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(54) Title: PROCESS FOR THE MANUFACTURE OF 6,10-DIMETHYLUNDECAN-2-ONE, ISOPHYTOL, ALPHA-TOCOPHEROL (ACETATE) AND FURTHER INTERMEDIATES THEREOF

(57) Abstract: The present invention is directed to a process for the manufacture of 6,10-dimethylundecan-2-one comprising the step of hydrogenating (5Z)-nerylacetone 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. The 6,10-dimethylundecan-2-one obtained according to the process of the present invention may be used as starting material for isophytol and α-tocopherol (acetate) via 3,7,11-trimethyl-dodec-1-en-3-ol ("tetrahydronerolidol"; THNL), 6,10,14-trimethylpentadec-5-en-2-one ("(5E/5Z)-5,6-dehydro-C18-ketone") and 6,10,14-pentadecane-2-one ("C18-ketone") or alternatively via 3,7,11-trimethyl-dodec-1-yn-3-ol, 6,10,14-trimethylpentadec-4,5-dien-2-one ("C18-allene-ketone") and 6,10,14-pentadecane-2-one ("C18-ketone"). Thus, the present invention is also directed to such processes which comprise the step of hydrogenating (5Z)-nerylacetone according to the process of the present invention.

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Process for the manufacture of 6,10-dimethylundecan-2-one, isophytol, α-tocopherol (acetate) and further intermediates thereof

The present invention is directed to a process for the manufacture of 6,10-dimethylundecan-2-one comprising the step of hydrogenating (5Z)-neryl-acetone (=(Z)-6,10-dimethylundeca-5,9-dien-2-one) 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 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 (5Z)-nerylacetone is used as starting material for the synthesis of 6,10-dimethylundecan-2-one, the hydrogenation reaction is much faster than in the case, where a mixture of (5Z)-nerylacetone (= (Z)-6,10-dimethylundeca-5,9-dien-2-one) and (5E)-geranylacetone (=(E)-6,10-dimethylundeca-5,9-dien-2-one) is used. Therefore, it is advantageous, especially for an industrial process, where hundreds of tons are produced, to use as starting material for obtaining 6,10-dimethylundecan-2-one cis/trans-isomeric pure (5Z)-nerylacetone, because the time savings have an immense influence on the overall production costs.

The 6,10-dimethylundecan-2-one obtained according to the process of the present invention may be used as starting material for isophytol and α-tocopherol (acetate) via 3,7,11-trimethyl-dodec-1-en-3-ol ("tetrahydro-nerolidol"; THNL), 6,10,14-trimethylpentadec-5-en-2-one ("(5E/5Z)-5,6-dehydro-C18-ketone") and 6,10,14-pentadecane-2-one or alternatively via

3,7,11-trimethyl-dodec-1-yn-3-ol, 6,10,14-trimethylpentadec-4,5-dien-2-one ("C18-allene-ketone") and 6,10,14-pentadecane-2-one ("C18-ketone"). Thus, the present invention is also directed to such processes which comprise the step of hydrogenating (5Z)-nerylacetone according to the process of the present invention.

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-dimethylundecan-2-one is the starting material for isophytol. Thus, an improvement in the synthesis of 6,10-dimethylundecan-2-one 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-dimethylundecan-2-one comprising the step of hydrogenating (5Z)-nerylacetone 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. 1**). This process corresponds to the first step (step a)) in the process for the manufacture of 3,7,11-trimethyl-dodec-1-en-3-ol ("tetrahydronerolidol"; THNL), 3,7,11-trimethyl-dodec-1-yn-3-ol, 6,10,14-trimethylpentadec-4,5-dien-2-one ("C18-allene-ketone"), 6,10,14-trimethylpentadec-5-en-2-one, 6,10,14-pentadecane-2-one ("C18-ketone"), isophytol and α-tocopherol or its acetate.

Starting material

The (5Z)-nerylacetone 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 (5E)-geranylacetone by any method known to the person skilled in the art.

Nerylacetone may for example be synthesized starting from linalool (see Fig. 9) in a Carroll reaction as described in CN-A 102 115 437, WO 2010/046199, DE 198 40 746 and JP-A 2002 121 165 or by reaction with isopropenyl alkyl ethers as described in DE 196 49 564 or by reaction with the dimethylacetal of acetone as described by P. Baeckstroem and L. Li in Tetrahedron 1991, 47(32), 6521-6532. An alternative synthesis is disclosed by Sato, Kikumasa; Miyamoto, Osamu; Inoue, Seiichi; Kobayashi, Toru; and Furusawa, Fumio in Chemistry Letters, 1981, 1711-14 ("A stereoselective formation of (Z)-2-methyl-2-alkenol by the Wittig reaction: its application to a synthesis of nerylacetone and (Z,Z)-farnesylacetone").

It is preferred that the hydrogenation of (5Z)-nerylacetone is performed in the presence of (5E)-geranylacetone of below 10 mol-%, preferably below 5 mol-%, more preferably below 2 mol-%, based on the total amount of (5E)-geranylacetone and (5Z)-nerylacetone. Thus, a mixture of (5E)-geranylacetone and (5Z)-nerylacetone, where the amount of (5E)-geranylacetone is up to 10 mol-%, based on the total amount of the mixture, may also be used successfully.

More preferably, however, the hydrogenation of (5Z)-nerylacetone is performed using (5Z)-nerylacetone as cis/trans isomeric pure (5Z)-nerylacetone.

The term "cis/trans isomeric pure", as used in this document, refers to the purity in respect to the amount of the isomers having different cis/trans (or E/Z) configuration at the carbon-carbon double bond as sole difference. A compound considered as "cis/trans isomeric pure" has more than 99-mol % of the compound with the indicated configuration.

In other words, "cis/trans isomeric pure (5Z)-nerylacetone" is a mixture of as more than 99 mol-% (5Z)-nerylacetone and less than 1 mol-% of (5E)-geranylacetone.

Most preferred, the hydrogenation of using (5Z)-nerylacetone is performed in the absence of (5E)-geranylacetone.

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.

If the active metal catalyst is used on a support/carrier material, the active metal catalyst 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 mass of active metal catalyst 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 (5Z)-nerylacetone.

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 out 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 organic solvents are heptane and ethanol.

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 (5Z)-nerylacetone.

Process for the manufacture of 3,7,11-trimethyl-dodec-1-yn-3-ol

The 6,10-dimethylundecan-2-one obtained according to the process of the present invention is ethynylated according to any process known to the person skilled in the art to yield 3,7,11-trimethyl-dodec-1-yn-3-ol (see **Fig. 6**). The ethynylation may either be performed with acetylene, ammonia and a base, for example potassium hydroxide, or with an ethynyl Grignard.

Thus, the present invention is directed to a process for the manufacture of 3,7,11-trimethyl-dodec-1-yn-3-ol comprising the following steps:

a) hydrogenating (5Z)-nerylacetone with hydrogen in the presence of a catalyst to obtain 6,10-dimethylundecan-2-one according to the process of the present invention;

b1) ethynylating 6,10-dimethylundecan-2-one obtained in step a) to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol.

Process for the manufacture of 3,7,11-trimethyl-dodec-1-en-3-ol ("tetrahydronerolidol"; THNL)

The 3,7,11-trimethyl-dodec-1-yn-3-ol is then hydrogenated in presence of a Lindlar catalyst to THNL. Alternatively 6,10-dimethylundecan-2-one may be reacted with vinyl Grignard according to a process known by the person skilled in the art to THNL (**see Fig. 2**).

Thus, the present invention is directed to a process for the manufacture of 3,7,11-trimethyl-dodec-1-en-3-ol comprising the following steps:

a) hydrogenating (5Z)-nerylacetone with hydrogen in the presence of a catalyst to obtain 6,10-dimethylundecan-2-one according to the process of the present invention;

b1) ethynylating 6,10-dimethylundecan-2-one to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol;

c1) hydrogenating 3,7,11-trimethyl-dodec-1-yn-3-ol to obtain 3,7,11-trimethyl-dodec-1-en-3-ol.

A further object of the present invention is also a process for the manufacture of 3,7,11-trimethyl-dodec-1-en-3-ol comprising the following steps:

a) hydrogenating (5Z)-nerylacetone 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-dimethylundecan-2-one;

b2) vinylating 6,10-dimethylundecan-2-one by addition of a vinyl Grignard reagent to yield 3,7,11-trimethyl-dodec-1-en-3-ol.

That means that in the process for the manufacture of 3,7,11-trimethyl-dodec-1-en-3-ol a step b2) can be performed instead of performing step b1) and c1) to obtain 3,7,11-trimethyl-dodec-1-en-3-ol.

Process for the manufacture of a mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one

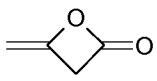
Such a mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one can be obtained by C3 elongation of tetrahydronerolidol ("THNL") (**see Fig. 3**). An example is the reaction of THNL with isopropenyl methyl ether or with isopropenyl ethyl ether in the presence of a catalyst to the mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one. As catalyst either an acid or an ammonium salt can be used.

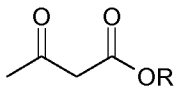
The process wherein the catalyst is an acid, preferably wherein the catalyst is selected from the group consisting of phosphoric acid, sulfuric acid, p-toluenesulfonic acid, methanesulfonic acid, trichloroacetic acid, oxalic acid and mixtures thereof, is further described in WO 2009/019132 whose content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

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.

Alternatively the C3 elongation of THNL may also be carried out according to the process as described in JP-A 2002-121 165.

Furthermore the C3 elongation of THNL may also be carried out with one of the following reagents according to processes known to the person skilled in the art.





Process for the manufacture of 6,10,14-trimethylpentadec-4,5-dien-2-one

6,10,14-trimethylpentadec-4,5-dien-2-one can be obtained by C3 elongation of 3,7,11-trimethyl-dodec-1-yn-3-ol as obtained according to the process of the present invention. The C3 elongation is preferably carried out by reacting 3,7,11-trimethyl-dodec-1-yn-3-ol with isopropenyl methyl ether or with isopropenyl ethyl ether in the presence of a catalyst, to obtain 6,10,14-trimethylpentadec-4,5-dien-2-one (see **Fig. 7**).

As catalyst either an acid or an ammonium salt can be used.

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 and mixtures thereof, is further described in WO 2008/092655 whose content is hereby incorporated by reference.

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

The present invention is also directed to a process for the manufacture of 6,10,14-trimethylpentadecan-2-one comprising the following steps:

a) hydrogenating (5Z)-nerylacetone with hydrogen in the presence of a catalyst to obtain 6,10-dimethylundecan-2-one according to the process of the present invention;

b1) ethynylating 6,10-dimethylundecan-2-one obtained in step a) to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol (see **Fig. 6**);

c1) hydrogenating 3,7,11-trimethyl-dodec-1-yn-3-ol obtained in step b1) to obtain 3,7,11-trimethyl-dodec-1-en-3-ol (tetrahydronerolidol);

C3 elonging the thus obtained 3,7,11-trimethyl-dodec-1-en-3-ol, preferably by reacting it with isopropenyl methyl ether or with isopropenyl ethyl ether in the presence of a catalyst, to obtain a mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one;

hydrogenating the thus obtained mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one with hydrogen in the presence of a catalyst to obtain 6,10,14-trimethylpentadecan-2-one.

Instead of steps b1) and c1) the following step can also be performed:

b2) vinylating 6,10-dimethylundecan-2-one obtained in step a) by addition of a vinyl Grignard reagent to yield 3,7,11-trimethyl-dodec-1-en-3-ol (see **Fig. 2**).

The present invention is also directed to an alternative process for the manufacture of 6,10,14-trimethylpentadecan-2-one comprising the following steps:

a) hydrogenating (5Z)-nerylacetone with hydrogen in the presence of a catalyst to obtain 6,10-dimethylundecan-2-one according to the process of the present invention;

b1) ethynylating 6,10-dimethylundecan-2-one obtained in step a) to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol;

C3 elonging 3,7,11-trimethyl-dodec-1-yn-3-ol as obtained in step b1), preferably by reacting it with isopropenyl methyl ether or with isopropenyl ethyl ether in the presence of a catalyst, to obtain 6,10,14-trimethylpentadec-4,5-dien-2-one (see **Fig. 7**);

hydrogenating the thus obtained 6,10,14-trimethylpentadec-4,5-dien-2-one with hydrogen in the presence of a catalyst to obtain 6,10,14-trimethylpentadecan-2-one (see **Fig. 8**).

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

Since 6,10,14-trimethylpentadecan-2-one ("C18-ketone") is an important starting material for isophytol (**see Fig. 5**), 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.

Thus, the present invention is directed to a process for the manufacture of isophytol comprising the following steps:

a) hydrogenating (5Z)-nerylacetone 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-dimethylundecan-2-one according to the process of the present invention as described in detail above;
b1) ethynylating 6,10-dimethylundecan-2-one to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol;
c1) hydrogenating 3,7,11-trimethyl-dodec-1-yn-3-ol with hydrogen in the presence of a Lindlar catalyst to obtain 3,7,11-trimethyl-dodec-1-en-3-ol;
d) C3 elonging 3,7,11-trimethyl-dodec-1-en-3-ol, preferably with isopropenyl methyl ether or with isopropenyl ethyl ether, in the presence of a catalyst to obtain a mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one;
e) hydrogenating the mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one with hydrogen in the presence of a catalyst to obtain 6,10,14-trimethylpentadecan-2-one;
f1) ethynylating 6,10,14-trimethylpentadecan-2-one to obtain 3,7,11,15-tetramethylhexadec-1-yn-3-ol;
g1) hydrogenating 3,7,11,15-tetramethylhexadec-1-yn-3-ol with hydrogen in the presence of a Lindlar catalyst to obtain isophytol.

The steps b1), c1), d), e), f1) and g1) may be carried out according to methods known to the person skilled in the art. The ethynylation (steps b1) and f1)) 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 (steps c1) and g1)).

Instead of steps b1) and c1) a step b-c2) may be performed as follows: vinylating 6,10-dimethylundecan-2-one by addition of a vinyl Grignard reagent to yield 3,7,11-trimethyl-dodec-1-en-3-ol.

Instead of steps f1) and g1) a step f-g2) may be performed as follows: Vinylating 6,10,14-trimethylpentadecan-2-one to obtain isophytol.

Alternatively isophytol may be manufactured by a process comprising the steps as follows which is also an embodiment of the present invention:

a) hydrogenating (5Z)-nerylacetone with hydrogen in the presence of a catalyst to obtain 6,10-dimethylundecan-2-one according to the process of the present invention;

b1) ethynylating 6,10-dimethylundecan-2-one obtained in step a) to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol;

d2) C3 elonging 3,7,11-trimethyl-dodec-1-yn-3-ol obtained in step b1), preferably with isopropenyl methyl ether or with isopropenyl ethyl ether, in the presence of a catalyst to obtain 6,10,14-trimethylpentadec-4,5-dien-2-one;

e2) hydrogenating 6,10,14-trimethylpentadec-4,5-dien-2-one obtained in step d2) with hydrogen in the presence of a catalyst to obtain 6,10,14-trimethylpentadecan-2-one;

f1) ethynylating 6,10,14-trimethylpentadecan-2-one obtained in step e2) to obtain 3,7,11,15-tetramethylhexadec-1-yn-3-ol;

g1) hydrogenating 3,7,11,15-tetramethylhexadec-1-yn-3-ol obtained in step f1) with hydrogen in the presence of a Lindlar catalyst to obtain 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:

i) manufacturing isophytol as described above;

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

Step ii) may also be performed according to any method known in the prior art.

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

Examples

Standard Protocol for Hydrogenation Reactions

A mixture of the substrate nerylacetone/geranylacetone (20 g) (either cis/trans isomeric pure (5Z)-nerylacetone or a mixture of (5E)-geranylacetone and (5Z)-nerylacetone) and solvent (20 g) is added to a 125 ml steel autoclave. 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 quantitative GC analysis.

Hydrogenation Results

The examples given below show that the hydrogenation of (5Z)-nerylacetone alone proceeds faster than the hydrogenation of a mixture of (5E)-geranylacetone and (5Z)-nerylacetone. The sample of cis/trans isomeric pure (5Z)-nerylacetone used had less than 1% of (5E)-geranylacetone.

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	Neryl-/Geranyl-acetone	Solvent	Amount of Catalyst [mg]	Temperature [°C]	Pressure [bar H_2]	Time to completion of reaction [min]	Conversion [%]	Yield of "C13-ketone" [%]
1	E/Z-isomers	Heptane	60	80	3	310	>99	>99
2	Z-isomer only*	Heptane	60	80	3	150	>99	97
3	E/Z-isomers	Ethanol	30	80	6	270	>99	99
4	Z-isomer*	Ethanol	30	80	6	160	>99	99
5	E/Z-isomers	Heptane	60	80	2	1700	>99	97
6	Z-isomer*	Heptane	60	80	2	1200	>99	>99

*cis/trans isomeric pure (5Z)-nerylacetone

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

Example	Neryl-/Geranyl-acetone	Solvent	Amount of Catalyst [mg]	Temperature [°C]	Pressure [bar H_2]	Time to completion of reaction [min]	Conversion [%]	Yield of "C13-ketone" [%]
7	E/Z-isomers	Heptane	120	80	3	330	>99	98
8	Z-isomer*	Heptane	120	80	3	180	>99	98
9	E/Z-isomers	Ethanol	120	80	6	600	>99	97
10	Z-isomer*	Ethanol	120	80	6	550	>99	99

*cis/trans isomeric pure (5Z)-nerylacetone

Claims

1. A process for the manufacture of 6,10-dimethylundecan-2-one comprising the step of hydrogenating (5Z)-nerylacetone 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 comprises preferably 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 (5Z)-nerylacetone.

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 (5Z)-nerylacetone.

11. A process for the manufacture of 3,7,11-trimethyl-dodec-1-yn-3-ol comprising the following steps:

a) hydrogenating (5Z)-nerylacetone with hydrogen in the presence of a catalyst to obtain 6,10-dimethylundecan-2-one according to a process according to any one or more of claims 1 to 10;

b1) ethynylating 6,10-dimethylundecan-2-one obtained in step a) to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol.

12. A process for the manufacture of 3,7,11-trimethyl-dodec-1-en-3-ol comprising the following steps:

a) hydrogenating (5Z)-nerylacetone with hydrogen in the presence of a catalyst to obtain 6,10-dimethylundecan-2-one according to a process according to any one or more of claims 1 to 10;

b1) ethynylating 6,10-dimethylundecan-2-one obtained in step a) to obtain 3,7,11-trimethyl-dodec-1-yn-3-ol;

c1) hydrogenating 3,7,11-trimethyl-dodec-1-yn-3-ol obtained in step b1) to obtain 3,7,11-trimethyl-dodec-1-en-3-ol.

13. The process for the manufacture of 3,7,11-trimethyl-dodec-1-en-3-ol according to claim 12, wherein instead of steps b1) and c1) the following step is performed:

b2) vinylating 6,10-dimethylundecan-2-one obtained in step a) by addition of a vinyl Grignard reagent to yield 3,7,11-trimethyl-dodec-1-en-3-ol.

14. A process for the manufacture of a mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one comprising the step of C3 elonging 3,7,11-trimethyl-dodec-1-en-3-ol as obtained according to a process as in claim 12 or 13, preferably by reacting it with isopropenyl methyl ether or with isopropenyl ethyl ether in the presence of a catalyst, to obtain a mixture of (5E)-6,10,14-trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one.

15. A process for the manufacture of 6,10,14-trimethylpentadec-4,5-dien-2-one comprising the step of C3 elonging 3,7,11-trimethyl-dodec-1-yn-3-ol as obtained according to a process as in claim 11, preferably by reacting it with isopropenyl methyl ether or with isopropenyl ethyl ether in the presence of a catalyst, to obtain 6,10,14-trimethylpentadec-4,5-dien-2-one.

16. The process according to claim 14, wherein the C3 elongation is carried out by reaction with isopropenyl methyl ether or with isopropenyl ethyl ether in the presence of a catalyst, and 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.

17. A process for the manufacture of 6,10,14-trimethylpentadecan-2-one comprising the step of either hydrogenating the mixture of (5E)-6,10,14-

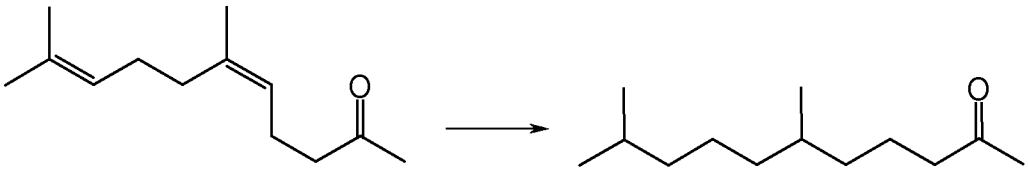
trimethylpentadec-5-en-2-one and (5Z)-6,10,14-trimethylpentadec-5-en-2-one as obtained according to a process as claimed in claim 14 with hydrogen in the presence of a catalyst to obtain 6,10,14-trimethylpentadecan-2-one, or hydrogenating 6,10,14-trimethylpentadec-4,5-dien-2-one as obtained according to a process as claimed in claim 15 with hydrogen in the presence of a catalyst to obtain 6,10,14-trimethylpentadecan-2-one.

18. A process for the manufacture of isophytol comprising the following steps:
f1) ethynylating 6,10,14-trimethylpentadecan-2-one as obtained according to a process as claimed in claim 17 to obtain 3,7,11,15-tetramethylhexadec-1-yn-3-ol;
g1) hydrogenating 3,7,11,15-tetramethylhexadec-1-yn-3-ol obtained in step f1) with hydrogen in the presence of a Lindlar catalyst to obtain isophytol.

19. The process according to claim 18, whereby instead of steps f1) and g1) a step f-g2) may be performed as follows: vinylating 6,10,14-trimethylpentadecan-2-one obtained according to a process as claimed in claim 17 to obtain isophytol.

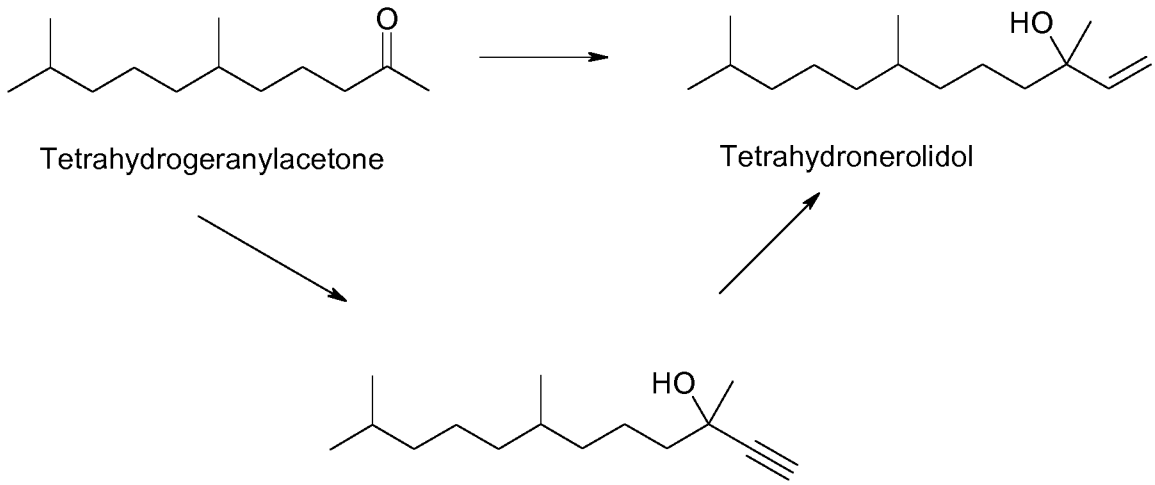
20. A process for the manufacture of α-tocopherol and its acetate, respectively, comprising the following steps:
i) manufacturing isophytol according to claim 18 or 19;
ii) coupling isophytol as obtained in step i) with 2,3,5-trimethylhydroquinone or 2,3,5-trimethylhydroquinone acetate to obtain α-tocopherol or its acetate.

Fig. 1



(5Z)-Nerylacetone Tetrahydrogeranylacetone

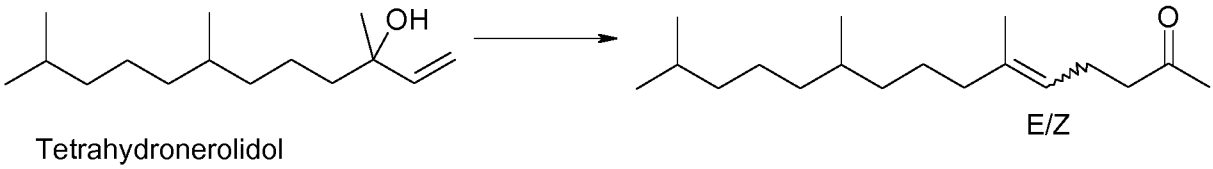
Fig. 2



Tetrahydrogeranylacetone Tetrahydronerolidol

3,7,11-trimethyl-1-dodecyne-3-ol

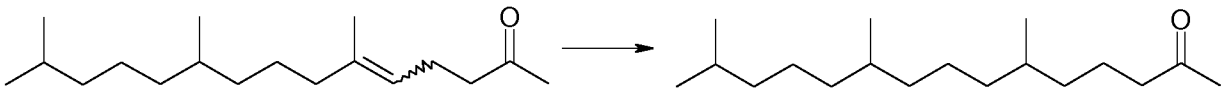
Fig. 3



Tetrahydronerolidol

5,6-Dehydro-C18-ketone

Fig. 4



5,6-Dehydro-C18-ketone

C18-ketone

Fig. 5

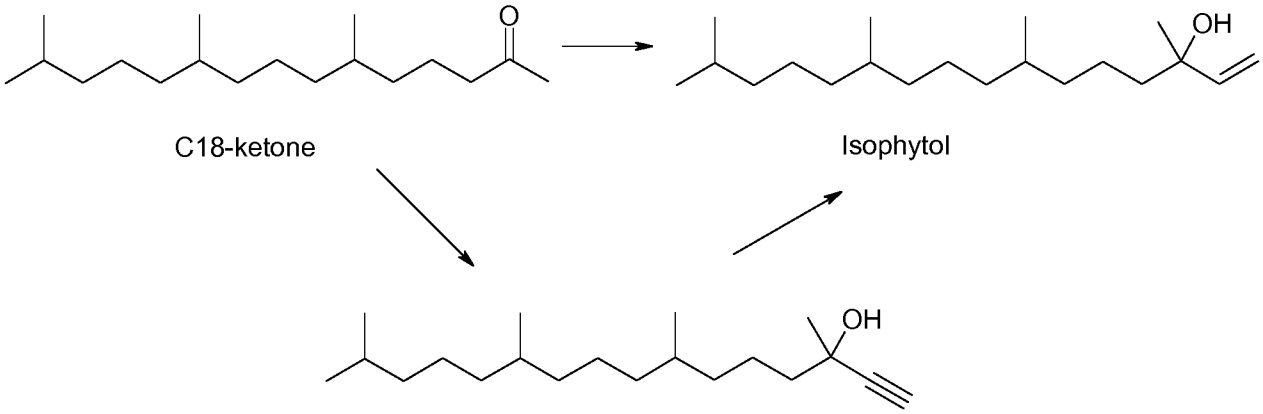
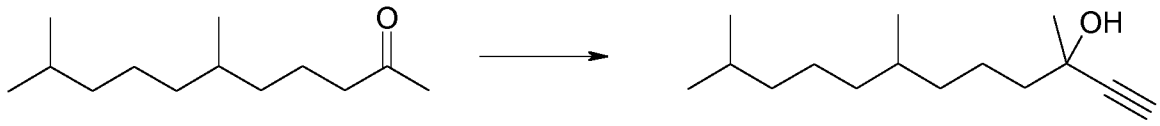


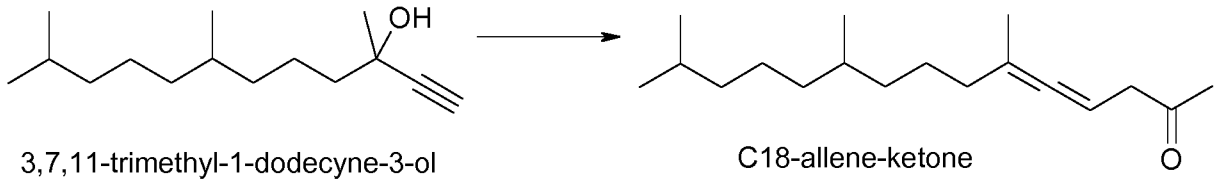
Fig. 6



Tetrahydrogeranylacetone

3,7,11-trimethyl-1-dodecyne-3-ol

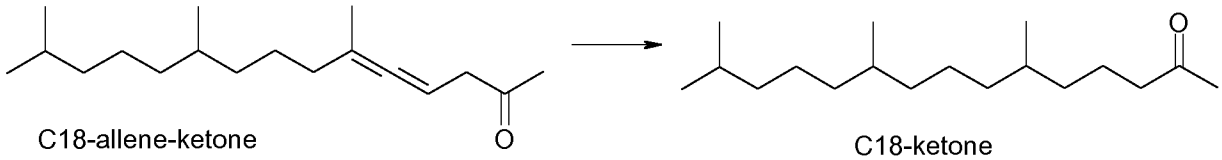
Fig. 7



3,7,11-trimethyl-1-dodecyne-3-ol

C18-allene-ketone

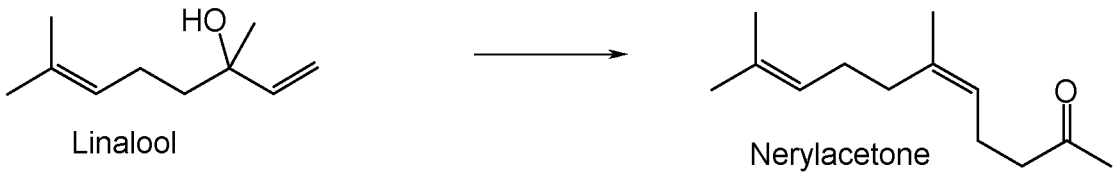
Fig. 8



C18-allene-ketone

C18-ketone

Fig. 9



Linalool

Nerylacetone

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/081396

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/72 C07C29/17 C07C29/42 C07C45/62
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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/066863 A1 (DSM IP ASSETS BV [NL]; BONRATH WERNER [DE]; MENGES FREDERIK [DE]; NETS) 29 June 2006 (2006-06-29) examples 10-12	1-10
A	WO 2014/096065 A1 (DSM IP ASSETS BV [NL]) 26 June 2014 (2014-06-26) claims 1,13; figure 2	11-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2018	06/02/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Matés Valdivielso, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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