(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 June 2017 (15.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/098050 A1

(51) International Patent Classification:
C07C 45/62 (2006.01) *C07C 45/29* (2006.01)
C07C 49/04 (2006.01) *C07C 45/38* (2006.01)
C07C 45/72 (2006.01) *C07C 33/02* (2006.01)
C07C 49/203 (2006.01) *C07C 33/042* (2006.01)
C07C 29/17 (2006.01) *C07C 47/21* (2006.01)
C07C 29/38 (2006.01) *C07D 311/72* (2006.01)

(21) International Application Number:
PCT/EP2016/080664

(22) International Filing Date:
12 December 2016 (12.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
EP15199585.9 11 December 2015 (11.12.2015) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

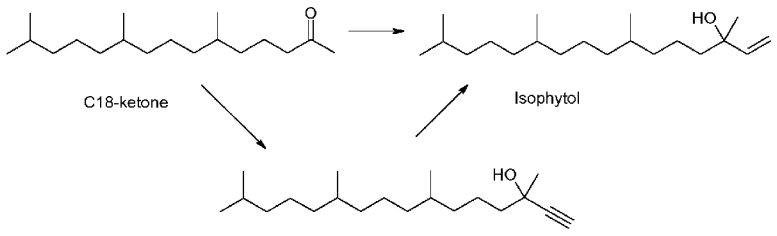
Published:

— *with international search report (Art. 21(3))*

WO 2017/098050 A1

(54) Title: PROCESS FOR THE MANUFACTURE OF 6,10,14-TRIMETHYLPENTADECAN-2-ONE, ISOPHYTOL AND ALPHA-TOCOPHEROL

Fig. 4



(57) Abstract: The present invention is directed to a process for the manufacture of 6,10,14-trimethylpentadecan-2-one ("C18-ketone") comprising the step of hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon double bonds over carbon-oxygen double bonds. Preferably the catalyst comprises a metal selected from the group consisting of palladium, platinum, rhodium, iridium and nickel and mixtures thereof. A process for the preparation of (2E,6E)-farnesal by selective oxidation of (2E,6E)-farnesol and a process for the manufacture of a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone from (2E,6E)-farnesal is also disclosed.

PROCESS FOR THE MANUFACTURE OF 6,10,14-TRIMETHYLPENTADECAN-2-ONE, ISOPHYTOL AND ALPHA-TOCOPHEROL

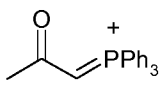
The present invention is directed to a process for the manufacture of 6,10,14-trimethylpentadecan-2-one ("C18-ketone") comprising the step of hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon double bonds over carbon-oxygen double bonds (see **Fig. 3**). Preferably the catalyst comprises a metal selected from the group consisting of palladium, platinum, rhodium, iridium and nickel and mixtures thereof. More preferably the catalyst comprises a metal selected from the group consisting of palladium, platinum and mixtures thereof. Even more preferably the catalyst is a metal selected from the group consisting of palladium, platinum and mixtures thereof. Most preferably the catalyst is palladium.

Surprisingly the inventors of the present invention discovered that when a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone is used to obtain C18-ketone, the hydrogenation reaction is much faster than in the case, where a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone, (3Z,5E,9E)-3,4-dehydrofarnesylacetone, (3E,5Z,9E)-3,4-dehydrofarnesylacetone, (3Z,5Z,9E)-3,4-dehydrofarnesylacetone, (3E,5E,9Z)-3,4-dehydrofarnesylacetone, (3E,5Z,9Z)-3,4-dehydrofarnesylacetone, (3Z,5E,9Z)-3,4-dehydrofarnesylacetone and (3Z,5Z,9Z)-3,4-dehydrofarnesylacetone or any other mixture of the double bond stereoisomers of 3,4-dehydrofarnesylacetone comprising more double bond stereoisomers than the two isomers (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone is used. Therefore, it is advantageous,

especially for an industrial process, where hundreds of tons are produced, to use as starting material for obtaining C18-ketone a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone, because the time savings have an immense influence on the overall production costs.

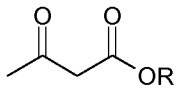
Manufacture of a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone

Such a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone can be obtained from (2E,6E)-farnesal (**see Fig. 2**), either by a Wittig reaction with e.g. 2-oxopropyltriphenylphosphonium chloride (or the equivalent bromide or iodide salt) (I) or by an aldol condensation with acetone (II) and a base (whereby dehydrofarnesylacetone is predominantly obtained as the (3EZ,5E,9E) isomer) or by a Knoevenagel reaction (III) followed by decarboxylation or by Horner-Wadsworth-Emmons chemistry using a suitable phosphonate, for example dimethyl 2-oxopropyl-phosphonate or diethyl 2-oxopropylphosphonate. This synthesis of (2E,6E)-farnesal is also an embodiment of the present invention.



(I)

(II)



(III)

Manufacture of (2E,6E)-farnesal (**see Fig. 1**)

(2E,6E)-Farnesal can be obtained by selective oxidation of (2E,6E)-farnesol (see **Fig. 1**), e.g. by the use of manganese oxide in a solvent with only a small change in the carbon-carbon double bond geometry. Alternatively, oxygen and palladium catalysts as described in Kakiuchi et al, Bull Chem Soc Jpn, 2001, 165-172 (especially page 168, Table 3, example 11) may be used for the selective oxidation of (2E,6E)-farnesol to (2E,6E)-farnesal. This selective oxidation is also an embodiment of the present invention.

The (2E,6E)-farnesol may itself be extracted from natural sources or obtained by fermentation or synthesized synthetically and, if needed, separated from (2Z,6E)-, (2E,6Z)- and (2Z,6Z)-farnesol by any method known to the person skilled in the art.

Process for the manufacture of isophytol, α-tocopherol and α-tocopheryl acetate

Since the mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone is an important starting material for isophytol, and thus for α-tocopherol and its acetate, the present invention is also directed to a process for the manufacture of isophytol and for the manufacture of α-tocopherol and its acetate, respectively, comprising the process according to the present invention.

Therefore, a further object of the present invention is a process for the manufacture of isophytol comprising the following steps:

a) selectively oxidizing (2E,6E)-farnesol to (2E,6E)-farnesal according to the process of the present invention;
b) converting (2E,6E)-farnesal either by a Wittig reaction or by an aldol condensation with acetone and a base or by a Knoevenagel reaction followed by decarboxylation or by Horner-Wadsworth-Emmons chemistry using a suitable phosphonate to obtain a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone according to the process of the present invention;
c) hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst according to the process of the present invention to obtain 6,10,14-trimethylpentadecan-2-one;

d1) ethynylating 6,10,14-trimethylpentadecan-2-one to obtain 3,7,11,15-tetramethylhexadec-1-yn-3-ol;
e1) hydrogenating 3,7,11,15-tetramethylhexadec-1-yn-3-ol to isophytol.

Alternatively, the isophytol may be produced according to a process comprising the following steps which is also an object of the present invention:

a) selectively oxidizing (2E,6E)-farnesol to (2E,6E)-farnesal according to the process of the present invention;
b) converting (2E,6E)-farnesal either by a Wittig reaction or by an aldol condensation with acetone and a base or by a Knoevenagel reaction followed by decarboxylation or by Horner-Wadsworth-Emmons chemistry using a suitable phosphonate to obtain a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone according to the process of the present invention;
c) hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst according to the process of the present invention to obtain 6,10,14-trimethylpentadecan-2-one;
d2) vinylating 6,10,14-trimethylpentadecan-2-one by addition of a vinyl Grignard reagent to yield isophytol.

A further object of the present invention is a process for the manufacture of α-tocopherol and α-tocopheryl acetate, respectively, comprising the following steps:

a) selectively oxidizing (2E,6E)-farnesol to (2E,6E)-farnesal according to the process of the present invention;

b) converting (2E,6E)-farnesal either by a Wittig reaction or by an aldol condensation with acetone and a base or by a Knoevenagel reaction followed by decarboxylation or by Horner-Wadsworth-Emmons chemistry using a suitable phosphonate to obtain a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone according to the process of the present invention;

c) hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst according to the process of the present invention to obtain 6,10,14-trimethylpentadecan-2-one;

d1) ethynylating 6,10,14-trimethylpentadecan-2-one to obtain 3,7,11,15-tetramethylhexadec-1-yn-3-ol;

e1) hydrogenating 3,7,11,15-tetramethylhexadec-1-yn-3-ol to isophytol;

f) coupling isophytol with 2,3,5-trimethylhydroquinone or its acetate to obtain α-tocopherol or its acetate.

Alternatively, the α-tocopherol or its acetate (α-tocopheryl acetate) may be produced according to a process comprising the following steps which is also an object of the present invention:

a) selectively oxidizing (2E,6E)-farnesol to (2E,6E)-farnesal according to the process of the present invention;

b) converting (2E,6E)-farnesal either by a Wittig reaction or by an aldol condensation with acetone and a base or by a Knoevenagel reaction followed by decarboxylation or by Horner-Wadsworth-Emmons chemistry using a suitable phosphonate to obtain a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone according to the process of the present invention;

c) hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst according to the process of the present invention to obtain 6,10,14-trimethylpentadecan-2-one;

d2) vinylating 6,10,14-trimethylpentadecan-2-one by addition of a vinyl Grignard reagent to yield isophytol;

f) condensing isophytol with 2,3,5-trimethylhydroquinone or its acetate to obtain α-tocopherol or its acetate.

The steps d1), e1), d2) and f) may be carried out according to methods known to the person skilled in the art. The ethynylation e.g. may either be performed with acetylene, ammonia and potassium hydroxide or with ethynyl Grignard. The following hydrogenation of the CC triple bond to a C=C double bond is then carried out with a Lindlar catalyst.

Detailed description

There was a need to further optimize the synthesis of isophytol, an important starting material for α-tocopherol and its acetate (α-tocopheryl acetate). 6,10,14-trimethylpentadecan-2-one (in the following called "C18-ketone") is the starting material for isophytol. Thus, an improvement in the synthesis of C18-ketone leads also to an improvement in the synthesis of isophytol.

This need is fulfilled by the present invention, which is directed to a process for the manufacture of 6,10,14-trimethylpentadecan-2-one ("C18-ketone") comprising the step of hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon double bonds over carbon-oxygen double bonds. This process is an important step in the process for the manufacture of isophytol and α-tocopherol or its acetate.

Starting material

Preferably a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone is used, where the content of other C=C double bond stereoisomers is below 50 mol-%, preferably below 20 mol-%, more preferably below 10 mol-%, even more preferably below 5 mol-%, most preferably below 2 mol-% or below 0.5 mol-%, based on the total amount of the mixture. Thus, a mixture, where the amount of non-(3EZ,5E,9E)-3,4-dehydrofarnesylacetone isomers is up to 49 mol-%, preferably up to 20 mol-%, more preferably up to 10 mol-%, based on the total amount of the mixture, may also be used successfully. More preferably, however, a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone is used, where (3E,5Z,9E)-3,4-dehydrofarnesylacetone, (3Z,5Z,9E)-3,4-dehydrofarnesylacetone, (3E,5E,9Z)-3,4-dehydrofarnesylacetone, (3E,5Z,9Z)-3,4-dehydrofarnesyl-acetone, (3Z,5E,9Z)-3,4-dehydrofarnesylacetone and (3Z,5Z,9Z)-3,4-dehydrofarnesylacetone are only present in traces, i.e. in an amount of less than 0.5 mol-% each, more preferably in an amount of less than 0.1 mol-% each. Most preferably a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone is used, where neither (3E,5Z,9E)-3,4-dehydrofarnesylacetone nor (3Z,5Z,9E)-3,4-dehydrofarnesylacetone nor (3E,5E,9Z)-3,4-dehydrofarnesylacetone nor (3E,5Z,9Z)-3,4-dehydrofarnesylacetone nor (3Z,5E,9Z)-3,4-dehydrofarnesylacetone nor (3Z,5Z,9Z)-3,4-dehydrofarnesylacetone are present.

Catalyst

Preferably the catalyst comprises a metal selected from the group consisting of palladium, platinum, rhodium, iridium and nickel and mixtures thereof. More preferably the catalyst comprises a metal selected from the group consisting of palladium, platinum and mixtures thereof.

Even more preferably the catalyst is a metal selected from the group consisting of palladium, platinum and mixtures thereof. Most preferably the catalyst is palladium.

Of the catalysts described above, those catalysts are even more preferred that comprise a support/carrier being selected from the group consisting of carbon, graphite, inorganic oxides, inorganic carbonates, inorganic sulfates, as well as mixtures thereof where the active component (i.e. the metal) is deposited on. Preferred support/carrier materials are carbon, silicon dioxide, aluminum oxide and calcium carbonate, as well as mixtures thereof. An example for such mixtures are silica-alumina-mixtures.

The most preferred catalysts according to the present invention are palladium on carbon and palladium on alumina.

If the active metal is used on a support/carrier material, the active metal content is preferably in the range of from 0.5 to 20 weight%, more preferably in the range of from 2 to 5 weight%, most preferably in the range of approximately 5 weight%, based on the total weight of active metal and support.

The amount of the active component of the catalyst (being preferably a metal selected from the group consisting of palladium, platinum, rhodium, iridium and nickel and mixtures thereof) is preferably in the range of from 0.0001 to 1 weight%, more preferably in the range of from 0.001 to 0.5 weight%, most preferably in the range of from 0.01 to 0.1 weight%, based on the weight of the starting material, the mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone.

Reaction conditions

The hydrogenation reaction is preferably carried out at a temperature in the range of from 10 to 150°C, more preferably at a temperature in the range of from 20 to 100°C, most preferably at a temperature in the range of from 50 to 90°C.

The hydrogenation reaction is preferably carried out at a hydrogen pressure in the range of from 1 to 25 bar hydrogen absolute, more preferably at a hydrogen pressure in the range of from 2 to 10 bar hydrogen absolute, even more preferably at a hydrogen pressure in the range of from 2 to 6 bar hydrogen absolute, further more preferably at a hydrogen pressure in the range of from 2.5 to 4 bar hydrogen absolute most preferably at a hydrogen pressure of around 3 bar hydrogen absolute.

Solvent

The hydrogenation reaction can be carried without solvent or in the presence of an organic solvent. Preferably the reaction is carried out in an organic solvent.

The organic solvent is preferably selected from the group consisting of hydrocarbons, halogenated hydrocarbons, alcohols, ethers, esters, amides, nitriles and ketones and mixtures thereof. More preferred are C_4-C_{10} aliphatic hydrocarbons, C_6-C_{10} aromatic hydrocarbons, C_6-C_{10} aromatic hydrocarbons substituted with one or more C_1-C_4 linear alkyl groups or C_3-C_4 branched alkyl groups or halogens, C_1-C_4 linear alcohols or C_3-C_4 branched alcohols, acyclic and cyclic C_4-C_{10} ethers, C_3-C_{10} esters, C_3-C_{10} ketones and mixtures thereof.

Especially preferred organic solvents are selected from the group consisting of hexane, heptane, toluene, methanol, ethanol, n-propanol, 2-propanol, n-butanol, tetrahydrofuran, 2-methyl-tetrahydrofuran, dioxane, ethyl acetate, isopropyl acetate, acetone, and mixtures thereof. The most preferred solvent is heptane.

The amount of solvent is preferably in the range of from 0 to 100 volumes (0 = solvent free), more preferably in the range of from 0.1 to 10 volumes, most preferably in the range of from 1 to 5 volumes, based on the volume of the starting material, the mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone.

The invention is now further illustrated in the following non-limiting examples.

Examples

Standard Protocol for Hydrogenation Reactions

A mixture of the substrate dehydrofarnesylacetone (200 mg) (either a mixture of (3EZ,5EZ,9E) or (3EZ,5EZ,9EZ) isomers and solvent (2 g) is added to a glass reactor. The catalyst is added and the reactor is sealed. The mixture is purged three times with nitrogen (pressurise to 5 bar, then release) and three times with hydrogen (pressurise to 5 bar, then release). The reactor is heated to the desired temperature and then pressurised with hydrogen to the desired pressure. Stirring is started at 1000 rpm and the hydrogen uptake is recorded. After a total experiment time of 18 hours the reaction mixture is cooled to room temperature, the pressure is released and a sample taken for GC area% analysis.

Hydrogenation Results

The examples given below show that the hydrogenation of (3EZ,5EZ,9E) - dehydrofarnesylacetone proceeds faster than the hydrogenation of (3EZ,5EZ,9EZ)-dehydrofarnesylacetone.

The following catalysts are used:

- a 5% Pd/Al_2O_3 egg-shell catalyst with a BET surface area of 93 m^2/g and a pore volume of 0.3 ml/g as e.g. commercially available from Evonik under the tradename “5% Pd/Al_2O_3 E 213 R/D”;
- a 5% Pd/C as e.g. commercially available from Evonik under the tradename “5% Pd/C E 101 O/D”

Table 1: Catalyst used = 5% Palladium on Carbon as commercially available from Evonik

Example	Dehydro-farnesylacetone	Solvent	Amount of Catalyst [mg]	Temperature [°C]	Pressure [bar H_2]	Time to completion of reaction [min]	Conversion [%]	Yield of "C18-ketone" [%]
1	(3EZ,5EZ,9EZ)	Heptane	5	70	3	720	>99	99
2	(3EZ,5EZ,9E)	Heptane	5	70	3	630	>99	99

Table 2: Catalyst used = 5% Palladium on Alumina as commercially available from Evonik

Example	Dehydro-farnesylacetone	Solvent	Amount of Catalyst [mg]	Temperature [°C]	Pressure [bar H_2]	Time to completion of reaction [min]	Conversion [%]	Yield of "C18-ketone" [%]
3	(3EZ,5EZ,9EZ)	Heptane	5	60	6	680	>99	99
4	(3EZ,5EZ,9E)	Heptane	5	60	6	590	>99	99

Claims

1. A process for the manufacture of 6,10,14-trimethylpentadecan-2-one ("C18-ketone") comprising the step of hydrogenating a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon double bonds over carbon-oxygen double bonds.

2. The process according to claim 1, whereby the catalyst preferably comprises a metal selected from the group consisting of palladium, platinum, rhodium, iridium and nickel and mixtures thereof, more preferably whereby the catalyst comprises a metal selected from the group consisting of palladium, platinum and mixtures thereof, even more preferably whereby the catalyst is a metal selected from the group consisting of palladium, platinum and mixtures thereof, most preferably whereby the catalyst is palladium.

3. The process according to claim 1 and/or 2, whereby the catalyst preferably comprises a carrier/support being selected from the group consisting of carbon, graphite, inorganic oxides, inorganic carbonates, inorganic sulfates, as well as mixtures thereof where the metal is deposited on, more preferably the catalyst comprises a carrier/support being selected from the group consisting of carbon, silicon dioxide, aluminum oxide and calcium carbonate, as well as mixtures thereof, where the metal is deposited on.

4. The process according to one or more of claims 1 to 3, wherein the hydrogenation reaction is carried out at a temperature in the range of from 10 to 150°C, preferably at a temperature in the range of from 20 to 100°C, more preferably at a temperature in the range of from 50 to 90°C.

5. The process according to any one or more of claims 1 to 4, wherein the hydrogenation reaction is carried out at a hydrogen pressure in the range of from 1 to 25 bar hydrogen absolute, preferably at a hydrogen pressure in the range of from 2 to 10 bar hydrogen absolute, more preferably at a hydrogen pressure in the range of from 2 to 6 bar hydrogen absolute, even more preferably at a hydrogen pressure in the range of from 2.5 to 4 bar hydrogen absolute, most preferably at a hydrogen pressure of around 3 bar hydrogen absolute.

6. The process according to any one or more of claims 1 to 5, wherein the amount of the active component of the catalyst (being preferably a metal selected from the group consisting of palladium, platinum, rhodium, iridium and nickel and mixtures thereof) is in the range of from 0.0001 to 1.0 weight-%, preferably in the range of from 0.001 to 0.5 weight-%, more preferably in the range of from 0.01 to 0.1 weight-%, based on the weight of the starting material, the mixture of (3E,5E,9E)-3,4-dehydro-farnesyl-acetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone.

7. The process according to any one or more of claims 1 to 6, wherein the hydrogenation reaction is carried out in an organic solvent.

8. The process according to claim 7, wherein the organic solvent is selected from the group consisting of hydrocarbons, halogenated hydrocarbons, alcohols, ethers, esters, amides, nitriles and ketones and mixtures thereof, preferably wherein the organic solvent is selected from the group

consisting of C_4-C_{10} aliphatic hydrocarbons, C_6-C_{10} aromatic hydrocarbons, C_6-C_{10} aromatic hydrocarbons substituted with one or more C_1-C_4 linear alkyl groups or C_3-C_4 branched alkyl groups or halogens, C_1-C_4 linear alcohols or C_3-C_4 branched alcohols, acyclic and cyclic C_4-C_{10} ethers, C_3-C_{10} esters, C_3-C_{10} ketones and mixtures thereof.

9. The process according to claim 8, wherein the organic solvent is selected from the group consisting of hexane, heptane, toluene, methanol, ethanol, n-propanol, 2-propanol, n-butanol, tetrahydrofuran, 2-methyl-tetrahydrofuran, dioxane, ethyl acetate, isopropyl acetate, acetone, and mixtures thereof

10. The process according to any one or more of claims 7 to 9, wherein the amount of solvent is in the range of from 0.01 to 100 volumes, more preferably in the range of from 0.1 to 10 volumes, most preferably in the range of from 1 to 5 volumes, based on the volume of the starting material, the mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone.

11. The process according to any one or more of the preceding claims, wherein the starting material, the mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone, is obtained from (2E,6E)-farnesal either by a Wittig reaction or by an aldol condensation with acetone and a base or by a Knoevenagel reaction followed by decarboxylation or by Horner-Wadsworth-Emmons chemistry using a suitable phosphonate.

12. The process according to claim 11, wherein the (2E,6E)-farnesal is obtained from (2E,6E)-farnesol by selective oxidation.

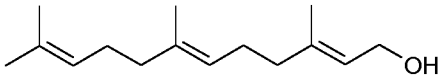
13. A process for the manufacture of isophytol comprising a process according to any one or more of the preceding claims.

14. A process for the manufacture of α-tocopherol or α-tocopheryl acetate comprising a process according to any one or more of the preceding claims.

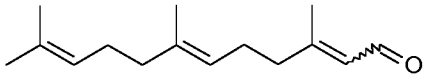
15. A process for the manufacture of (2E,6E)-farnesal by selective oxidation of (2E,6E)-farnesol.

16. A process for the manufacture of a mixture of (3E,5E,9E)-3,4-dehydrofarnesylacetone and (3Z,5E,9E)-3,4-dehydrofarnesylacetone comprising the step of either reacting (2E,6E)-farnesal by a Wittig reaction or by an aldol condensation with acetone and a base or by a Knoevenagel reaction followed by decarboxylation or by Horner-Wadsworth-Emmons chemistry using a suitable phosphonate.

Fig. 1

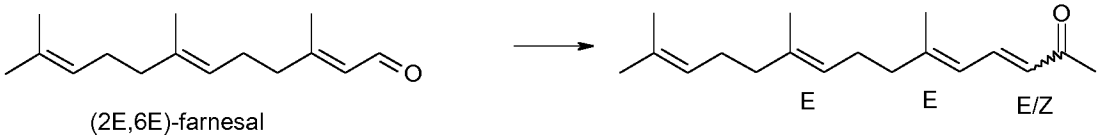


(2E,6E)-farnesol



(2E,6E)-farnesal

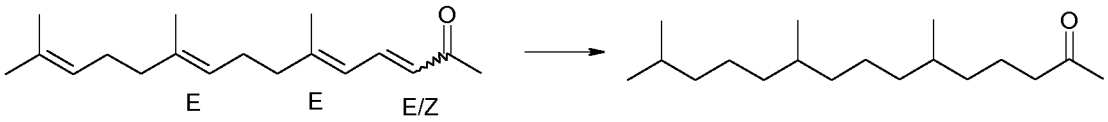
Fig. 2



(2E,6E)-farnesal

(3E/Z,5E,9E)-3,4-dehydro-farnesyl acetone

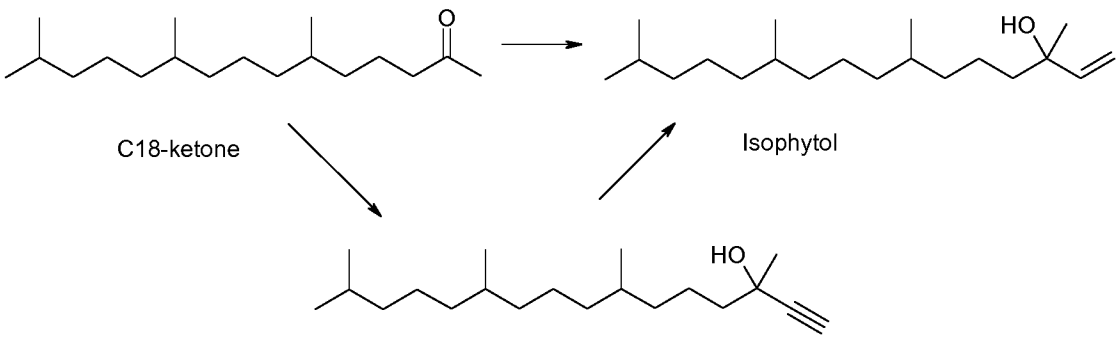
Fig. 3



(3E/Z,5E,9E)-3,4-dehydro-farnesyl acetone

C18-ketone

Fig. 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/080664

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C45/62 C07C49/04 C07C45/72 C07C49/203 C07C29/17
C07C29/38 C07C45/29 C07C45/38 C07C33/02 C07C33/042
C07C47/21 C07D311/72

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)
C07C C07D

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZOBRIST, F. ET AL.: "Zur Kenntnis der Sesquiterpene. 86. Mitteilung. Die Cyclisation von Farnesyliden-aceton", HELVETICA CHIMICA ACTA, vol. 32, no. 4, 1949, pages 1192-1197, XP55336924, ISSN: 0018-019X, DOI: 10.1002/hlca.19490320405 reaction scheme; page 1194; compounds II, VII page 1195, lines 12-15 page 1197, last paragraph ----- -/--	1-14,16

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2017	31/01/2017

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NAVES, Y.-R.: "Etudes sur les matières végétales volatiles XCII. Sur la farnésylidène-acétone", HELVETICA CHIMICA ACTA, vol. 32, no. 5, 1949, pages 1802-1805, XP55337115, ISSN: 0018-019X, DOI: 10.1002/hlca.19490320556 page 1803, paragraph 2 Farnésylidène-acétone; Octahydro-farnésilydène-acétone.; page 1804, paragraph 5-6	1-14,16
Y	DATABASE WPI Week 197911 1979 Thomson Scientific, London, GB; AN 1979-20563B XP002766181, -& JP S54 14906 A (KURARAY CO LTD) 3 February 1979 (1979-02-03) abstract page 1, column 1; compounds (IV-1) page 2, column 2	1-14,16
Y	SARYCHEVA, I.K. ET AL.: "New synthesis of 2,6,10,14-tetramethyl-15-hexadecen-14-ol, isophytol", ZHURNAL OBSHCHEI KHIMII, vol. 28, 1958, pages 647-651, XP009193141, page 647, last paragraph - page 648, paragraph 2; compounds (IV), (V) page 649, paragraph 4. - page 650, paragraph 1; compound (V)	1-14,16
Y	WO 2014/096098 A1 (DSM IP ASSETS B.V.) 26 June 2014 (2014-06-26) abstract figures 4,5	1-14,16
Y	US 5 955 636 A (KIDO YOICHI ET AL) 21 September 1999 (1999-09-21) Scheme; columns 1-2, paragraph 2.	1-14,16
X	CN 104 387 221 A (SHENZHEN MAIN LUCK PHARMACEUTICALS INC.) 4 March 2015 (2015-03-04)	15
Y	abstract; claims 1,2	1-14,16
Y	US 4 005 147 A (FISCHER ROMAN ET AL) 25 January 1977 (1977-01-25) column 10; example 25	1-14,16

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1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAKAJO, S. ET AL.: "Membrane properties of sodium 2- and 6-(poly)prenyl-substituted polyprenyl phosphates", NEW JOURNAL OF CHEMISTRY, vol. 25, no. 7, 2001, pages 917-929, XP55336851, ISSN: 1144-0546, DOI: 10.1039/b101802g page 920, column 1, paragraph 5; compounds 39,40,41 Scheme 1, step e; page 926; compounds 39,40 -----	15
A	KAKIUCHI, N. ET AL.: "Pd(II)-hydrotalcite-catalyzed selective oxidation of alcohols using molecular oxygen", BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 74, no. 1, 2001, pages 165-172, XP009171442, ISSN: 0009-2673, DOI: 10.1246/BCSJ.74.165 cited in the application page 168; example 11; table 3 -----	15

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/080664

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP S5414906 A	03-02-1979	JP S5414906 A	03-02-1979
		JP S6113453 B2	14-04-1986
WO 2014096098 A1	26-06-2014	CN 104854071 A	19-08-2015
		EA 201500665 A1	30-12-2015
		EP 2935185 A1	28-10-2015
		JP 2016506393 A	03-03-2016
		US 2015329456 A1	19-11-2015
		WO 2014096098 A1	26-06-2014
US 5955636 A	21-09-1999	AT 218527 T	15-06-2002
		CN 1178784 A	15-04-1998
		CN 1393435 A	29-01-2003
		DE 69712984 D1	11-07-2002
		DE 69712984 T2	16-01-2003
		DE 69731007 D1	04-11-2004
		DE 69731007 T2	23-02-2006
		EP 0816321 A1	07-01-1998
		EP 1122236 A2	08-08-2001
		US 5955636 A	21-09-1999
		US 6232506 B1	15-05-2001
CN 104387221 A	04-03-2015	NONE	
US 4005147 A	25-01-1977	BE 789849 A1	09-04-1973
		CH 603520 A5	15-08-1978
		DE 2150992 A1	19-04-1973
		FR 2156246 A1	25-05-1973
		GB 1390465 A	16-04-1975
		US 4005147 A	25-01-1977