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(54) Title: PROCESS FOR THE MANUFACTURE OF 2,6,10-TRIMETHYLLUNDECA-5,9-DIENAL

(57) Abstract: The present invention relates to an improved process for the manufacture of 2,6,10-trimethylundeca-5,9-dienal (Darzens reaction, saponification, decarboxylation).



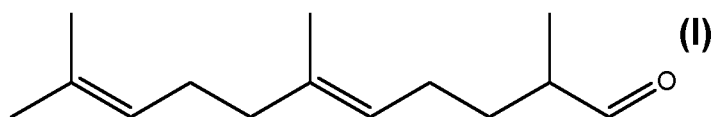
WO 2018/069457 A1

PROCESS FOR THE MANUFACTURE OF 2,6,10-TRIMETHYLUNDECA-5,9-DIENAL

The present invention relates to an improved process for the manufacture of 2,6,10-trimethylundeca-5,9-dienal.

5

2,6,10-Trimethylundeca-5,9-dienal (compound of formula (I))



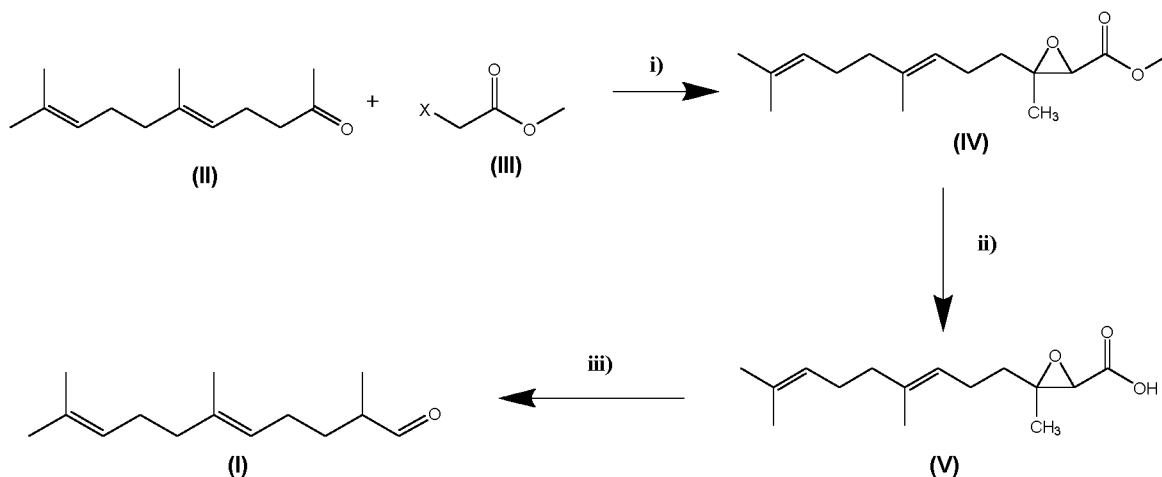
10 is a colorless to pale yellow clear liquid, which is also known as Profarnesal® as well as Oncidal®. Profarnesal® cannot be found in nature and therefore needs to be synthesized.

The odor of Profarnesal® is described mainly as aldehydic-floral odor reminiscent of nerolidol.

15

Due to the importance of 2,6,10-trimethylundeca-5,9-dienal the objective of the invention was to provide an improved process for the manufacture of 2,6,10-trimethylundeca-5,9-dienal.

20 The synthesis of 2,6,10-trimethylundeca-5,9-dienal is carried out according to the following reaction scheme:



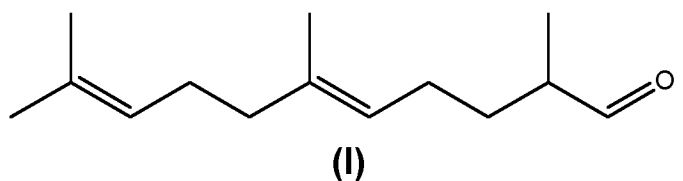
- 2 -

It was found that it is very advantageous to use NaOR in step i), wherein R is C₁-C₄-alkyl (preferably methyl or ethyl) as a base and methyl chloroacetate or methyl bromoacetate (compound (III)) with X being Cl or Br) as α-haloester at a low temperature, preferably at a temperature ≤ -15°C.

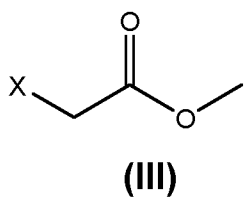
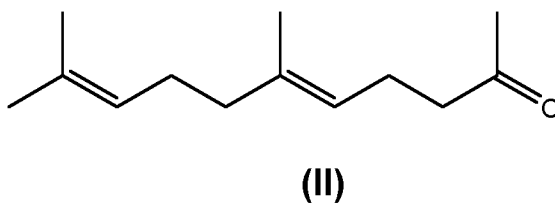
5

Furthermore, the decarboxylation (step iii)) can be carried out also in a continuous manner; additionally, the decarboxylation is carried out without any metal powder.

- 10 Therefore, the present invention relates to a process (P) for the manufacture of the compound of formula (I) comprising the following steps



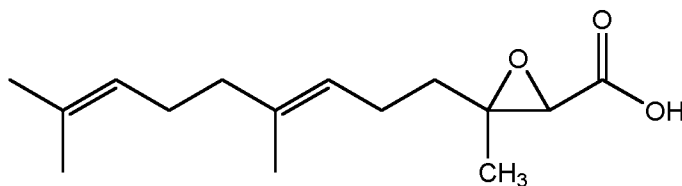
- 15 i) a Darzens reaction of a compound of formula (II) and a compound of formula (III)



20

wherein X is Cl or Br, preferably Cl,
 in the presence of NaOR with R being C₁-C₄-alkyl,
 followed by
 ii) a saponification reaction to form the compound of formula (V)

- 3 -



(V)

and

iii) a decarboxylation reaction of the compound of formula (V) to form the compound of formula (I), whereby preferably no metal catalyst such as a copper catalyst is used.

In the following the process steps are discussed in more detail.

Step (i)

10

This step is a glycidic ester condensation, whereby an α,β -epoxy ester (=glycidic ester) is formed.

It was found that it is very advantageous to use NaOR, wherein R is C₁-C₄-alkyl (preferably methyl or ethyl, more preferably methyl) as a base and methyl chloroacetate or methyl bromoacetate (preferably methyl chloroacetate) as α -haloester at a low temperature, preferably at a temperature $\leq -15^\circ\text{C}$.

20

Due to the choice of these reaction parameters the conversion of the starting material is increased significantly.

It is also possible to isolate the reaction product, i.e. the compound of formula (IV), if needed and desired.

After the glycidic ester condensation took place, remaining base can be neutralized with an acid.

Step ii)

- 4 -

This step is the saponification of the glycidic ester (the α,β -epoxy ester of formula (IV)) into the corresponding acid (compound of formula (V)). It is preferably carried out in the presence of a base. Example of such a base is NaOH. Excess of the base is neutralized after the reaction with an acid. Examples of such a base
5 are HCl or H₂SO₄.

In a preferred embodiment of the present invention step i) and step ii) are done in sequence without isolating the reaction product of the first reaction step, i.e. without isolating the compound of formula (IV).

10

The steps i) and ii) are usually carried out in a solvent (preferred) or a mixture of solvents (less preferred). Suitable solvents are aliphatic hydrocarbons or aromatic hydrocarbons or any mixture thereof. Examples of aliphatic hydrocarbons are straight and branched C₆₋₁₀-alkanes and C₆₋₁₀-cylcoalkanes such as cyclohexane, n-
15 hexane and n-heptane. Examples of aromatic hydrocarbons are benzene, toluene, o-xylene, m-xylene and p-xylene. Especially suitable are n-hexane, n-heptane, benzene, o-xylene, m-xylene, p-xylene and toluene. Preferred are n-hexane, n-heptane and toluene. Most preferred are n-heptane and toluene.

20 Therefore, the present invention relates to a process (P1), which is process (P), wherein steps i) and ii) are carried out in at least one solvent.

Furthermore, the present invention relates to a process (P1'), which is process (P1), wherein steps i) and ii) are carried out in at least one aliphatic hydrocarbon
25 or in at least one aromatic hydrocarbon.

Therefore, the present invention relates to a process (P1''), which is process (P1), wherein steps i) and ii) are carried out in at least one solvent chosen from the consisting of n-hexane, n-heptane, benzene, o-xylene, m-xylene, p-xylene and
30 toluene.

- 5 -

The reaction temperature of step i) is preferably $\leq -15^{\circ}\text{C}$. More preferably the reaction temperature is in a range of from -45°C to -15°C , most preferably the reaction temperature is in a range of from -30°C to -15°C .

- 5 Thus, the present invention relates to a process (P2), which is either process (P) or (P1) or (P1') or (P1''), wherein step i) is carried out at a reaction temperature $\leq -15^{\circ}\text{C}$.

- Thus, the present invention relates to a process (P2'), which is either process (P)
10 or (P1) or (P1') or (P1''), wherein step i) is carried out at a reaction temperature in the range of from -45°C to -15°C .

- Thus, the present invention relates to a process (P2''), which is either process (P)
or (P1) or (P1') or (P1''), wherein step i) is carried out at a reaction temperature
15 in the range of from -30°C to -15°C .

- The starting material (compound (II) and compound (III) can be added in equimolar amounts with respect to each other. Preferably the compound of formula (III) is added in excess; i.e. the molar ratio of the compound of the formula (III) to the
20 compound of formula (II) is in the range of from 1.1:1 to 2:1.

Step ii) is usually carried out at slightly elevated temperature, usually up to 60°C .

- Therefore, the present invention relates to a process (P3), which is either process
25 (P) or (P1) or (P1') or (P1'') or (P2) or (P2') or (P2''), wherein step ii) is carried out at elevated temperature.

- Therefore, the present invention relates to a process (P3'), which is either process (P) or (P1) or (P1') or (P1'') or (P2) or (P2') or (P2''), wherein step ii) is carried
30 out at a reaction temperature in the range of from 30°C to 60°C .

- 6 -

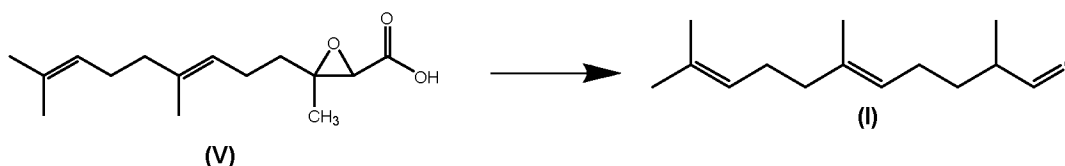
The reaction product of step ii), which is the compound of formula (V) is extracted from the reaction mixture with an aliphatic hydrocarbon or with an aromatic hydrocarbon (such as the ones given above) and it can be washed with an aqueous phase.

5

Usually the reaction product is not isolated completely but left solved in the solvent (the aliphatic hydrocarbon or the aromatic hydrocarbon).

Step iii)

10



15

The reaction product of step ii), which is the compound of formula (V) in at least one organic solvent as given above, is decarboxylated in step iii) to the compound of formula (I).

This is done by heating up the reaction mixture to a temperature of at least 160°C (preferably to a temperature in the range of from 160-300°C) and removing the side-products by distillation.

20

These reaction conditions are very mild and no metal powder is needed. In the prior art copper powder is essential for this step. Because the process of the present invention does not need any heavy metals such as copper, waste is avoided. Thus, it is an ecological process.

25

The invention is now illustrated by the following example. All percentages given are related to the weight.

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Example**Steps i) and ii)**

- 5 In a 250-ml glass reactor 19.5 g (100 mmol) of geranyl acetone, 50 ml of toluene, 12.4 ml (140 mmol) of methyl chloroacetate are charged. The mixture is stirred and cooled to -20°C (internal temperature). 7.85 g (140 mmol) of sodium methoxide are added in a powder dropping funnel. The base is added to the reaction mixture within 2 hours. The mixture is held at -20°C for 1 hour. After
10 heating to ambient temperature (ca. 20°C), 20 ml of 5 % w/w sulfuric acid are added drop-wise to the reaction mixture.

Afterwards 37.6 ml (150 mmol) of sodium hydroxide (4 M) are added. The mixture is stirred at ambient temperature (22°C) for 2 hours. A slightly viscous liquid is
15 obtained.

Step iii)

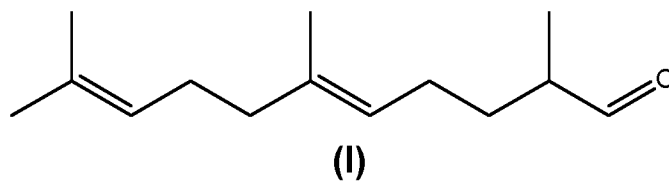
To the slightly viscous liquid of step ii) 120 g of n-heptane are added and this
20 solution is fed through the tube reactor heated at 240°C.

The crude product is distilled over a short distillation column (Vigreux 10 cm, bath temperature = 147°C, head temperature = 90°C - 96°C, pressure = 0.3 mbar) to give Profarnesal® in an overall yield of 55.8%.

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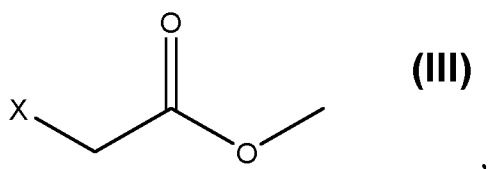
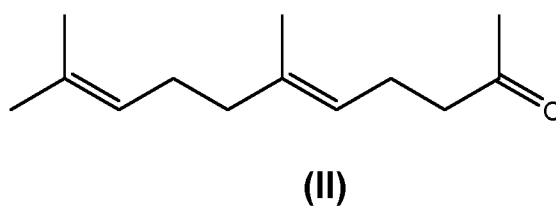
Claims

1. A process for the manufacture of the compound of formula (I)



comprising the following steps:

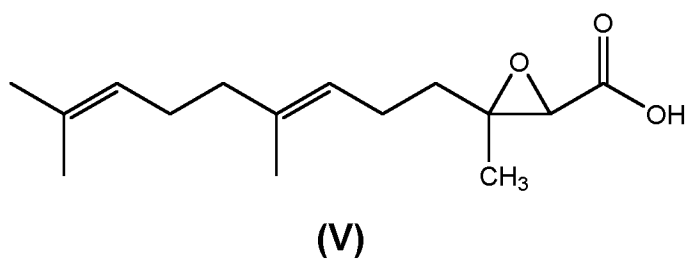
- i) a Darzens reaction of a compound of formula (II) and a compound of formula (III),



wherein X is Cl or Br,

in the presence of NaOR, wherein R is C₁-C₄-alkyl, followed by

- ii) a saponification reaction to form the compound of formula (V)



and

- 9 -

iii) a decarboxylation reaction of the compound of formula (V) to form the compound of formula (I).

2. The process according to claim 1, wherein steps i) and ii) are carried out in
5 at least one solvent.

3. The process according to claim 2, wherein the solvent is at least one aliphatic hydrocarbon or at least one aromatic hydrocarbon or any mixture thereof.

10

4. The process according to claim 2, wherein the at least one solvent is chosen from the group consisting of benzene, toluene, o-xylene, m-xylene, p-xylene, cyclohexane, n-hexane and n-heptane.

15 5. The process according to anyone of the preceding claims, wherein the reaction temperature of step i) is $\leq -15^{\circ}\text{C}$, preferably in the range of from -45°C to -15°C , more preferably in the range of from -30°C to -15°C .

6. The process according to anyone of the preceding claims, wherein step ii) is
20 carried out at a reaction temperature in the range of from 30°C to 60°C .

7. The process according to anyone of the preceding claims, wherein step iii) is carried out at a reaction temperature of $\geq 160^{\circ}\text{C}$.

25 8. The process according to anyone of the preceding claims, wherein the decarboxylation (step iii) is carried out in the absence of a metal catalyst.

9. The process according to claim 8, wherein the metal catalyst is a copper catalyst.

30

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/076088

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C45/58 C07D303/48 C07C47/21
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)

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.
X	US 3 939 202 A (MATSUI MASANAO ET AL) 17 February 1976 (1976-02-17) example 1 -----	1-9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search

12 January 2018

Date of mailing of the international search report

23/01/2018

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/076088

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US 3939202	A	17-02-1976	FR 2216263 A1	30-08-1974
			GB 1420886 A	14-01-1976
			US 3939202 A	17-02-1976
