results of the structure determination of the substance. It is stated that the 6-O-higher-acyl ascorbic acid-2-phosphoric acid ester produced by this process is improved both in stability and in lipid solubility, and the uptake thereof into

cells is facilitated. However, among these substances, ascorbic acid-2-phosphoric acid ester-6-palmitic acid ester sodium salt and an aqueous solution thereof are not yet satisfactory in view of the stability thereof.

- 5 Patent Document 1: JP-B-52-1819
 Patent Document 2: JP-A-02-279690
 Patent Document 3: JP-A-59-170085
 Patent Document 4: JP-A-61-152613
 Patent Document 5: JP-A-10-298174

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Disclosure of Invention

An object of the present invention is to provide an ascorbic acid derivative which has solved the above-mentioned problems encountered in the prior art, and a process for producing such an ascorbic acid derivative.

15 Another object of the present invention is to provide a 6-O-higher-acyl ascorbic acid-2-phosphoric acid ester and/or a salt thereof which have been improved in stability and have a novel structure, a process for producing the same, and a preparataion (such as cosmetic material) using the 6-O-higher-acyl ascorbic acid-2-phosphoric acid ester and/or a salt thereof.

25 As a result of earnest study, the present inventors have found that newly synthesized 6-O-higher-acyl ascorbic acid-2-phosphoric acid esters and/or salts thereof wherein the acyl group (fatty acid residue) at the 6-position thereof is branched at the α -position have greatly improved in the stability thereof, as compared with conventional 6-O-higher-acyl ascorbic acid-2-phosphoric acid esters having a linear fatty acid residue and/or salts thereof. The present invention has been accomplished based on this discovery.

30 The ascorbic acid derivative according to the present invention represented by the general general formula (1) is characterized in that the higher fatty acid ester at the 6-position is a fatty acid ester

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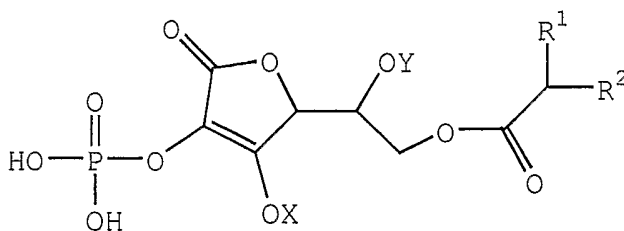
branched at the α -carbon.

According to the present inventors' experiments, it has been found that the ester bond of the conventional 6-O-higher linear fatty acid esters is decomposed or cloven during the storage thereof so as to cause a reduction in the ratio of the ascorbic acid-2-phosphoric acid ester remaining after the storage. On the contrary, the ascorbic acid-2-phosphoric acid-6-fatty acid ester according to the present invention has an improved stability. According to the present inventors' investigation and knowledge, it is presumed that the fatty acid ester (such as ascorbic acid-2-phosphoric acid-6-fatty acid ester which has been synthesized from a fatty acid branched at the α carbon, as a starting material has a reinforced or strengthened ester bond.

More specifically, the present invention relates to the following matters.

[1] An ascorbic acid derivative, which is a compound represented by the following general formula (1) or a salt thereof:

[Chemical Formula 1]



(1)

(wherein X and Y each represents H or a protective group for OH, R^1 and R^2 each represents an alkyl group having from 1 to 19 carbon atoms, which may be linear or branched, and the total number of carbon atoms in R^1 and R^2 is an integer of 5 to 22).

[2] The ascorbic acid derivative according to [1], which is a salt with one or more metal selected from the group consisting of alkali metal, alkaline earth metal,

aluminum, iron, zinc and bismuth.

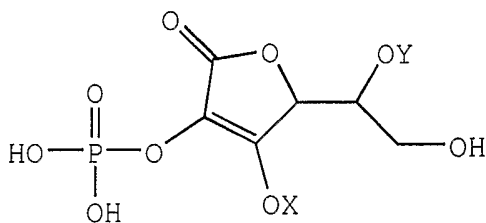
[3] The ascorbic acid derivative according to [1], which is a salt with ammonia, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine or 2-amino-1-methylpropanol.

[4] The ascorbic acid derivative according to any one of [1] to [3], wherein the total number of carbon atoms in R^1 and R^2 of the general formula (1) is an integer of 8 to 18.

[5] The ascorbic acid derivative according to [4], wherein R^1 and R^2 of the general formula (1) are a linear alkyl group, and the total number of carbon atoms in the linear alkyl groups of R^1 and R^2 is 14 or 16.

[6] The ascorbic acid derivative according to [5], wherein in the general formula (1), R^1 is $n\text{-C}_9\text{H}_{19}$, and R^2 is $n\text{-C}_7\text{H}_{15}$; or R^1 is $n\text{-C}_8\text{H}_{17}$, and R^2 is $n\text{-C}_6\text{H}_{13}$.

[7] A process for producing an ascorbic acid derivative according to any one of [1] to [6], comprising a step of reacting a compound represented by the following general formula (2) and/or a salt thereof:
[Chemical Formula 2]



(2)

(wherein X and Y each represents H or a protective group for OH), with at least one selected from fatty acid, fatty acid salt, fatty acid ester, fatty acid halide, and/or fatty acid anhydride.

[8] The process for producing an ascorbic acid derivative according to [7], wherein the reaction is performed in the presence of a condensing agent and/or dehydrating agent.

[9] The process for producing an ascorbic acid

derivative according to [8], wherein the dehydrating agent is sulfuric acid.

[10] The process for producing an ascorbic acid derivative according to any one of [7] to [9], wherein
5 the reaction is conducted in a solvent selected from the group consisting of: water, acetone, dioxane, toluene, ethylbenzene, methyl-tert-butyl ether, and sulfuric acid.

[11] A vitamin C preparation comprising the ascorbic acid derivative according to any one of [1] to
10 [6] as an effective ingredient.

[12] A collagen production accelerator comprising the ascorbic acid derivative according to any one of [1] to [6] as an effective ingredient.

[13] A whitening preparation comprising the ascorbic acid derivative according to any one of [1] to
15 [6] as an effective ingredient.

[14] A skin preparation for external use, comprising the ascorbic acid derivative according to any one of [1] to [6] as an effective ingredient.

[15] The skin preparation for external use according to [14], which contains an ascorbic acid-2-phosphoric acid ester and/or a salt thereof.

[16] The skin preparation for external use according to [14], which contains sodium salt, potassium salt, magnesium salt or zinc salt of the ascorbic acid-2-phosphoric acid ester.

[17] A cosmetic material comprising the skin preparation for external use according to any one of [14] to [16].

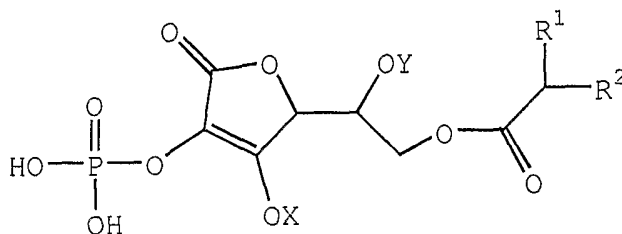
[18] A composition comprising the ascorbic acid derivative according to any one of [1] to [6], in the form of a medical or pharmaceutical preparation, an agrochemical preparation or an animal drug preparation.

[19] A composition comprising the ascorbic acid derivative according to any one of [1] to [6], in the
35 form of a food or feed additive.

Best Mode for Carrying Out the Invention

Hereinbelow, the present invention will be described in detail with reference to the accompanying drawings as desired. In the following description, "%" and "part(s)"
 5 representing a quantitative proportion or ratio are those based on mass, unless otherwise noted specifically.
 (Ascorbic acid derivative)

The ascorbic acid derivative according to the present invention is a compound represented by the
 10 following general formula (1) and/or a salt thereof:
 [Chemical Formula 3]



(1)

15 (wherein X and Y each represents H or a protective group for OH, R¹ and R² each represents an alkyl group having from 1 to 19 carbon atoms, which may be linear or branched, and the total number of carbon atoms in R¹ and R² is an integer of 5 to 22).

20 In the present invention, unless otherwise noted specifically, the ascorbic acid or ascorbic acid derivative may preferably be an L-form.

The ascorbic acid derivative according to the present invention is less liable to be oxidized and has
 25 an excellent stability, because the 2-position of the ascorbic acid is esterified into a phosphoric acid ester.

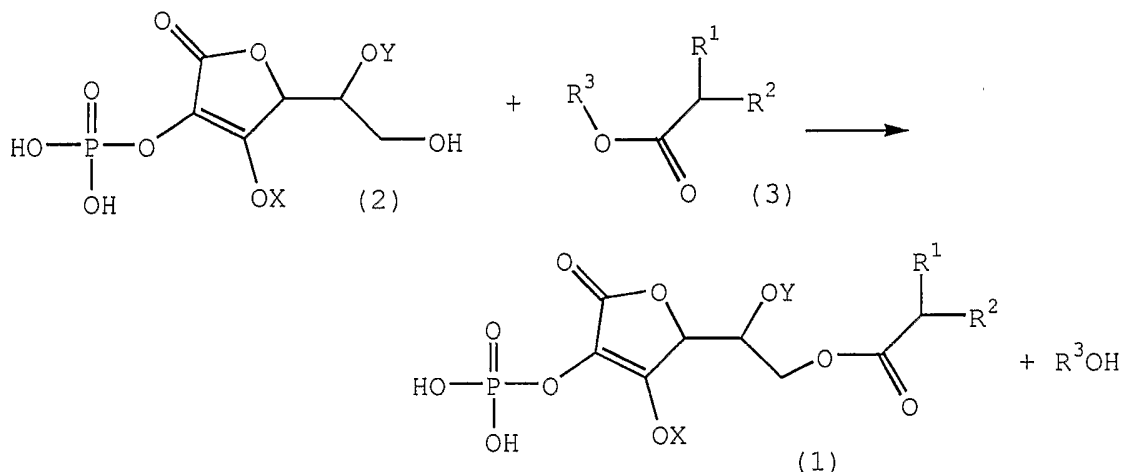
Further, in the ascorbic acid derivative according to the present invention, the 6-position thereof is esterified into a higher fatty acid ester, and therefore,
 30 this compound can have an appropriate lipid solubility, and has a characteristic such that the uptake thereof into cells is facilitated. In addition, the phosphoric acid group at the 2-position in this compound is readily

hydrolyzed by phosphatase in a living body and the higher fatty acid ester at the 6-position is an ester with a primary alcohol (6-position) which is susceptible to the action of lipase or esterase, this compound may easily be converted into ascorbic acid in a living body.

(Production process-1 for ascorbic acid derivative)

The compound represented by the general formula (1) and/or a salt according to the present invention can be produced, for example, according to the following reaction formula:

[Chemical Formula 4]



(wherein X and Y each represents H or a protective group for OH, R¹ and R² each represents an alkyl group having from 1 to 19 carbon atoms, the total number of carbon atoms in R¹ and R² is from 5 to 22, and R³ represents a hydrogen atom, a cation or an alkyl group having from 1 to 5 carbon atoms).

More specifically, a compound represented by the formula (2) and/or a salt thereof is reacted with at least one of a fatty acid branched at the α carbon represented by the formula (3), and an ester and a salt thereof, to produce an ascorbic acid-2-phosphoric acid-6-fatty acid ester (1) and/or a salt thereof.

(Dehydrating or condensing agent)

The above-described reaction may preferably be

performed in the presence of a dehydrating or condensing agent.

The dehydrating or condensing agent to be used in such a case is not particularly limited. Preferred
5 examples of the condensing agent may include: N,N'-dicyclohexyl carbodiimide, N,N'-diisopropyl carbodiimide, N-ethyl-N'-3-dimethylaminopropyl carbodiimide, benzotriazole-1-yl-tris(dimethylamino)phosphonium
hexafluorophosphide salt, diphenylphosphoryl azide for
10 optimum as condensing agent. Among these, it is preferred to use N,N'-diisopropylcarbodiimide. Preferred examples of the dehydrating agent may include: phosphorus pentoxide, solid phosphoric acid, a titanium oxide, an alumina and a sulfuric acid. Among these, it is
15 preferred that sulfuric acid (preferably, concentrated sulfuric acid of 95 mass % or more) is used, and the concentrated sulfuric acid, an ascorbic acid-2-phosphoric acid ester salt and a fatty acid or an ester or salt thereof are mixed and reacted.

20 In the fatty acid ester of the formula (3), R³ represents an alkyl ester having from 1 to 5 carbon atoms, and may preferably be a lower alkyl ester having from 1 to 3 carbon atoms, more preferably a methyl ester or an ethyl ester.

25 The reaction time and the reaction temperature may vary depending on whether the fatty acid is a free acid, an ester or a salt, or on the kind and amount of the condensing agent. However, the reaction time may generally be from 1 to 120 hours, preferably from 4 to 10
30 hours, and the reaction temperature may generally be from 5 to 70°C, preferably from 30 to 50°C.

The water content to be carried over from the starting materials or catalyst into the reaction solution may suitably be 10% or less, preferably 2% or less.
35 (Solvent)

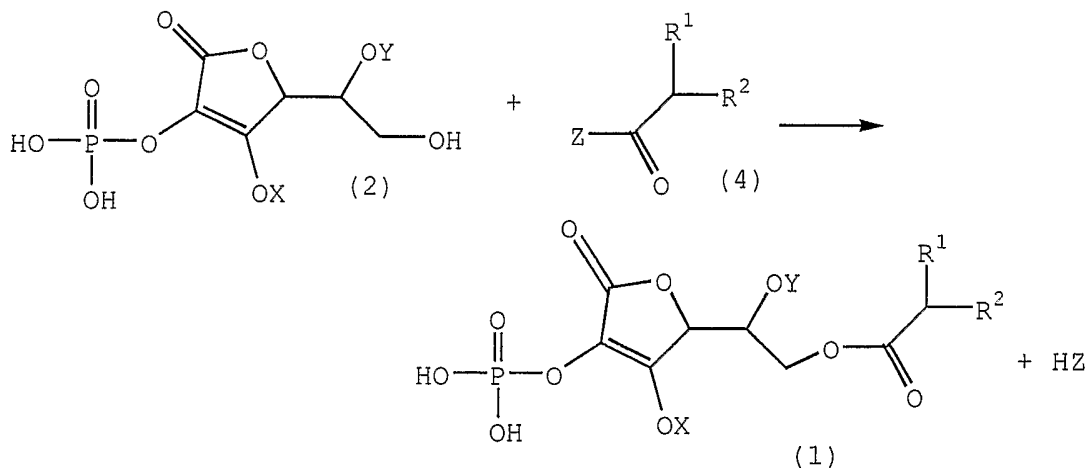
when a solvent is used in this reaction, sulfuric acid per se as a condensing agent can also be used as the

solvent. Alternatively, it is also possible to select the solvent from other solvents capable of dissolving the starting materials. Specific examples of such other solvents may include: water, acetone, dioxane, toluene, ethylbenzene and methyl-tert-butyl ether, etc.

(Production process-2 for ascorbic acid derivative)

The compound represented by the general formula (1) and/or a salt according to the present invention can also be produced, for example, according to the following reaction formula:

[Chemical Formula 5]



(wherein X and Y each represents H or a protective group for OH, R¹ and R² each represents an alkyl group having from 1 to 19 carbon atoms, the total number of carbon atoms in R¹ and R² is from 5 to 22, and Z represents a halide).

More specifically, an ascorbic acid-2-phosphoric acid represented by the general formula (2) and/or a salt thereof is reacted with a fatty acid halide branched at the α carbon represented by the general formula (4) to produce an ascorbic acid-2-phosphoric acid-6-fatty acid ester (1) and/or a salt thereof.

(Base)

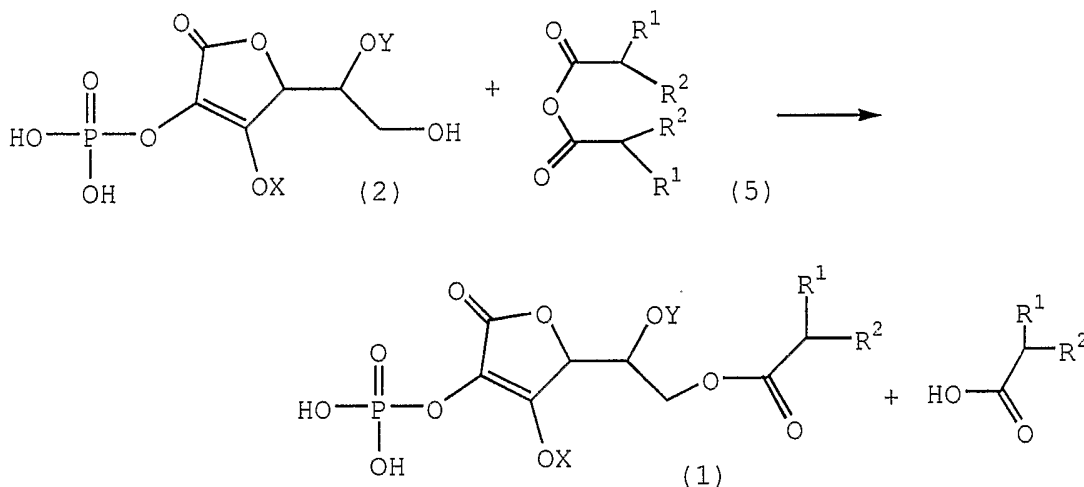
The above-described reaction may preferably be performed in the presence of a base. The base is not particularly limited, as long as it is a base which is

usually usable as a dehydrohalogenating agent in the reaction of an alcohol with an acid halide. Preferred examples thereof may include tertiary amines such as pyridine and triethylamine.

5 (Production process-3 for ascorbic acid derivative)

The compound represented by the general formula (1) and/or a salt thereof can also be produced, for example, according to the following reaction formula:

[Chemical Formula 6]



10

(wherein X and Y each represents H or a protective group for OH, R¹ and R² each represents an alkyl group having from 1 to 19 carbon atoms, and the total number of carbon atoms in R¹ and R² is from 5 to 22).

15

More specifically, a fatty acid anhydride branched at the α carbon represented by the formula (5) is reacted with an ascorbic acid-2-phosphoric acid represented by the general formula (2) and/or a salt thereof, to produce an ascorbic acid-2-phosphoric acid-6-fatty acid ester represented by the formula (1) and/or a salt thereof.

20

(Mole ratio)

In the production process according to the present invention, the starting materials may be used in equimolar amounts in any of the above-mentioned reactions. However, it is possible to use either one of

25

the starting materials may be present in slight excess (e.g., either one of the starting materials may be present in about 1.0-3.0, more preferably about 1.0 - 1.5 in terms of the mole ratio therebetween), as long as
5 substantially no problem arises during the purification or isolation to be effected after the predetermined reaction.

(Purification and/or isolation)

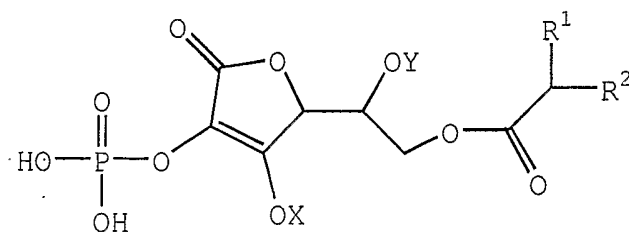
The purification or isolation method is not
10 particularly limited. More specifically, the purification or isolation may be performed by using a general method such as solvent extraction, washing, salting out or column chromatography. For example, the reaction product may be isolated or purified by ether
15 extraction or washing with non-polar solvent such as hexane. If desired, the thus obtained product may further be purified by reverse phase chromatography or the like.

Both of the group represented by X and Y at the 3-
20 and 5-positions of the ascorbic acid of the formula (2) may preferably be H. However, in any of the above-mentioned reactions, these groups may be substituted by a protective group which is not substantially affected by the reaction.

25 <Specific examples of non-susceptible protective group>
acyl group, alkanesulphonyl group, benzenesulphonyl group which may be substituted, dialkyl carbamoyl group, benzyl group, alkyl group, silyl group
(Salt of ascorbic acid derivative)

30 The salt of the compound represented by the following general formula (1) may be obtained in the following manner:

[Chemical Formula 7]



(1)

(wherein X and Y each represents H or a protective group for OH, R¹ and R² each represents an alkyl group having
 5 from 1 to 19 carbon atoms, which may be linear or branched, and the total number of carbon atoms in R¹ and R² is an integer of 5 to 22)

Thus, the obtained ascorbic acid-2-phosphoric acid-6-higher fatty acid ester is, for example, neutralized
 10 with an appropriate base (for example, sodium hydroxide, potassium hydroxide, magnesium oxide, calcium hydroxide, ammonia, monoethanolamine, diethanolamine, triethanolamine or dicyclohexylamine) in a solvent capable of dissolving the ester, such as water or
 15 methanol, whereby a salt with the base can be obtained.

The kind of the salt of ascorbic acid derivative is not particularly limited, as long as the usage or application of the salt of ascorbic acid derivative is not substantially impaired. In view of easy
 20 availability, and compounding thereof into formulations, the salt may preferably be those containing alkali metals, alkaline earth metals, aluminum, iron, zinc and bismuth. Among these, preferred are alkali metals such as sodium and potassium, and alkaline earth metals such
 25 as calcium and magnesium. These may be used individually or in combination of two or more species thereof.

(Protection of hydroxyl group)

In the compound represented by the above general formula (1), the hydroxyl group at 3-or 5-position can also be protected by a conventionally known group which
 30 is readily converted into a hydroxyl group. The present invention may include compounds having such a protective group (for example, acyl group, alkanesulfonyl group, a

benzenesulfonyl group which may be substituted, or dialkylcarbamoyl group, benzyl group, alkyl group, silyl group, etc.). The protective group may be introduced into the predetermined compound, before or after the esterification reaction at the 6-position.

This reaction can be applied not only to the process for producing a 6-O-higher fatty acid ester of ascorbic acid-2-phosphoric acid according to the present invention, but also to the production of a conventionally known 6-O-lower fatty acid ester wherein R^1 and R^2 in the above general formula (1) each independently represents CH_3 or C_2H_5 .

(Preparation)

The ascorbic acid derivative according to the present invention exhibits a vitamin C activity which has remarkably been improved both in stability and in lipid solubility, as compared with those of conventionally known ascorbic acid derivatives. Accordingly, vitamin C can be supplied by the ascorbic acid derivative according to the present invention per se, or by a preparation (vitamin C preparation) containing the ascorbic acid derivative according to the present invention. The usage or application of the ascorbic acid derivative according to the present invention is not particularly limited. For example, vitamin C can be effectively supplied when the ascorbic acid derivative according to the present invention is blended in medical or pharmaceutical preparations, agricultural chemicals, foods, feeds or cosmetic preparations, etc.

(Higher fatty acid ester)

The ascorbic acid derivative according to the present invention may suitably be L-form in view of the vitamin C activity thereof. Further, the higher fatty acid ester at the 6-position is characterized in that it is a fatty acid ester branched at the α carbon. As described above, according to the present inventors' experiment, it has been found that the ester bond of

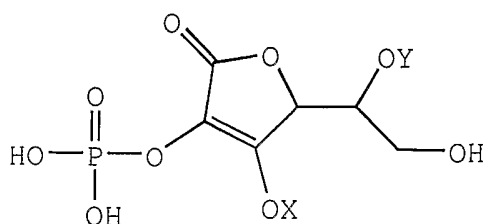
conventional 6-O-higher linear fatty acid esters are decomposed or cloven during the storage thereof to cause a reduction in the ratio of an ascorbic acid-2-phosphoric acid ester remaining after the storage. On the contrary, it is presumed that in the ascorbic acid derivative according to the present invention (e.g., an ascorbic acid-2-phosphoric acid-6-fatty acid ester which has been synthesized from a fatty acid branched at the α carbon), the ester bond is reinforced or strengthened, and therefore the ascorbic acid derivative according to the present invention shows an improved stability in a stability test.

In view of the lipid solubility, preferred examples of the 6-O-higher fatty acid ester may include 2-butylhexanoic acid ester, 2-hexyldecanoic acid ester and 2-heptylundecylic acid ester. (Collagen production accelerator, external skin agent, etc.)

The ascorbic acid derivative obtained by the production process according to the present invention has a collagen production accelerating effect and a whitening effect and therefore, it can also be used as a collagen production accelerator or a whitening agent. Further, the ascorbic acid derivative can be effectively used as a skin agent for external application, for example, by formulating it with another skin agent.

When the ascorbic acid derivative is used as a skin agent, the skin agent for external application according to the present invention may contain an ascorbic acid-2-phosphoric acid ester represented by the following general formula (2) and/or a salt thereof, in addition to the ascorbic acid derivative (represented by the general formula (1)) obtained by the production process according to the present invention:

[Chemical Formula 8]



(2)

(wherein X and Y each represents H or a protective group for OH). In an embodiment wherein the ascorbic acid-2-phosphoric acid ester represented by the following

5 general formula (2) and/or a salt thereof is contained, it also is possible to achieve an advantageous effect of providing an ascorbic acid source to both of epidermis (or cuticle) and dermis (or corium).

10 (Ascorbic acid-2-phosphoric acid ester)

Hereinbelow, the ascorbic acid-2-phosphoric acid ester and/or a salt thereof are described in more detail.

The ascorbic acid-2-phosphoric acid ester according to the present invention may be any one of D-form, L-form

15 and DL-form, but may preferably be L-form. The salt of the ascorbic acid-2-phosphoric acid ester may be, for example, a compound wherein a phosphoric acid ester is bonded to the 2-position of the ascorbic acid, and the phosphoric acid group of the phosphoric acid ester forms

20 a salt with a base.

Specific examples of the salt of ascorbic acid-2-phosphoric acid ester may include: alkali metal salt, alkaline earth metal salt, Zn salt, Al salt, Ti salt, etc. Among these, in an economical point of view,

25 preferred are Na salt, K salt, Mg salt and Zn salt, and more preferred are Na salt and Mg salt.

(Collagen production accelerating effect)

In the present invention, the collagen production accelerating effect means that when the hydroxyproline content, for example, in skin tissue is measured by an

30 amino acid analysis method and the thus obtained data is used as an index of collagen production accelerating effect, the hydroxyproline amount in the test area (or

segment) is at least 1.2 to 2 times that in the control area.

In the present invention, the collagen production accelerator, the whitening agent or the skin agent for external application can be used while the effect thereof per se is emphasized as a main effect. However, it is also possible to further add another ingredient thereto so as to modify or adjust the effect.

In the collagen production accelerator, whitening agent or skin agent for external application, the amount of the ascorbic acid derivative obtained by the production process according to the present invention which has been blended into these preparations may appropriately be selected in view of the degree of the desired effect or the relationship with other ingredients to be used in combination therewith. However, it may be, for example, from 0.01 to 30% by mass, preferably from 0.03 to 20% by mass, based on the entire amount of the preparation.

In order to make use of the collagen production accelerating effect and/or the whitening effect, another additive (e.g., known ingredient effective against aging of skin, known ingredient effective in accelerating the collagen production and suppressing wrinkle, known whitening agents, etc.) may be added.

It is possible to blend as such an additive, those such as tea extract, t-AMCHA, L-lysine, L-arginine, caffeine, tannin, verapamil, tranexamic acid, tranexamic acid derivative, hyaluronic acid, glycyrrhiza extract, glabridin, hydrothermal extracts of fruits such as quince, raspberry and avocado, white wine yeast extract, various Japanese and Chinese crude drugs or extracts thereof, aroma extract, tocopherol acetate, glycyrrhizic acid, glycyrrhizic acid derivatives, arbutin, koji (or malt), glucose, fructose, mannose, sucrose, trehalose, phytoglycogen, retinoic acid, retinol, retinol acetate and retinol palmitate.

A biologically active substance to be described later, which can be used as a whitening agent, may also be used in combination.

Also, various base ingredients can be added
5 according to the dosage form or shape of the skin agent for external application.

Such a base ingredient can be added according to various specific usage, applications or purposes. Specific examples of the base ingredient may include:
10 liquid oils and fats, solid oils and fats, waxes, ester oil, hydrocarbon oil, silicone resin, silicone, anionic surfactant, anion-type surfactant, cationic surfactant, amphoteric surfactant, nonionic surfactant, lower alcohol, sterols, water-soluble polymer, sequestering
15 agent (e.g., disodium edetate, trisodium edetate, sodium citrate, sodium polyphosphate, sodium metaphosphate, gluconic acid), neutralizer, pH adjusting agent, bactericide or anti-fungus agent, and perfume.

In a case where the ascorbic acid of the present
20 invention is applied to skin, another ingredient which is generally usable in skin preparations can be blended, as long as such addition does not substantially impair the effect of the present invention. Specific examples of the ingredient to be used may include: medicaments,
25 agents, drugs, medicines, mediums, pharmaceuticals, pharmaceutical preparations as described in Japanese Standards of Cosmetic Ingredients (JSCI), 2nd Edition, Annotation, compiled by Nippon Koteisho Kyokai, issued by Yakuji Nippo, Ltd. (1984), Specifications of Ingredient Other Than Those Listed in JSCI, supervised by
30 Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, issued by Yakuji Nippo, Ltd. (1993), Specifications of Ingredient Other Than Those Listed in JSCI, Supplement, supervised by
35 Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, issued by Yakuji Nippo, Ltd. (1993), The Comprehensive Licensing Standards of

Cosmetics by Category, supervised by Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, issued by Yakuji Nippo, Ltd. (1993), and Kesho-hin Genryo Jiten (Handbook of Cosmetic
5 Ingredients), Nikko Chemicals (1991), etc.

Specific examples of the materials or agents which can be added to the preparation according to the present invention will be enumerated below. These examples include, e.g., oil, higher alcohol, fatty acid,
10 ultraviolet absorber, powder, pigment, surfactant, polyhydric alcohol and sugar, polymer, biologically active ingredient, solvent, antioxidant, perfume and antiseptic. However, as a matter of course, those usable in the present invention are not limited to these
15 examples.

(1) Specific examples of oil

(Ester-type oil phase ingredient)

Triglyceryl 2-ethylhexanoate, cetyl 2-ethylhexanoate, isopropyl myristate, butyl myristate,
20 isopropyl palmitate, ethyl stearate, octyl palmitate, isocetyl isostearate, butyl stearate, butyl myristate, ethyl linoleate, isopropyl linoleate, ethyl oleate, isocetyl myristate, isostearyl myristate, isostearyl palmitate, octyldodecyl myristate, isocetyl isostearate,
25 diethyl sebacate, diisopropyl adipate, isoarachyl neopentanoate, caprylic-capric acid triglyceride, trimethylolpropane tri-2-ethylhexanoate, trimethylolpropane triisostearate, pentaerythritol tetra-2-ethylhexanoate, cetyl caprylate, decyl laurate, hexyl
30 laurate, decyl myristate, myristyl myristate, cetyl myristate, stearyl stearate, decyl oleate, cetyl ricinoleate, isostearyl laurate, isotridecyl myristate, isocetyl myristate, isostearyl myristate, isocetyl palmitate, isostearyl palmitate, octyl stearate, isocetyl
35 stearate, isodecyl oleate, octyldodecyl oleate, octyldodecyl linoleate, isopropyl isostearate, cetostearyl 2-ethylhexanoate, stearyl 2-ethylhexanoate,

hexyl isostearate, ethylene glycol dioctanoate, ethylene glycol dioleate, propylene glycol dicaprate, propylene glycol di(caprylate/caprinate), propylene glycol dicaprylate, neopentyl glycol dicaprate, neopentyl glycol dioctanoate, glyceryl tricaprylate, glyceryl triundecylate, glyceryl triisopalmitate, glyceryl triisostearate, octyldodecyl neopentanoate, isostearyl octanoate, octyl isononanoate, hexyldecyl neodecanoate, octyldodecyl neodecanoate, isocetyl isostearate, isostearyl isostearate, octyldecyl isostearate, polyglycerin oleate, polyglycerin isostearate, dipropyl carbonate, dialkyl carbonate (C12-18), triisocetyl citrate, triisoarachyl citrate, triisooctyl citrate, lauryl lactate, myristyl lactate, cetyl lactate, octyldecyl lactate, triethyl citrate, acetyltriethyl citrate, acetyltributyl citrate, trioctyl citrate, diisostearyl malate, 2-ethylhexyl hydroxystearate, 2-ethylhexyl succinate, diisobutyl adipate, diisopropyl sebacate, dioctyl sebacate, cholesteryl stearate, cholesteryl isostearate, cholesteryl hydroxystearate, cholesteryl oleate, dihydrocholesteryl oleate, phytosteryl isostearate, phytosteryl oleate, isocetyl 12-stearoylhydroxystearate, stearyl 12-stearoylhydroxystearate and isostearyl 12-stearoylhydroxystearate.

(Hydrocarbon-type oil phase ingredient)

Squalane, liquid paraffin, α -olefin oligomer, isoparaffin, ceresin, paraffin, liquid isoparaffin, polybutene, microcrystalline wax and petrolatum.

(Animal and plant oil, hardened oil thereof, and wax of natural origin)

Animal oils and hardened oils thereof, such as beef tallow, hardened beef tallow, lard, hardened lard, horse oil, hardened horse oil, mink oil, orange roughy oil, fish oil, hardened fish oil and egg yolk oil; plant oils and hardened oils thereof such as avocado oil, almond oil, olive oil, cacao oil, apricot kernel oil, coconut

oil, sesame oil, wheat germ oil, rice germ oil, rice bran oil, safflower oil, shea butter, soybean oil, evening primrose oil, tsubaki oil, corn oil, rapeseed oil, hardened rapeseed oil, palm kernel oil, hardened palm kernel oil, palm oil, hardened palm oil, peanut oil, hardened peanut oil, castor oil, hydrogenated castor oil, sunflower oil, grape seed oil, jojoba oil, hardened jojoba oil, macadamia nut oil, meadowfoam seed oil, cottonseed oil, hardened cottonseed oil; and waxes such as beeswax, high acid number beeswax, lanolin, reduced lanolin, liquid lanolin, carnauba wax and montan wax. (Silicone-type oil phase ingredient)

Dimethylpolysiloxane, methylphenylpolysiloxane, methylcyclopolysiloxane, octamethylpolysiloxane, decamethylpolysiloxane, dodecamethylcyclosiloxane, methylhydrogenpolysiloxane, polyether-modified organopolysiloxane, dimethylsiloxane·methylcetyloxysiloxane copolymer, dimethylsiloxane·methylstearoxysiloxane copolymer, alkyl-modified organopolysiloxane, terminal-modified organopolysiloxane, dimethiconol, silicone gel, acryl silicone, trimethylsiloxysilicic acid and silicone RTV rubber.

(Fluorine-type oil phase ingredient)

Perfluoropolyether, fluorine-modified organopolysiloxane, fluorinated pitch, fluorocarbon, fluoroalcohol and fluoroalkyl·polyoxyalkylene-comodified organopolysiloxane.

(2) Specific examples of higher alcohol

Lauryl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, isostearyl alcohol, oleyl alcohol, behenyl alcohol, 2-ethylhexanol, hexadecyl alcohol and octyl dodecanol.

(3) Specific examples of fatty acid

Caprylic acid, capric acid, undecylenic acid, lauric acid, myristic acid, palmitic acid, palmitoleic acid, stearic acid, isostearic acid, oleic acid, linoleic acid,

linolenic acid, arachic acid, arachidonic acid, behenic acid, erucic acid and 2-ethylhexanoic acid.

(4) Specific examples of ultraviolet absorber

Para-aminobenzoic acid, amyl para-aminobenzoate,
5 ethyldihydroxypropyl para-aminobenzoate, glyceryl para-aminobenzoate, ethyl para-aminobenzoate, octyl para-aminobenzoate, octyldimethyl para-aminobenzoate, ethylene glycol salicylate, octyl salicylate, triethanolamine salicylate, phenyl salicylate, butylphenyl salicylate,
10 benzyl salicylate, octyl para-methoxycinnamate, 2-ethylhexyl para-methoxycinnamate, glyceryl mono-2-ethylhexanoate di-para-methoxycinnamate, isopropyl para-methoxycinnamate, diethanolamine para-methoxyhydrocinnamate, diisopropyl·diisopropylcinnamic
15 acid ester mixture, urocanic acid, ethyl urocanate, hydroxymethoxybenzophenone, hydroxymethoxybenzophenone sulfonic acid and a salt thereof, dihydroxymethoxybenzophenone, sodium dihydroxymethoxybenzophenonedisulfonate,
20 dihydroxybenzophenone, dihydroxydimethoxybenzophenone, hydroxyoctoxybenzophenone, tetrahydroxybenzophenone, butylmethoxydibenzoylmethane, 2,4,6-trianilino-p-(carbo-2-ethylhexyl-1-oxy)-1,3,5-triazine, 2-(2-hydroxy-5-methylphenyl)benzotriazole, methyl-O-aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate,
25 phenylbenzimidazole sulfuric acid, 3-(4-methylbenzylidene)camphor, isopropyldibenzoylmethane, 2-ethylhexyl 4-(3,4-dimethoxyphenylmethylene)-2,5-dioxy-1-imidazolidinepropionate, and polymer derivatives and
30 silane derivatives thereof.

(5) Specific examples of powder and pigment

Pigments such as Food Red 104, Food Red 201, Food Yellow 4, Food Blue 1 and Food Black 401; lake pigments such as Food Yellow 4 AL lake and Food Yellow 203 BA
35 lake; polymers such as nylon powder, silk powder, urethane powder, silicone powder, polymethyl methacrylate powder, cellulose powder, starch, silicone elastomer

spherical powder and polyethylene powder; color pigments such as yellow iron oxide, red iron oxide, black iron oxide, chromium oxide, carbon black, ultramarine and iron blue; white pigments such as zinc oxide, titanium oxide and cerium oxide; extender pigments such as talc, mica, sericite, kaolin and plate barium sulfate; pearl pigments such as mica titanium; metal salts such as barium sulfate, calcium carbonate, magnesium carbonate, aluminum silicate and magnesium silicate; inorganic powders such as silica and alumina; metal soaps such as aluminum stearate, magnesium stearate, zinc palmitate, zinc myristate, magnesium myristate, zinc laurate and zinc undecylenate; bentonite; smectite; and boron nitride. The shape (e.g., sphere, bar, needle, plate, amorphous, scale, spindle) and the particle size of these powders are not particularly limited.

These powders may or may not be previously surface-treated by a conventionally known surface treatment such as fluorine compound treatment, silicone treatment, silicone resin treatment, pendant treatment, saline coupling agent treatment, titanium coupling agent treatment, lubricant treatment, N-acylated lysine treatment, polyacrylic acid treatment, metal soap treatment, amino acid treatment, lecithin treatment, inorganic compound treatment, plasma treatment and mechanochemical treatment.

(6) Specific examples of surfactant

(Anionic surfactant)

Fatty acid soap, α -acyl sulfonate, alkyl sulfonate, alkylallyl sulfonate, alkylnaphthalene sulfonate, alkyl sulfate, POE alkyl ether sulfate, alkylamide sulfate, alkyl phosphate, POE alkyl phosphate, alkylamide phosphate, alkyloylalkyl taurine salt, N-acylamino acid salt, POE alkyl ether carbonate, alkyl sulfosuccinate, sodium alkylsulfoacetate, acylated hydrolyzed collagen peptide salt and perfluoroalkylphosphoric acid ester.

(Cationic surfactant)

Alkyltrimethylammonium chloride,
stearyltrimethylammonium chloride,
stearyltrimethylammonium bromide,
cetostearyltrimethylammonium chloride,
5 distearyldimethylammonium chloride,
stearyldimethylbenzylammonium chloride,
behenyltrimethylammonium bromide, benzalkonium chloride,
behenic acid amidopropyldimethyl hydroxypropylammonium
chloride, diethylaminoethylamide stearate,
10 dimethylaminoethylamide stearate,
dimethylaminopropylamide stearate and lanolin derivative
quaternary ammonium salt.
(Amphoteric surfactant)

Carboxybetaine type, amidobetaine type, sulfobetaine
15 type, hydroxysulfobetaine type, amidosulfobetaine type,
phosphobetaine type, aminocarboxylate type, imidazoline
derivative type and amidoamine type.
(Nonionic surfactant)

Propylene glycol fatty acid ester, glycerin fatty
20 acid ester, polyglycerin fatty acid ester, sorbitan fatty
acid ester, POE sorbitan fatty acid ester, POE sorbitol
fatty acid ester, POE glycerin fatty acid ester, POE
alkyl ether, POE fatty acid ester, POE hydrogenated
castor oil, POE castor oil, POE·POP copolymer, POE·POP
25 alkyl ether, polyether-modified silicone lauric acid
alkanolamide, alkylamine oxide and hydrogenated soybean
phospholipid.
(Natural-type surfactant)

Lecithin, saponin and sugar-type surfactant.

30 (7) Specific examples of polyhydric alcohol and sugar

Ethylene glycol, diethylene glycol, polyethylene
glycol, propylene glycol, dipropylene glycol,
polypropylene glycol, glycerin, diglycerin, polyglycerin,
3-methyl-1,3-butanediol, 1,3-butylene glycol, sorbitol,
35 mannitol, raffinose, erythritol, glucose, sucrose, fruit
sugar, xylitol, lactose, maltose, maltitol, trehalose,
alkylated trehalose, mixed isomerized sugar, sulfated

trehalose and pullulan. Chemically modified products thereof can also be used.

(8) Specific examples of polymer compound

Anionic polymer compounds such as acrylic acid
5 ester/methacrylic acid ester copolymer (PLUS-SIZE,
produced by Go'o Kagaku K.K.), vinyl acetate/crotonic
acid copolymer (Resin 28-1310, produced by NSC), vinyl
acetate/crotonic acid/vinyl neodecanate copolymer (28-
2930, produced by NSC), methyl vinyl ether maleic acid
10 half ester (GANTREZ ES, produced by ISP), T-butyl
acrylate/ethyl acrylate/methacrylic acid copolymer
(RUBIMER, produced by BASF), vinylpyrrolidone/vinyl
acetate/vinyl propionate copolymer (RUBISCOL VAP,
produced by BASF), vinyl acetate/crotonic acid copolymer
15 (RUBISET CA, produced by BASF), vinyl acetate/crotonic
acid/vinylpyrrolidone copolymer (RUBISET CAP, produced by
BASF), vinylpyrrolidone/acrylate copolymer (RUBIFLEX,
produced by BASF), acrylate/acrylamide copolymer
(ULTRAHOLD, produced by BASF), vinyl acetate/butyl
20 maleate·isobornyl acrylate copolymer (ADVANTAGE, produced
by ISP), carboxy vinyl polymer (CARBOPOL, produced by BF
Goodrich) and acrylic acid·alkyl methacrylate copolymer
(PAMUREN, produced by BF Goodrich); amphoteric polymer
compounds such as acetic acid amphoteric compound of
25 dialkylaminoethyl methacrylate polymer (YUKAFORMER,
produced by Mitsubishi Chemical) and octylacrylamide
acrylate/hydroxypropyl acrylate/butylaminoethyl
methacrylate copolymer (AMPHOMER, produced by NSC);
cationic polymer compounds such as quaternized compound
30 of vinylpyrrolidone/dimethylaminoethyl methacrylate
(GAFQUAT, produced by ISP) and methyl vinyl imidazolium
chloride/vinylpyrrolidone copolymer (RUBICOTE, produced
by BASF); and nonionic polymer compounds such as
polyvinylpyrrolidone/vinyl acetate copolymer (RUBISCOL
35 VA, produced by BASF) and
vinylpyrrolidone/dimethylaminoethyl methacrylate
copolymer (COPOLYMER VC713, produced by ISP).

In addition, polymer compounds of natural origin, such as cellulose and derivatives thereof, calcium alginate, pullulan, agar, gelatin, tamarind seed polysaccharides, xanthane gum, carrageenan, high-methoxyl pectin, low-methoxyl pectin, guar gum, gum arabi, crystal cellulose, arabino galactan, karaya gum, tragacanth gum, alginic acid, albumin, casein, cardrun, gellan gum and dextran, can also be suitably used.

(9) Specific examples of biologically active ingredient

The biologically active ingredient may include substances which are capable of imparting some biological activity to skin, when such a substance is applied to the skin. Specific examples thereof may include: whitening ingredient, anti-inflammatory, age resistor, ultraviolet protection, slimming agent, skin tightening agent, antioxidant, hair restorer, hair growing agent, moisturizer, blood circulation accelerator, antibacterial agent, bactericide, desiccant, cooling agent, warming agent, vitamin compound, amino acid, wound healing accelerator, torpent, analgetic, cell activator and enzyme ingredient.

Suitable examples of the ingredient to be blended therefor may include: angelica extract, avocado extract, hydrangea extract, althea extract, arnica extract, aloe extract, apricot extract, apricot core extract, ginkgo extract, fennel extract, turmeric extract, oolong tea extract, rose fruit extract, echinacea leaf extract, scutellaria root extract, phellodendron bark extract, goldthread extract, barley extract, hypericum extract, white nettle extract, watercress extract, orange extract, sea salt, seaweed extract, hydrolyzed elastin, hydrolyzed wheat powder, hydrolyzed silk, chamomile extract, carrot extract, artemisia capillaris extract, glycyrrhiza extract, sabdariffa extract, pyracantha fortuneana fruit extract, kiwi extract, cinchona extract, cucumber extract, guanosine, gardenia extract, sasa albobmarginata extract, sophora root extract, walnut extract,

grapefruit extract, clematis extract, chlorella extract,
mulberry bark extract, gentian extract, black tea
extract, yeast extract, burdock extract, fermented rice
bran extract, rice germ oil, comfrey extract, collagen,
5 cowberry extract, asiasarum root extract, bupleurum
falcatum root extract, umbilical cord extract, salvia
extract, saponaria extract, bamboo grass extract,
crataegus extract, zanthoxylum fruit extract, shiitake
mushroom extract, rehmannia root extract, lithospermum
10 root extract, perilla extract, linden extract,
filipendula extract, peony root extract, calamus rhizome
extract, birch extract, horsetail extract, ivy extract,
hawthorn extract, sambucus nigra extract, yarrow extract,
peppermint extract, sage extract, mallow extract, cnidium
15 rhizome extract, swertia herb extract, soy extract,
jujube extract, wild thyme extract, green tea extract,
clove extract, cogon extract, citrus unshiu peel extract,
angelica root extract, calendula extract, peach seed
extract, bitter orange extract, houttuynia extract,
20 tomato extract, natto extract, ginseng extract, garlic
extract, wild rose extract, hibiscus sabdariffa flower
extract, ophiopogon tuber extract, parsley extract,
honey, witch hazel extract, pellitory extract, isodonis
extract, matricaria extract, loquat extract, coltsfoot
25 extract, butterbur scape extract, Poria cocos extract,
butcher bloom extract, grape extract,
propolis, luffa extract, safflower extract,
peppermint extract, linden extract, peony extract, hop
extract, pine extract, horse chestnut extract, skunk
30 cabbage extract, sapindaceae extract, balm mint extract,
peach extract, cornflower extract, eucalyptus extract,
saxifrage extract, citrus extract, coix seed extract,
mugwort extract, lavender extract, apple extract, lettuce
extract, lemon extract, Chinese milk vetch extract, rose
35 extract, rosemary extract, Roman chamomile extract and
royal jelly extract.

Other examples may include biopolymers such as

deoxyribonucleic acid, mucopolysaccharide, sodium
hyaluronate, sodium chondroitin sulfate, collagen,
elastin, chitin, chitosan and hydrolyzed eggshell
membrane; moisture retentive ingredients such as amino
5 acid, hydrolyzed peptide, sodium lactate, urea, sodium
pyrrolidonecarboxylate, betaine, whey and
trimethylglycine; oily ingredients such as sphingolipid,
ceramide, phytosphingosine, cholesterol, cholesterol
derivatives and phospholipid; anti-inflammatory such as
10 ϵ -aminocaproic acid, glycyrrhizic acid, β -glycyrrhetic
acid, lysozyme chloride, guaiazulene and hydrocortisone;
vitamins such as vitamin A, vitamin B₂, vitamin B₆,
vitamin D, vitamin E, calcium pantothenate, biotin and
nicotinic acid amide; active ingredients such as
15 allantoin, diisopropylamine dichloroacetate and 4-
aminomethylcyclohexanecarboxylic acid; antioxidants such
as tocopherol, carotenoid, flavonoid, tannin, lignin and
saponin; cell activators such as α -hydroxy acid and β -
hydroxy acid; blood circulation accelerators such as γ -
20 orizanol and vitamin E derivatives; wound healing agents
such as retinol and retinol derivatives; whitening agents
such as albumin, kojic acid, placenta extract, sulfur,
ellagic acid, linoleic acid, tranexamic acid and
glutathione; and hair growing agents such as
25 cepharanthine, glycyrrhiza extract, capsicum tincture,
hinokitiol, iodized garlic extract, pyridoxine
hydrochloride, DL- α -tocopherol, DL- α -tocopheryl acetate,
nicotinic acid, nicotinic acid derivatives, calcium
pantothenate, D-pantothenyl alcohol, acetyl
30 pantothenylethyl ether, biotin, allantoin,
isopropylmethylphenol, estradiol, ethynyl estradiol,
capronium chloride, benzalkonium chloride,
diphenhydramine hydrochloride, Takanal, camphor,
salicylic acid, vanillylamide nonylate, vanillylamide
35 nonanoate, pyroctone olamine, glyceryl pentadecanoate, L-
menthol, mononitroguaiacol, resorcinol, γ -aminobutyric

acid, benzethonium chloride, mexiletine hydrochloride, auxin, female hormone, cantharis tincture, cyclosporine, zinc pyrithione, hydrocortisone, minoxidil, polyoxyethylene sorbitan monostearate, peppermint oil and
5 SADANISHIKI extract.

(10) Specific examples of antioxidant

Sodium hydrogensulfite, sodium sulfite, erythorbic acid, sodium erythorbate, dilauryl thiodipropionate, tocopherol, tolylbiguanide, nordihydroguaiaretic acid,
10 parahydroxy anisole, butylhydroxy anisole, dibutylhydroxy toluene, ascorbyl stearate, ascorbyl palmitate, octyl gallate, propyl gallate, carotenoid, flavonoid, tannin, lignin, saponin and plant extracts having antioxidant effect, such as apple extract and clove extract.

(11) Specific examples of solvent

Purified water, ethanol, lower alcohol, ethers, LPG, fluorocarbon, N-methylpyrrolidone, fluoroalcohol, volatile linear silicone and next generation fleon (such
15 as fluorocarbon, chlorofluorocarbon, CFC).

(Cosmetic composition)

The cosmetic composition according to the present invention may further contain an existing or known emulsifier or the like in a general concentration.

(Skin agent)

The skin agent for external application according to
25 the present invention can also be used as a cosmetic material such as skin milk, skin cream, foundation cream, massage cream, cleansing cream, shaving cream, cleansing foam, skin lotion, lotion, pack, shampoo, rinse, hair
30 growing agent, hair nourishment, hair dye, hair conditioner, dentifrice, gargle, permanent waving agent, ointment, bath preparation and body soap.

(Cosmetic material)

The cosmetic material can be obtained by blending
35 the skin agent for external application according to the present invention with, for example, alcohol such as ethanol or propylene glycol; an antiseptic such as methyl

para-hydroxybenzoate, ethyl para-hydroxybenzoate, butyl para-hydroxybenzoate or propyl para-hydroxybenzoate; and a purified water. However, the cosmetic material is not particularly limited to these specific examples.

5 The cosmetic material according to the present invention is classified, for example, into makeup cosmetics such as foundation, face powder, eye shadow, eyeliner, eyebrow, cheek, lipstick and nail color; basic cosmetics such as milky lotion, cream, lotion, calamine
10 lotion, sun screen agent, suntan agent, after-shave lotion, pre-shave lotion, pack, acne countermeasure cosmetic and essence; hair care cosmetics such as shampoo, rinse, conditioner, hair color, hair tonic, hair setting agent, hair nourishment and permanent waving
15 agent; body powder, deodorant, depilatory, soap, body shampoo, bath preparation, hand soap and perfume. The present invention can be used as respective cosmetic materials.

 The shape or form of the cosmetic material according to the present invention is not particularly limited.
20 The cosmetic material may have a conventionally known shape or form such as two-layer structure, water-in-oil emulsion, oil-in-water emulsion, gel, spray, mousse, oil, solid, sheet and powder.

25 (Use of ascorbic acid derivative)

 The ascorbic acid derivative according to the present invention can be used as a medical or pharmaceutical preparation, agrochemical preparation, an animal drug preparation, a food additive and a feed
30 additive. The content of the ascorbic acid derivative may vary depending on use and therefore, cannot be indiscriminately specified. However, the amount applied may appropriately be increased or decreased according to the purpose and use. The amount required as an ascorbic
35 acid may appropriately be adjusted in accordance with the Pharmaceutical Affairs Law, the Law for Control over Agricultural Medicines, the Regulations for Control of

Animal Drugs, ETC., and the Food Sanitation Law.

[Examples]

The present invention is described in greater detail below by referring to Examples. However, the present invention is not limited to these Examples.

<Example A- 1>

L-Ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt:

In 500 g of 95% sulfuric acid, 131 mmol (35 g) of 2-hexyldecanoic acid was dissolved at 40°C. To the resulting solution, 146 mmol (50 g) of L-ascorbic acid-2-phosphate sodium salt was added and uniformly stirred for 6 hours. The thus obtained mixture was left standing at room temperature for 24 hours, and thereafter the reaction mixture was poured into 780 g of ice water and the resultant precipitate was extracted with 590 g of methyl-tert-butyl ether. To the resultant ether solution, 590 g of 13% brine was added and then a 20%-aqueous sodium hydroxide solution was added until the pH of the mixture became about 8. The methyl-tert-butyl ether layer was separated by a separating funnel and 300 g of methanol was added to the methyl-tert-butyl ether layer, whereby precipitate was deposited. This precipitate was separated by centrifugation, washed with a small amount of methanol and then dried under reduced pressure, to obtain 21 g of L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt in a powder form (yield: 27%).

The structure was identified by the nuclear magnetic resonance spectrum.

^1H NMR (270 MHz, D_2O ; ^1H NMR apparatus, trade name: JNM-EX270, mfd. by Nihon Denshi K.K. (JEOL Ltd.)) δ :

0.89 ppm (t, 6H, $J=6.6\text{Hz}$), 1.30-1.63 (b, 24H), 2.45 (hep, 1H, $J=6.6\text{Hz}$), 4.20-4.35 (m, 3H), 4.47 (s, 1H)

^{13}C NMR (67.8 MHz, D_2O ; ^{13}C NMR apparatus, trade name: JNM-EX270, mfd. by Nihon Denshi K.K.) δ :

16.4 ppm (s, 1C), 25.0 (s, 1C), 25.2 (s, 1C), 29.4
(s, 1C), 29.6 (s, 1C), 31.5 (s, 1C), 31.9 (s, 1C),
32.1 (s, 1C), 34.0 (s, 1C), 34.5 (s, 1C), 47.6 (s,
1C), 67.6 (s, 1C), 69.6 (s, 1C), 80.8 (s, 1C), 115.3
5 (d, 1C, J=7.3 Hz), 178.2 (s, 1C), 179.4 (s, 1C),
180.4 (s, 1C)

³¹P NMR (109 MHz, D₂O; ³¹P NMR apparatus, trade name: JNM-
EX270, mfd. by Nihon Denshi K.K.) δ: 4.3 ppm

10 <Example A- 2>

L-Ascorbic acid-2-phosphoric acid-6-(2'-n-
heptylundecanoate) sodium salt:

The procedure was repeated in the same manner as in
Example A-1, except for using 2-n-heptylundecanoic acid
15 according to the present invention in place of 2-
hexyldecanoic acid used in Example A-1, to obtain 16 g of
L-ascorbic acid-2-phosphoric acid-6-(2'-n-
heptylundecanoate) sodium salt in a powder form (yield:
26%).

20 The structure was identified by the nuclear magnetic
resonance spectrum.

¹H NMR (270 MHz, D₂O) δ:

0.89 ppm (t, 6H, J=6.6Hz), 1.30-1.63 (b, 24H), 2.43
(hep, 1H, J=6.3Hz), 4.18-4.36 (m, 3H), 4.57 (s, 1H)

25 ¹³C NMR (67.8 MHz, D₂O) δ:

16.5 ppm (s, 1C), 25.2 (s, 1C), 25.3 (s, 1C), 29.5
(s, 1C), 29.6 (s, 1C), 31.6 (s, 1C), 31.9 (s, 1C),
32.1 (s, 1C), 32.3 (s, 1C), 33.9 (s, 1C), 34.4 (s,
1C), 34.6 (s, 1C), 47.5 (s, 1C), 67.2 (s, 1C), 69.4
30 (s, 1C), 80.3 (s, 1C), 115.8 (d, 1C, J=6.1 Hz),
173.8 (s, 1C), 178.3 (d, 1C, J=3.7 Hz), 179.9 (s,
1C)

³¹P NMR (109 MHz, D₂O) δ: 4.1 ppm

35 <Test Example A-1>

The L-ascorbic acid-2-phosphoric acid-6-(2'-

hexyldecanoate) sodium salt obtained in Example A-1 was dissolved in purified water so as to provide to a concentration of 2 mass %, and the thus obtained solution was charged into a glass bottle with a lid and left standing at 40°C (under light-shielding condition) for 10 days. The ratio of the compound remaining after the storage was analyzed by using a high-performance liquid chromatograph equipped with Shodex (registered trademark of Showa Denko K.K.) SB802.5 HQ (mfd. by Showa Denko K.K.) column.

(Measurement Conditions for High-Performance Liquid Chromatography)

Column: Shodex (registered trademark of Showa Denko K.K.) OHpak SB802.5 HQ
Temperature: 40°C
Eluent: 0.03M Na₂SO₄ + 0.03M H₃PO₄/tetrahydrofuran = 1:2
Flow rate: 0.5 ml/min
Amount injected: 20 μL
Detection: UV 270 nm

<Test Example A-2>

A stability test was performed in the same manner as in Test Example A-1 except for using the L-ascorbic acid-2-phosphoric acid-6-(2'-n-heptylundecanoate) sodium salt obtained in Example A-2, instead of the L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt obtained in Example A-1.

<Comparative Example A-1>

A stability test was performed in the same manner as in Test Example A-1 except for using an L-ascorbic acid-2-phosphoric acid-6-palmitic acid ester sodium salt which had been prepared by using the procedure as described in Patent Document 5 (JP-A-10-298174) appearing hereinbefore, instead of the L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt obtained in

Example A-1.

<Comparative Example A-2>

5 A stability test was performed in the same manner as in Test Example A-1 except for using an L-ascorbic acid-2-phosphate sodium salt (mfd. by Showa Denko K.K.) having excellent stability, instead of the L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt obtained in Example A-1.

10 The results obtained in the above Examples, Comparative Examples, and Test Examples are shown together in the following Table 1.

[Table 1]

	Ascorbic Acid Derivative	Residual Ratio (%)
Example A-1	L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt	95.3
Example A-2	L-ascorbic acid-2-phosphoric acid-6-(2'-n-heptylundecanoate) sodium salt	95.5
Comparative Example A-1	L-ascorbic acid-2-phosphoric acid-6-palmitatic acid ester sodium salt	88.6
Comparative Example A-2	L-ascorbic acid-2-phosphate sodium salt	96.9

15 Formulation examples of cosmetic materials are shown below. In these examples, "%" means mass %.

[Formulation Example A-1]

Cream (1):

Condensed hexaglyceryl ricinoleate	1.0%
Fine grain titanium oxide	5.0%
2-Octyldodecyl pivalate	8.0%
Glyceryl tri(caprylate-caprate)	3.0%
Methylphenylpolysiloxane	7.0%
Decamethylcyclopentasiloxane	2.0%
Cetanol	2.0%
2-Ethylhexyl para-methoxycinnamate	6.0%

- 35 -

4-tert-Butyl-4-methoxybenzoylmethane	2.0%
Decaglyceryl monoisostearate	3.0%
Xanthane gum	0.3%
L-Ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt	4.0%
Purified water in an amount so as to provide a total amount of 100%	

[Formulation Example A-2]

Cream (2):

Condensed hexaglyceryl ricinoleate	1.0%
2-Octyldodecyl pivalate	8.0%
Glyceryl tri(caprylate-caprate)	3.0%
Methylphenylpolysiloxane	7.0%
Decamethylcyclopentasiloxane	2.0%
Cetanol	2.0%
Decaglyceryl monoisostearate	3.0%
Xanthane gum	0.3%
L-Ascorbic acid-2-phosphoric acid-6-(2'-n-heptylundecanoate) sodium salt	4.0%
Purified water in an amount so as to provide a total amount of 100%	

5 [Formulation Example A-3]

Skin Lotion:

L-Ascorbic acid-2-phosphoric acid-6-(2'-n-heptylundecanoate) sodium salt	4.0%
Citric acid	0.016%
Sodium citrate	2.0%
1,3-Butylene glycol	3.0%
Ethanol	3.0%
Purified water in an amount so as to provide a total amount of 100%	

(Production Process)

The above ingredients were dissolved in purified water under heating at 50°C, and the resulting solution was cooled under stirring. Then the stirring was stopped

10

when the temperature became 30°C, and the thus obtained solution was left standing.

[Formulation Example A-4]

5 Milky Lotion:

L-Ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt	4.0%
Glycerin	8.0%
Butylene glycol	2.0%
Hydrogenated lecithin	0.1%
Sodium hyaluronate	0.05%
Hydroxy ethyl cellulose	0.3%
Xanthane gum	0.3%
Sodium citrate	1.0%
Polyethylene glycol-50 hydrogenated caster oil	0.5%
Methylparaben	0.2%
Purified water in an amount so as to provide a total amount of 100%	

(Production Process)

The above ingredients except for L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt were dissolved in purified water under heating at 80°C, the
10 resulting solution was cooled under stirring. Then, L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt was gradually added to the resultant solution at 50°C under stirring, the stirring was stopped when the
15 temperature became 40 to 35°C, and the thus obtained solution was left standing.

[Example B-1]

To the surface of a human skin tissue three-dimensional model (trademark: TESTSKIN LSD-d, mfd. by
20 Toyobo Co., Ltd.), 40 µL of a solution which had been obtained by dissolving each of the substances (1) to (3) to be tested in Dulbecco PBS (-), and the resultant skin tissue model was cultured at 37 °C in the presence of 5%

CO₂ for two hours. Then, the test solution was removed by aspiration, and thereafter the skin tissue model was cultured at 37 °C in the presence of 5% CO₂ for 2, 6 and 12 hours, respectively.

5 Each of the portions of the skin model which had been sampled at each culture time was washed with Dulbecco PBS (-), the surface portion was punched out by using a punch having a diameter of 6mm ϕ , and homogenized in a HEPES buffer solution (pH 7.2) to obtain a
10 homogenate. By use of the thus obtained homogenate, the amount of the ascorbic acid contained in the skin model was quantitatively analyzed by using a high performance liquid chromatography. The protein content in the skin model was quantitatively analyzed by using the Lowry
15 method.

1) 2% ascorbic acid-2-phosphate sodium salt

2) 0.5% ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt

3) 0.5% ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt
20

Measurement conditions for high performance liquid chromatography:

<Ascorbic acid>

25 Column: Shodex (Showa Denko K.K., registered trademark) Asahipak NH2P-50 4E

Temperature: 40 °C

Eluent: acetonitrile: 60mM H₃PO₄ = 80 : 20

Flow rate: 0.8ml/min

Detection: UV 245nm
30

As a result, the amount of the ascorbic acid at each culture time (unit: nmol/mg skin protein) was as follows.

	<u>2 hours after culture</u>	<u>6 hours after culture</u>	<u>12 hours after culture</u>
35 1)	30	24	5
2)	6	10	23
3)	5	11	26

As shown by the above results, it was found that when the ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt or 0.5% ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt was administered to the skin model, the concentration of the ascorbic acid in the tissue could easily be enhanced effectively so as to provide a concentration which is effective for accelerating the collagen synthesis, for a long period from the point immediately after the administration.

[Example B-2]

The collagen synthesis-accelerating effects of the following 1) to 3) test substances was compared with each other, by using a guinea pig model system having an incised (or cut) wound. The base material for dissolving each test substance was purified water containing 20% of ethanol, and 3% of propylene glycol.

- 1) 2% ascorbic acid-2-phosphate sodium salt
- 2) 1% ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt
- 3) 1% ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt

In this experiment, two incised wounds each having a length of 2cm were formed on the back of a guinea pig by using a scalpel, so that the incised wounds are positioned symmetrically with regard to the center portion of the back. Then, 0.2 ml of the test substance solution was administered thereto twice a day, for four days. After the last administration was completed, a skin piece of 2 cm x 2 cm (square shape) was surgically removed from the back of the guinea pig, so that the incised wound portions were positioned substantially at the center of the skin piece. Then, the tension required for the detachment of the incised wound surface was

measured. Five guinea pigs were used with respect to one kind of the test substances.

After the measurement of the above tension, a skin section was taken out from the skin piece, so that the incised wound portion was contained in the skin section and the section had a width of 5 mm on both sides of the incised wound portion (i.e., the thus obtained skin section had a total width of 10 mm). The resultant skin section was homogenized in 0.5 M acetic acid so as to provide a homogenate. Two parts by volume of a mixture of diethyl ether-ethanol (volume ratio = 1 : 3) was added to one part by volume of the homogenate solution, and mixed therewith under stirring, and the solvent layer was removed therefrom after centrifugation. Pepsin (mfd. by Wako Pure Chemical Industries, Ltd.) was added to the resultant solvent layer, and was reacted with the solvent layer at 15 °C for 16 hours. After the separation thereof by centrifugation, the resultant supernatant was freeze-dried. The protein content of the thus obtained skin sample was hydrolyzed with hydrochloric acid, and was subjected to amino acid analysis by use of AccQ•Tag Amino acid Analyzer (mfd. by Waters Co.).

The results of the detachment tension measurement for the incised wound portion to which each test substance had been applied, and the hydroxyproline content thereof were as follows. Herein, the hydroxyproline is a substance which can be taken as an index of collagen.

	Detachment tension (g/cm)	Hydroxyproline content (nmol/skin wet weight)
1)	123	32.1
2)	181	38.5
3)	187	37.6

As shown by the above results, it was found that the administration of each of the ascorbic acid-2-phosphoric

acid-6-(2'-hexyl decanoate) sodium salt or ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium had an effect of accelerating the collagen synthesis so as to promote the recovery of the incised wound surface.

5

[Formulation Example B-1]

Skin Lotion

Ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt

10		2.0%
	Citric acid	0.016%
	Sodium citrate	2.0%
	1,3-butylene glycol	3.0%
	Ethanol	3.0%
15	Purified water in an amount so as to provide a total amount of 100%	
	(Production process)	

The above ingredients were dissolved in purified water under warming at 50 °C, and the resultant mixture was cooled under stirring. When the temperature of the mixture became 30 °C, the stirring was stopped, and the mixture was left standing.

20

[Formulation Example B-2]

25

Skin Lotion

Ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt

		2.0%
	Citric acid	0.016%
30	Sodium citrate	2.0%
	1,3-butylene glycol	3.0%
	Ethanol	3.0%
	Purified water in an amount so as to provide a total amount of 100%	
35	(Production process)	

The above ingredients were dissolved in purified water under warming at 50 °C, and the resultant mixture

was cooled under stirring. When the temperature of the mixture became 30 °C, the stirring was stopped, and the mixture was left standing.

5 [Formulation Example B-3]

Cream :

Ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt

		2.0%
10	Cetanol	5.0%
	Cyclomethicone	4.0%
	Cetyl octanoate	4.0%
	Trioctanoin	2.0%
	Palmityl alcohol	1.0%
15	Dimethicone	0.3%
	Butylene glycol	7.0%
	Hydrogenated lecithin	1.0%
	Myristic acid poly glyceryl-10	1.0%
	Sodium citrate	2.0%
20	Methyl paraben	0.15%
	Propyl paraben	0.05%
	Xanthan gum	0.1%

Purified water in an amount so as to provide a total amount of 100%

25 (Production process)

The above ingredients (except for the ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt) were dissolved in purified water under warming at 80 °C, and the resultant mixture was cooled under stirring. At 30 50 °C, the ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt was gradually added to this mixture. When the temperature of the mixture became 35-30 °C, the stirring was stopped, and the mixture was left standing.

35

[Formulation Example B-4]

Cream :

	Ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt	2.0%
	Cetanol	5.0%
	Cyclomethicone	4.0%
5	Cetyl octanoate	4.0%
	Trioctanoin	2.0%
	Palmityl alcohol	1.0%
	Dimethicone	0.3%
	Butylene glycol	7.0%
10	Hydrogenated lecithin	1.0%
	Myristic acid poly glyceryl-10	1.0%
	Sodium citrate	2.0%
	Methyl paraben	0.15%
	Propyl paraben	0.05%
15	Xanthan gum	0.1%

Purified water in an amount so as to provide a total amount of 100%

(Production process)

The above ingredients (except for the ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt) were dissolved in purified water under warming at 80 °C, and the resultant mixture was cooled under stirring. At 50 °C, the ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt was gradually added to this mixture. When the temperature of the mixture became 35-30 °C, the stirring was stopped, and the mixture was left standing.

[Formulation Example B-5]

30 Milky Lotion:

	L-Ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt	2.0%
	Glycerin	8.0%
	Butylene glycol	2.0%
35	Hydrogenated lecithin	0.1%
	Sodium hyaluronate	0.05%
	Hydroxy ethyl cellulose	0.3%

	Xanthane gum	0.3%
	Sodium citrate	1.0%
	Polyethylene glycol-50 hydrogenated castor oil	0.5%
5	Methylparaben	0.2%
	Purified water in an amount so as to provide a total amount of 100%	
	(Production Process)	

10 The above ingredients except for L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt were dissolved in purified water under heating at 80°C, the resulting solution was cooled under stirring. Then, L-ascorbic acid-2-phosphoric acid-6-(2'-hexyldecanoate) sodium salt was gradually added to the resultant solution
15 at 50°C under stirring, the stirring was stopped, when the temperature became 40 to 35°C, and the thus obtained solution was left standing.

[Formulation Example B-6]

20	L-Ascorbic acid-2-phosphoric acid-6-(2'-heptyl undecanoate) sodium salt	2.0%
	Glycerin	8.0%
	Butylene glycol	2.0%
	Hydrogenated lecithin	0.1%
	Sodium hyaluronate	0.05%
25	Hydroxy ethyl cellulose	0.3%
	Xanthane gum	0.3%
	Sodium citrate	1.0%
	Polyethylene glycol-50 hydrogenated castor oil	0.5%
30	Methylparaben	0.2%
	Purified water in an amount so as to provide a total amount of 100%	
	(Production Process)	

35 The above ingredients except for L-ascorbic acid-2-phosphoric acid-6-(2'-heptyl undecanoate) sodium salt were dissolved in purified water under heating at 80°C, the resulting solution was cooled under stirring. Then,

L-ascorbic acid-2-phosphoric acid-6-(2'-heptyl undecanoate) sodium salt was gradually added to the resultant solution at 50°C under stirring, the stirring was stopped, when the temperature became 40 to 35°C, and the thus obtained solution was left standing.

Example C-1 (Whitening)

The quantities in the compositions in Examples appearing hereinafter are described in terms of mass % (wt. %).

Lotion (1)

The following ingredients 1) to 4) were uniformly dispersed and dissolved with each other so as to provide the following final concentrations. The resultant mixture was added to the ingredient 5) under stirring, to obtain Lotion (1).

1) Ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt	2.00
2) Ethanol	5.00
3) Propylene glycol	5.00
4) Methyl para-hydroxy benzoate	0.20
5) Purified water	87.8

Lotions (2) to (4)

Lotions (2) to (4) were prepared in the same manner as in the production of Lotion (1), except that each of the following ingredient was respectively used so as to provide the same concentration, instead of the ingredient (1) of Lotion (1).

Lotion (2):

Ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt

Lotion (3) (Comparative control reference):

Ascorbic acid-2-phosphoric acid sodium salt

Lotion (4) (Negative control):

Purified water

In each of the above lotions, the ingredients were uniformly dissolved, and all of the lotions showed a good stability with the elapse of time.

5

Example C-2

Lotion (5)

The following ingredients 1) to 4) were uniformly dispersed and dissolved with each other so as to provide the following final concentrations. The resultant mixture was added to the ingredient 5) under stirring, to obtain Lotion (5).

	1) Ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt	0.10
15	2) Ethanol	5.00
	3) Propylene glycol	5.00
	4) Methyl para-hydroxy benzoate	0.20
	5) Purified water	89.7

20 Lotions (6) to (8)

Lotions (6) to (8) were prepared in the same manner as in the production of Lotion (5), except that each of the following ingredient was respectively used so as to provide the same concentration, instead of the ingredient (1) of Lotion (5).

25

Lotion (6):

Ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt

30 Lotion (7) (Comparative control reference):

Ascorbic acid-2-phosphoric acid sodium salt

Lotion (8) (Negative control):

Purified water

35

In each of the above lotions, the ingredients were uniformly dissolved, and all of the lotions showed a good stability with the elapse of time.

Example C-3Gel-type preparation (1) for external use

5 The following ingredient 1) was uniformly dispersed in the following ingredient 2) so as to provide the following final concentration, and the resultant mixture was added to the ingredient 3) under stirring, to obtain an intended gel-type external preparation (1).

10	1) Ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt	10
	2) glycerol	20
	3) Octyl dodecyl myristate	70

Gel-type preparations (2) to (4) for external use

15 Gel-type external preparations (2) to (4) were prepared in the same manner as in the production of gel-type external preparation (1), except that each of the following ingredient was respectively used so as to provide the same concentration, instead of the ingredient
20 (1) of Gel-type preparation (1).

Gel-type preparation (2):

Ascorbic acid-2-phosphoric acid-6-(2'-n-heptyl undecanoate) sodium salt

25 Gel-type preparation (3) (Comparative control reference):

Ascorbic acid-2-phosphoric acid sodium salt

Gel-type preparation (4) (Negative control):

Purified water

30 In each of the above gel-type external preparations, the ingredients were uniformly dissolved, and all of the gel-type external preparations showed a good stability with the elapse of time.

35 Example C-4

(Effect of preventing pigmentation)

The hair of the entire surface on the back of each

of seven weeks-aged 30 male Wizer-Maple guinea pigs (WM, SPF) was trimmed by using electric hair clippers (0.05mm blade), and then the surface was shaven by using an electric shaver. Thereafter, the back surface was covered with an adhesive stretchable bandage (Silky-tex, the outside of which was covered with an aluminum foil) having four opening windows each having a size of 1.5 cm × 1.5 cm. With respect to the respective windows, each of Lotions (1) to (8) and Gel-type external preparations (1) to (4) which had been prepared in Examples C-1 to C-3, was sequentially applied to ten sites each in an amount of 0.05 ml. After four hours from the application of the preparations, the dosage sites were washed with water by using absorbent cotton impregnated with water, and then dried. Then, each of the animals was fixed onto a retention device, and the respective sites were irradiated with medium-wavelength ultraviolet ray (UVB) at a radiant exposure of 300 mJ/cm² with a distance of about 10 cm by using ultraviolet ray-irradiating device (mfd. by Shinano Seisakusho, Toshiba FL40S/E30-type fluorescent lamp, equipped with six SE lamps). After the irradiation, each of the same Lotions (1) to (8) and Gel-type external preparations (1) to (4) was again applied to the corresponding sites each in an amount of 0.05 ml.

These procedure was repeated for three days. After 14 days from the last irradiation, the degree of the resultant pigmentation (or chromatosis) was determined according to the following acceptance criteria in terms of scores. Further, the brightness of the skin was determined by using a color-difference meter (MINOLTA, CR-20) with respect to the four corners and central portion of each of the dosage/irradiation sites (total five sites). With respect to each of the preparations, the effect of preventing the pigmentation was judged from the average of score values (ten data for each preparation) and the average of brightness values (50 data for each preparation).

Acceptance criteria for pigmentation

- No pigmentation was recognized: Score 0 (zero)
 Slight pigmentation was recognized: Score 1
 Low-degree pigmentation was recognized: Score 2
 5 Middle-degree pigmentation was recognized: Score 3
 High-degree pigmentation was recognized: Score 4

Results (average)

	<u>Preparation</u>	<u>Score</u>	<u>Brightness</u>
10	Lotion (1)	0.8	63.0
	Lotion (2)	1.0	61.1
	Lotion (3)	2.1	61.8
	Lotion (4)	3.0	59.5
	Lotion (5)	2.0	61.7
15	Lotion (6)	2.2	62.1
	Lotion (7)	3.0	59.9
	Lotion (8)	3.0	60.1
	Gel-type ext. prep. (1)	0.5	63.5
	Gel-type ext. prep. (2)	0.8	62.8
20	Gel-type ext. prep. (3)	1.2	62.1
	Gel-type ext. prep. (4)	3.0	59.9

As described above, it was found that any of the lotions and gel-type external preparations containing the
 25 ascorbic acid derivative according to the present invention showed an excellent effect of preventing the pigmentation.

Example C-5

30 (Effect of removing pigmentation)

The hair of the entire surface on the back of each of six weeks-aged 30 male Wizer-Maple guinea pigs (WM, SPF) was trimmed by using electric hair clippers (0.05mm blade), and then the surface was shaven by using an
 35 electric shaver. Thereafter, the back surface was covered with an adhesive stretchable bandage (Silky-tex, the outside of which was covered with an aluminum foil)

having four opening windows each having a size of 1.5 cm
 × 1.5 cm. Then, each of the animals was fixed onto a
 retention device, and the respective sites were
 irradiated with medium-wavelength ultraviolet ray (UVB)
 at a radiant exposure of 750 mJ/cm² with a distance of
 about 10 cm by using ultraviolet ray-irradiating device
 (mfd. by Shinano Seisakusho, Toshiba FL40S/E30-type
 fluorescent lamp, equipped with six SE lamps). In a
 period of from four days after the irradiation to 28 days
 after the irradiation, twice a day (in the morning and in
 the evening), with respect to the respective windows,
 each of Lotions (1) to (8) and Gel-type external
 preparations (1) to (4) which had been prepared in
 Examples C-1 to C-3, was sequentially applied to ten
 sites each in an amount of 0.05 ml. After 28 days from
 the last irradiation, the degree of the resultant
 pigmentation was determined according to the acceptance
 criteria in terms of scores, in the same manner as in
 Example C-4. With respect to each of the preparations,
 the effect of removing the pigmentation was judged from
 the average of score values (ten data for each
 preparation).

Results (average)

	<u>Preparation</u>	<u>Score</u>
25	Lotion (1)	2.2
	Lotion (2)	2.4
	Lotion (3)	3.3
	Lotion (4)	3.5
30	Lotion (5)	2.9
	Lotion (6)	3.0
	Lotion (7)	3.5
	Lotion (8)	3.8
	Gel-type ext. prep. (1)	2.2
35	Gel-type ext. prep. (2)	2.5
	Gel-type ext. prep. (3)	2.9
	Gel-type ext. prep. (4)	3.5

As described above, it was found that any of the lotions and gel-type external preparations containing the ascorbic acid derivative according to the present invention showed a distinct effect of removing the pigmentation.

<Example D-1>

5 kg of basic ingredients comprising 43 mass % of cuttlefish meal, 15 mass % of lobster (or shrimp) meal, 10 mass % of fish meal, 10 mass % of crude (non-refined) fish oil (mfd. by Nippon Suisan K.K.), 10 mass % of beer yeast, 3 mass % of active gluten, 2 mass % of starch, 2 mass % of ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt prepared in Example A-1, and 5 mass % of mineral mixture, was subjected to mixing. Then, the moisture content of the thus obtained mixture was adjusted so as to provide a moisture content of 45 %. The mixture was extruded by using an extruder so as to provide a product temperature of 115 °C, then dried by a dryer so as to provide a moisture content of about 10%, to obtain pellets of feeding stuff.

<Comparative Example D-1>

Pellets of feeding stuff were prepared in the same manner as in Example D-1 except for using no ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt.

<Comparative Example D-2, Example D-3>

Feeding tests were conducted by using rainbow trouts. 20 rainbow trouts (average fish weight: 0.79kg) were provided, and accommodated in two compartments of a circulation and filtration-type water tank, so that each compartment accommodated 10 rainbow trouts. With respect to these rainbow trouts, feeding tests were conducted by using the feeding stuff which had been prepared in

Example D-1. Herein, the feeding stuff which had been prepared in Comparative Example D-1 was fed to the compartment for control test. The water temperature of the feeding period was adjusted to 18 °C and the feeding rate was set to 4% per the fish weight. After the termination of the feeding test, all of the ten fish was taken out, and the fish weights thereof were measured. With respect to the rainbow trouts of test area, the average fish weight became 0.85kg, while the average fish weight of the control area became 0.82kg.

From the above results, the effect of ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt according to the present invention was recognized.

<Example E-1>

25g of bees wax (mfd. by Noda wax Co., Ltd., melting point 60 °C) was added to 1 kg of egg yolk lecithin (mfd. by Kewpie Co., Ltd., trade name "PL-30", PC content about 25%), and the resulting mixture was stirred under warming at about 70 °C until a uniform mixture was formed. This conditions were maintained for five minutes, and then cooled. Subsequently, 25g of the ascorbic acid-2-phosphoric acid-6-(2'-hexyl decanoate) sodium salt prepared in Example A-1 was added, and the resulting mixture was stirred until a uniform mixture was formed to obtain a mixture. On the other hand, 2 kg of gelatine, 1 kg of glycerol, and 1.5 kg of water were sufficiently mixed with each other and the resultant mixture was shaped into a sheet. Two pieces of the thus formed gelatine sheet were set to a rotary type capsule forming machine, and the above mixture was injected in an amount of 300 mg per one capsule. The injection port of each capsule was sealed up under pressure to produce 3500 capsules.

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Industrial Applicability

The novel ascorbic acid derivative to be produced by

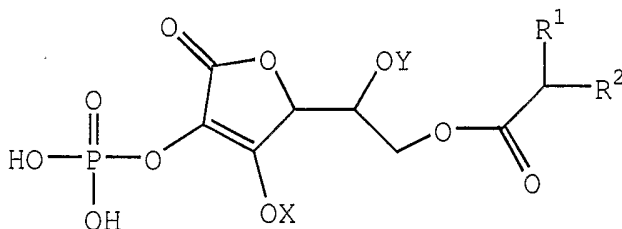
the production process according to the present invention is liable to be incorporated into cells, and therefore it can elevate the cumulative concentration of ascorbic acid in cells, even when it is administered into the cells in a small amount. In addition, this ascorbic acid derivative has an improved storage stability, as compared with conventional ascorbic acid derivatives. Accordingly, the ascorbic acid derivative according to the present invention can be widely used for various preparations such as vitamin C preparations, skin preparations for external use, medical or pharmaceutical preparations, agrochemical preparations, animal drug preparations, food additives, and feed additives, which contain an ascorbic acid derivative as an effective ingredient.

In addition, when the ascorbic acid derivative according to the present invention is incorporated into a cosmetic for preventing wrinkles, etc., the ascorbic acid derivative has an excellent effect of accelerating the collagen synthesis, and an excellent effect of suppressing the collagen decomposition, so that it can prevent or improve a change in the form or shape skin due to aging. Accordingly, the ascorbic acid derivative according to the present invention is widely applicable to medical or pharmaceutical preparations, quasi-drug products, cosmetics, etc.

CLAIMS

1. An ascorbic acid derivative, which is a compound represented by the following general formula (1) or a salt thereof:

5 [Chemical Formula 9]



(1)

10 (wherein X and Y each represents H or a protective group for OH, R¹ and R² each represents an alkyl group having from 1 to 19 carbon atoms, which may be linear or branched, and the total number of carbon atoms in R¹ and R² is an integer of 5 to 22).

15 2. The ascorbic acid derivative according to claim 1, which is a salt with one or more metal selected from the group consisting of alkali metal, alkaline earth metal, aluminum, iron, zinc and bismuth.

20 3. The ascorbic acid derivative according to claim 1, which is a salt with ammonia, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine or 2-amino-1-methylpropanol.

25 4. The ascorbic acid derivative according to any one of claims 1 to 3, wherein the total number of carbon atoms in R¹ and R² of the general formula (1) is an integer of 8 to 18.

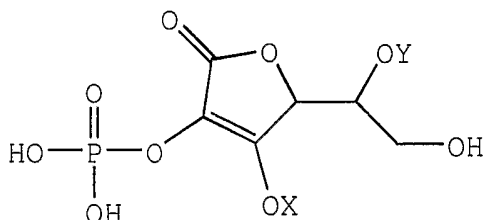
5. The ascorbic acid derivative according to claim 4, wherein R¹ and R² of the general formula (1) are a linear alkyl group, and the total number of carbon atoms in the linear alkyl groups of R¹ and R² is 14 or 16.

30 6. The ascorbic acid derivative according to claim 5, wherein in the general formula (1), R¹ is n-C₉H₁₉, and R² is n-C₇H₁₅; or R¹ is n-C₈H₁₇, and R² is n-C₆H₁₃.

7. A process for producing an ascorbic acid

derivative according to any one of claims 1 to 6,
 comprising a step of reacting a compound represented by
 the following general formula (2) and/or a salt thereof:
 [Chemical Formula 10]

5



(2)

(wherein X and Y each represents H or a protective group
 for OH), with at least one selected from fatty acid,
 10 fatty acid salt, fatty acid ester, fatty acid halide,
 and/or fatty acid anhydride.

8. The process for producing an ascorbic acid
 derivative according to claim 7, wherein the reaction is
 performed in the presence of a condensing agent and/or
 15 dehydrating agent.

9. The process for producing an ascorbic acid
 derivative according to claim 8, wherein the dehydrating
 agent is sulfuric acid.

10. The process for producing an ascorbic acid
 20 derivative according to any one of claims 7 to 9, wherein
 the reaction is conducted in a solvent selected from the
 group consisting of: water, acetone, dioxane, toluene,
 ethylbenzene, methyl-tert-butyl ether and sulfuric acid.

11. A vitamin C preparation comprising the ascorbic
 25 acid derivative according to any one of claims 1 to 6 as
 an effective ingredient.

12. A collagen production accelerator comprising
 the ascorbic acid derivative according to any one of
 claims 1 to 6 as an effective ingredient.

30 13. A whitening preparation comprising the ascorbic
 acid derivative according to any one of claims 1 to 6 as
 an effective ingredient.

14. A skin preparation for external use, comprising

the ascorbic acid derivative according to any one of claims 1 to 6 as an effective ingredient.

5 15. The skin preparation for external use according to claim 14, which contains an ascorbic acid-2-phosphoric acid ester and/or a salt thereof.

 16. The skin preparation for external use according to claim 14, which contains sodium salt, potassium salt, magnesium salt or zinc salt of the ascorbic acid-2-phosphoric acid ester.

10 17. A cosmetic material comprising the skin preparation for external use according to any one of claim 14 to 16.

 18. A composition comprising the ascorbic acid derivative according to any one of claims 1 to 6, in the form of a medical or pharmaceutical preparation, an agrochemical preparation or an animal drug preparation.

15 19. A composition comprising the ascorbic acid derivative according to any one of claims 1 to 6, in the form of a food or feed additive.

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/341 A61K31/215 C07F9/117		
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 7 A61K C07F		
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 practical, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	EP 1 074 242 A (BEIERSDORF AG) 7 February 2001 (2001-02-07) paragraph '0015!	1-19
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
° Special categories of cited documents :		
A document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed		*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family
Date of the actual completion of the international search 7 July 2003		Date of mailing of the international search report 29/07/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Zellner, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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