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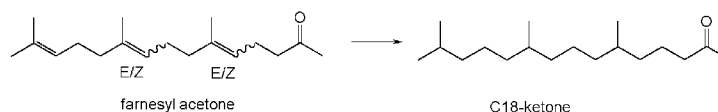
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(54) Title: PROCESS FOR THE MANUFACTURE OF 6,10,14-TRIMETHYLPENTADECAN-2-ONE

Fig. 1



(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 (5E, 9E)-farnesylacetone and (5Z, 9E)- farnesylacetone 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.

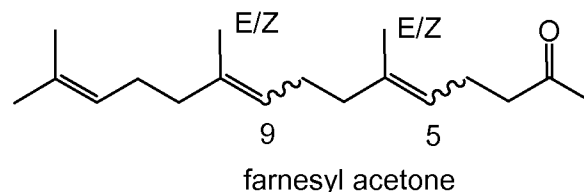


Process for the manufacture of 6,10,14-trimethylpentadecan-2-one

The present invention is directed to a process for the manufacture of 6,10,14-trimethylpentadecan-2-one ("C18-ketone") comprising the step of

- 5 hydrogenating a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone 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. More preferably the catalyst comprises a
- 10 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.

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- Surprisingly the inventors of the present invention discovered that when a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone is used to
- 20 obtain C18-ketone, the hydrogenation reaction is much faster than in the case, where a mixture of (5E,9E)-farnesylacetone, (5Z,9E)-farnesylacetone, (5E,9Z)-farnesylacetone and (5Z,9Z)-farnesylacetone 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
- 25 (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone, because the time savings have an immense influence on the overall production costs.

Manufacture of a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone

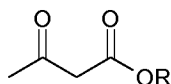
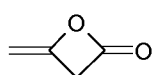
Such a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone can be
5 obtained by C3 elongation of (E)-nerolidol. An example is the reaction of (E)-
nerolidol with isopropenyl methyl ether or with isopropenyl ethyl ether in the
presence of a catalyst to the mixture of (5E,9E)-farnesylacetone and (5Z,9E)-
farnesylacetone. As catalyst either an acid or an ammonium salt can be used.

10 The process wherein the catalyst is an acid, preferably wherein the catalyst is
selected from the group consisting of phosphoric acid, sulfuric acid, p-
toluenesulfonic acid, methanesulfonic acid, trichloroacetic acid, oxalic acid
and mixtures thereof, is further described in WO 2009/019132 whose content is
hereby incorporated by reference.

15 The process wherein the catalyst is an ammonium salt, preferably wherein the
catalyst is selected from the group consisting of ammonium bromide,
ammonium chloride or di-ammonium phosphate, is further described in WO
2010/046199 whose content is hereby incorporated by reference.

20 Alternatively the C3 elongation of (E)-nerolidol may also be carried out
according to the process as described in JP-A 2002-121 165.

Furthermore the C3 elongation of (E)-nerolidol may also be carried out with
25 one of the following reagents according to processes known to the person
skilled in the art.



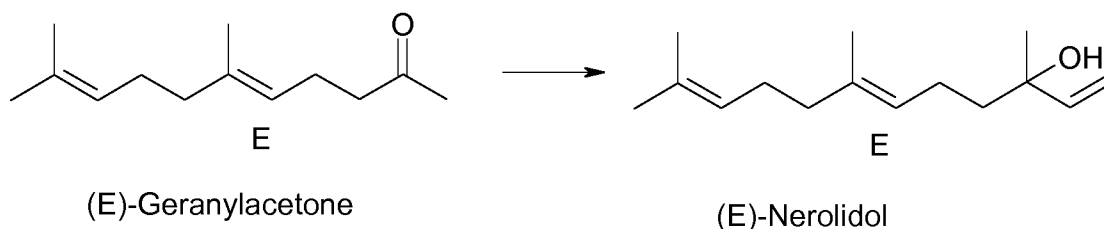
An example of a process where diketene is used is described in GB 788,301. An example of a process where acetoacetic esters are used (so-called “Carroll reaction”) is described in e.g. CN 102 115 437.

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Manufacture of (E)-nerolidol

The (E)-nerolidol used as starting material may come from natural sources or any other source or obtained by fermentation or may be synthesized synthetically and, if needed, separated from (Z)-nerolidol by any method known to the person skilled in the art.

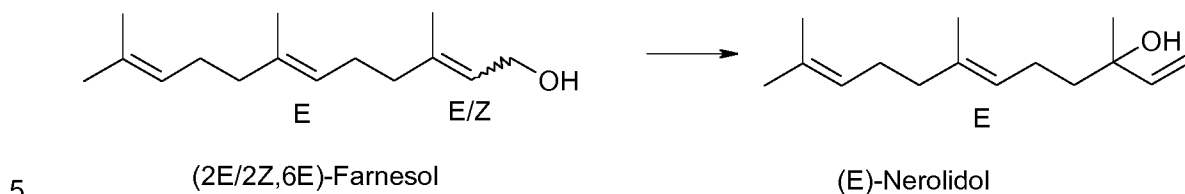
A further access to (E)-nerolidol is starting from (E)-geranylacetone which may itself be extracted from natural sources or any other source or obtained by fermentation or synthesized synthetically and, if needed, separated from (Z)-geranyl acetone by any method known to the person skilled in the art.



The (E)-geranyl acetone is then ethynylated according to any process known to the person skilled in the art and afterwards hydrogenated in presence of a Lindlar catalyst. The ethinylation may either be performed with acetylene, ammonia and a base, for example potassium hydroxide or with an ethynyl Grignard. Alternatively (E)-geranyl acetone may be reacted with vinyl Grignard according to a process known by the person skilled in the art.

Still another approach to (E)-nerolidol is by rearrangement of (2E,6E)-farnesol, (2Z,6E)-farnesol or any mixture thereof as e.g. described by S. Matsubara, T.

Okazoe, K. Oshima, K. Takai, H. Nozaki in *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844-849 and by J. Jacob, J. H. Espenson, J. H. Jensen, M. S. Gordon in *Organometallics* **1998**, *17*, 1835-1840.



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.

10

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

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The mixture of (2E,6E)-farnesol and (2Z,6E)-farnesol may itself be synthesized synthetically and, if needed, separated from (2E,6Z)- and (2Z,6Z)-farnesol by any method known to the person skilled in the art.

20

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

Since the mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone 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.

25

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

- 5 a) C3 prolonging (E)-nerolidol, preferably with isopropenyl methyl ether or with isopropenyl ethyl ether, in the presence of a catalyst to obtain a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone;
- b) hydrogenating a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon
10 double bonds over carbon-oxygen double bonds, to obtain 6,10,14-trimethylpentadecan-2-one;
- c1) ethynylating 6,10,14-trimethylpentadecan-2-one to obtain 3,7,11,15-tetramethylhexadec-1-yn-3-ol;
- d1) hydrogenating 3,7,11,15-tetramethylhexadec-1-yn-3-ol to isophytol.

15

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

- 20 a) C3 prolonging (E)-nerolidol, preferably with isopropenyl methyl ether or with isopropenyl ethyl ether, in the presence of a catalyst to obtain a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone;
- b) hydrogenating a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon
25 double bonds over carbon-oxygen double bonds, to obtain 6,10,14-trimethylpentadecan-2-one;
- c2) 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 its acetate, respectively, comprising the following steps:

- 5 a) C3 prolonging (E)-nerolidol, preferably with isopropenyl methyl ether or with isopropenyl ethyl ether, in the presence of a catalyst to obtain a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone;
- b) hydrogenating a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon
10 double bonds over carbon-oxygen double bonds, to obtain 6,10,14-trimethylpentadecan-2-one;
- c1) ethynylating 6,10,14-trimethylpentadecan-2-one to obtain 3,7,11,15-tetramethylhexadec-1-yn-3-ol;
- d1) hydrogenating 3,7,11,15-tetramethylhexadec-1-yn-3-ol to isophytol;
- 15 e) coupling isophytol with 2,3,5-trimethylhydroquinone or its acetate to obtain α -tocopherol or its acetate.

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

- a) C3 prolonging (E)-nerolidol, preferably with isopropenyl methyl ether or with isopropenyl ethyl ether, in the presence of a catalyst to obtain a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone;
- 25 b) hydrogenating a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone 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, to obtain 6,10,14-trimethylpentadecan-2-one;

- c2) vinylating 6,10,14-trimethylpentadecan-2-one by addition of a vinyl Grignard reagent to yield isophytol;
- e) condensing isophytol with 2,3,5-trimethylhydroquinone or its acetate to obtain α -tocopherol or its acetate.

5

The steps c1), d1), c2) and e) 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

10 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. 6,10,14-trimethylpenta-

15 decan-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

20 for the manufacture of 6,10,14-trimethylpentadecan-2-one ("C18-ketone") comprising the step of hydrogenating a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone 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 corresponds to step b) in

25 the process for the manufacture of isophytol and α -tocopherol or its acetate.

Starting material

Preferably a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone is used, where the content of (5E,9Z)-farnesylacetone and (5Z,9Z)-

30 farnesylacetone is below 43 mol-%, preferably below 20 mol-%, more preferably

below 10 mol-%, based on the total amount of the mixture. Thus, a mixture, where the amount of (5E,9Z) farnesylacetone and (5Z,9Z)-farnesylacetone is up to 43 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 a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone is used, where (5E,9Z)-farnesylacetone and (5Z,9Z)-farnesylacetone are only present in traces, i.e. in an amount of below 0.5 mol-% each, preferably in an amount of below 0.1 mol-% each. Most preferably a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone is used, where neither (5E,9Z)-farnesylacetone nor (5Z,9Z)-farnesylacetone 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.

More preferred catalysts are palladium on carbon, palladium on silica and palladium on alumina; most preferred is palladium on alumina.

- If the active component (i.e. the metal) is used on a support/carrier material,
- 5 the active component (i.e. the 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 the active component (i.e. the metal) and the support.
- 10 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
- 15 starting material, the mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone.

Reaction conditions

- 20 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.
- 25 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.

5 Solvent

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

- 10 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 C₄-C₁₀ aliphatic hydrocarbons, C₆-C₁₀ aromatic hydrocarbons, C₆-C₁₀ aromatic hydrocarbons substituted with one or more C₁-C₄ linear alkyl groups or C₃-C₄ branched alkyl groups or halogens, C₁-C₄ linear alcohols or C₃-C₄ branched alcohols, acyclic and
15 cyclic C₄-C₁₀ ethers, C₃-C₁₀ esters, C₃-C₁₀ 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-
20 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 =
25 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 (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone.

30

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

Examples

Standard Protocol for Hydrogenation Reactions

- 5 A mixture of the substrate farnesylacetone (20 g) and heptane (20 g) were added to a 125 ml steel autoclave. The catalyst was added and the reactor was sealed. The mixture was purged three times with nitrogen (pressurise to 5 bar, then release) and three times with hydrogen (pressurise to 5 bar, then release). The reactor was heated to the desired temperature and then
- 10 pressurised with hydrogen to the desired pressure. Stirring was started at 1000 rpm and the hydrogen uptake was recorded. After a total experiment time of 18 hours the reaction mixture was cooled to room temperature, the pressure was released and a sample taken for quantitative GC analysis.

15 Hydrogenation Results

“All isomers” means a mixture of (5E,9E)-farnesylacetone, (5Z,9E)-farnesylacetone, (5E,9Z)-farnesylacetone and (5Z,9Z)-farnesylacetone.

The following catalysts were used:

- 20 - a 5% Pd/Al₂O₃ egg-shell catalyst with a BET surface area of 93 m²/g and a pore volume of 0.3 ml/g as e.g. commercially available from Evonik under the tradename “5% Pd/Al₂O₃ E 213 R/D”;
- a 5% Pd/CaCO₃ egg-shell catalyst with a BET surface area of 8 m²/g, a bulk density of 0.37 kg/l, and whereby 50% of the particles have a size ≤ 5 μm as
- 25 e.g. commercially available from Evonik under the tradename “5% Pd/CaCO₃ E 407 R/D”.
- a 5% Palladium on carbon catalyst e.g. commercially available from Evonik under the tradename “5% Pd/C E 101 O/D”;
- a 5% Palladium on Silica catalyst as commercially available from Johnson
- 30 Matthey.

The results are summarized in tables 1-4.

Standard Protocol for Solvent-free Hydrogenation Reactions

- 5 A farnesylacetone (4 g) was added to a glass reactor. The catalyst was added and the reactor was sealed. The mixture was purged three times with nitrogen (pressurise to 5 bar, then release) and three times with hydrogen (pressurise to 5 bar, then release). The reactor was heated to the desired temperature and then pressurised with hydrogen to the desired pressure. Stirring was started at
- 10 1000 rpm and the hydrogen uptake was recorded. After a total experiment time of 18 hours the reaction mixture was cooled to room temperature, the pressure was released and a sample taken for GC analysis.

The results are summarized in tables 5-6.

15

Table 1: Catalyst used = Evonik E 101 O/D (5% Palladium on carbon)

Example	Farnesylacetone	Amount of catalyst [mg]	Temperature [°C]	Pressure [bar H ₂]	Time to completion of reaction [min]	Conversion [%]	Yield of "C18-ketone" [%]
1	All isomers	80	80	3	600	>99	91.5
2	(5E,9E)/(5Z,9E)	80	80	3	360	>99	95.9
3	All-isomers	80	60	21	200	>99	96.9
4	(5E,9E)/(5Z,9E)	80	60	21	65	>99	97.3

Table 2: Catalyst used = Evonik E 213 R/D (5% Palladium on Alumina)

Example	Farnesylacetone	Amount of catalyst [mg]	Temperature [°C]	Pressure [bar H ₂]	Time to completion of reaction [min]	Conversion [%]	Yield of "C18-ketone" [%]
5	All-isomers	160	80	3	290	>99	94.4
6	(5E,9E)/(5Z,9E)	160	80	3	130	>99	96.9

Table 3: Catalyst used = 5% Palladium on Silica as commercially available from Johnson Matthey

Example	Farnesylacetone	Amount of Catalyst [mg]	Temperature [°C]	Pressure [bar H ₂]	Time to completion of reaction [min]	Conversion [%]	Yield of "C18-ketone" [%]
7	All-isomers	800	80	3	230	>99	91.5
8	(5E,9E)/(5Z,9E)	800	80	3	170	>99	91.5

Table 4: Catalyst used = Evonik E 407 R/D (5% Palladium on Calcium Carbonate)

Example	Farnesylacetone	Amount of catalyst [mg]	Temperature [°C]	Pressure [bar H ₂]	Total Reaction Time [min]	Conversion [%]	Yield of "C18-ketone" [%]
9	All-isomers	160	70	21	900	>99	35.0
10	(5E,9E)/(5Z,9E)	160	70	21	900	>99	70.7

In both examples 9 and 10 no complete hydrogenation was achieved with 900 minutes. Therefore, samples were taken after this period of time and analysed.

Table 5: Catalyst used = Evonik E 101 O/D (5% Palladium on carbon)

Example	Farnesylacetone	Amount of catalyst [mg]	Temperature [°C]	Pressure [bar H ₂]	Time to completion of reaction [min]	Conversion [%]	Content of "C18-ketone" [GC area%]
11	All isomers	20	70	3	-	>99	82
12	(5E,9E)/(5Z,9E)	20	70	3	1260	>99	97
13	All-isomers	20	50	11	-	>99	64
14	(5E,9E)/(5Z,9E)	20	50	11	300	>99	99

For examples 11 and 13, the reactions were not complete after 1300 minutes and so were stopped and analysed. The starting material was fully converted but a mixture of the desired C18-ketone and intermediate products was found.

Table 6: Catalyst used = Evonik E 213 R/D (5% Palladium on Alumina)

Example	Farnesyl-acetone	Amount of catalyst [mg]	Temperature [°C]	Pressure [bar H ₂]	Time to completion of reaction [min]	Conversion [%]	Content of "C18-ketone" [GC area%]
15	All-isomers	40	70	3	960	>99	64
16	(5E,9E)/(5Z,9E)	40	70	3	540	>99	99
17	All-isomers	60	50	10	300	>99	99
18	(5E,9E)/(5Z,9E)	60	50	10	180	>99	99

For Example 18, 4.0 g of (5E,9E)/(5Z,9E) farnesylacetone (90% purity) gave, after filtration of the catalyst, 86% yield of C18-ketone.

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Claims

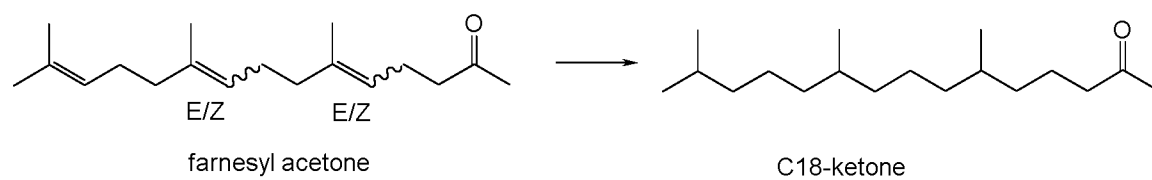
1. A process for the manufacture of 6,10,14-trimethylpentadecan-2-one (“C18-ketone”) comprising the step of hydrogenating a mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone with hydrogen in the presence of a catalyst, whereby the catalyst is capable of preferentially hydrogenating carbon-carbon double bonds over carbon-oxygen double bonds.
10
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.
15
20
3. The process according to claim 1 and/or 2, whereby the metal is preferably deposited on a carrier/support being selected from the group consisting of carbon, graphite, inorganic oxides, inorganic carbonates, inorganic sulfates, as well as mixtures thereof, more preferably the metal is deposited on a carrier/support being selected from the group consisting of carbon, silicon dioxide, aluminum oxide and calcium carbonate, as well as mixtures thereof.
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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.
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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 (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone.
 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, preferably 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 C₄-C₁₀ aliphatic hydrocarbons, C₆-C₁₀ aromatic hydrocarbons, C₆-C₁₀ aromatic hydrocarbons substituted with one or more C₁-C₄ linear alkyl groups or C₃-C₄ branched alkyl groups or halogens, C₁-C₄ linear alcohols or C₃-C₄ branched alcohols, acyclic and cyclic C₄-C₁₀ ethers, C₃-C₁₀ esters, C₃-C₁₀ ketones and mixtures thereof, more preferably wherein the organic solvent is selected from the group consisting of hexane, heptane, toluene, methanol, ethanol, n-

- 5 propanol, 2-propanol, n-butanol, tetrahydrofuran, 2-methyl-
tetrahydrofuran, dioxane, ethyl acetate, isopropyl acetate, acetone, and
mixtures thereof.
8. The process according to claim 7, wherein the amount of solvent is in
10 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
(5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone.
- 15 9. The process according to any one or more of the preceding claims,
wherein the starting material, the mixture of (5E,9E)-farnesylacetone and
(5Z,9E)-farnesylacetone, is obtained by reacting (E)-nerolidol with
isopropenyl methyl ether or with isopropenyl ethyl ether in the presence
of a catalyst.
- 20 10. The process according to claim 9, wherein the catalyst is an acid,
preferably wherein the catalyst is selected from the group consisting of
phosphoric acid, sulfuric acid, p-toluenesulfonic acid, methanesulfonic
acid, trichloroacetic acid, oxalic acid and mixtures thereof.
- 25 11. The process according to claim 9, wherein the catalyst is an ammonium
salt, preferably wherein the catalyst is selected from the group consisting
of ammonium bromide, ammonium chloride or di-ammonium phosphate.
- 30 12. The process according to any one or more of the preceding claims,
wherein the mixture of (5E,9E)-farnesylacetone and (5Z,9E)-
farnesylacetone contains (5E,9Z)-farnesylacetone and (5Z,9Z)-
farnesylacetone, and wherein the content of (5E,9Z)-farnesylacetone and
(5Z,9Z)-farnesylacetone is below 43 mol-%, preferably below 20 mol-%,

- 5 more preferably below 10 mol-%, based on the total amount of the mixture.
13. The process according to claim 11, wherein the mixture of (5E,9E)-farnesylacetone and (5Z,9E)-farnesylacetone contains neither (5E,9Z)-
10 farnesylacetone nor (5Z,9Z)-farnesylacetone.
14. A process for the manufacture of isophytol comprising a process according to any one or more of the preceding claims.
- 15 15. A process for the manufacture of α -tocopherol or its acetate comprising a process according to any one or more of the preceding claims.

Fig. 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/080661

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D311/72 C07C29/17 C07C29/42 C07C45/62 C07C49/04 C07C33/03 ADD. 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) C07D C07C 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		
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Y	the whole document	9-11, 15
Y	US 2 411 969 A (PAUL KARRER ET AL) 3 December 1946 (1946-12-03) the whole document	15
	----- -/-	
☒ Further documents are listed in the continuation of Box C. ☒ See patent family 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 application or patent 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 6 March 2017		Date of mailing of the international search report 14/03/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Kleidernigg, Oliver

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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