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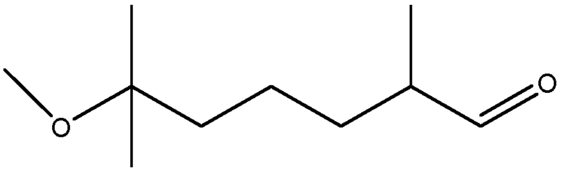
(54) **Title:** PROCESS FOR THE MANUFACTURE OF 6-METHOXY-2,6-DIMETHYLHEPTANAL

(57) **Abstract:** The present invention relates to an improved process for the manufacture of 6-methoxy-2,6-dimethylheptanal.

Process for the manufacture of 6-methoxy-2,6-dimethylheptanal

The present invention relates to an improved process for the manufacture of 6-methoxy-2,6-dimethylheptanal.

6-Methoxy-2,6-dimethylheptanal (compound of formula (I))

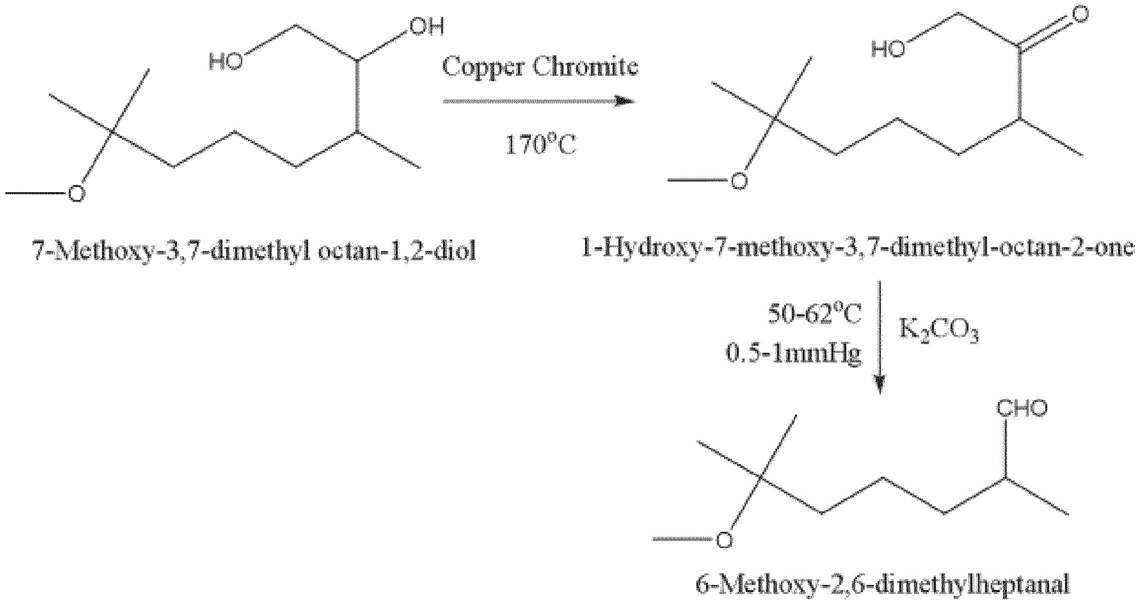


(I)

which is also known as methoxy melonal, is a colorless to pale yellow clear viscous liquid. The odor of this compound is described mainly as light floral odor, having a slightly fruity note with a watery citrus character.

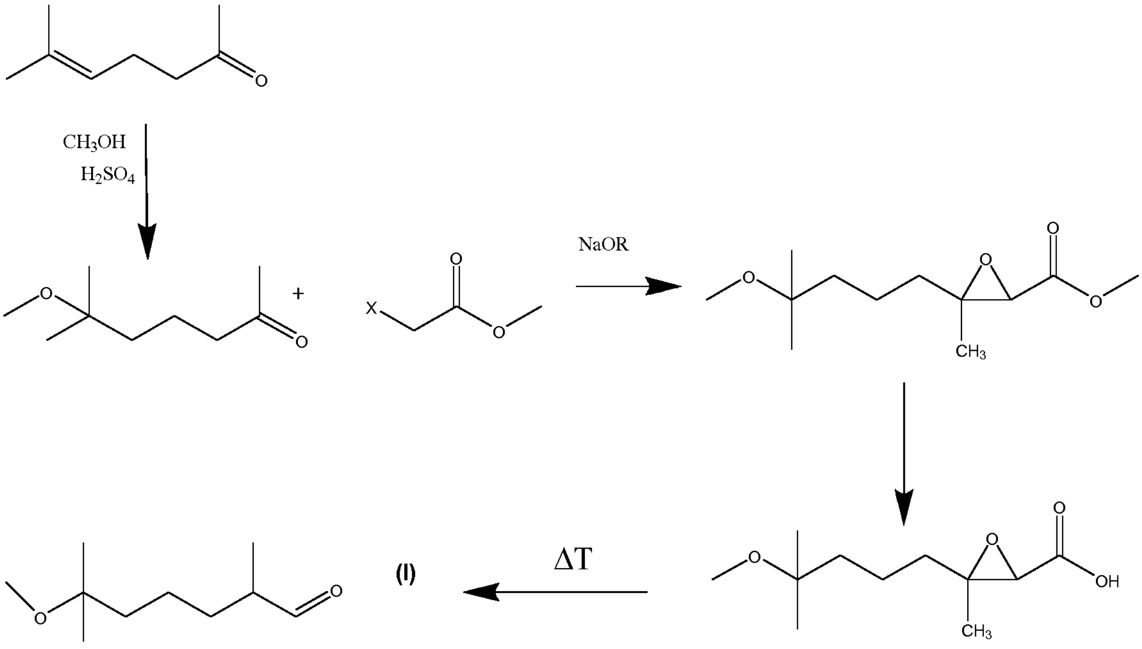
6-Methoxy-2,6-dimethylheptanal is used in many fragrance applications. It is a very important ingredient to add a fresh floral odor type to products.

6-Methoxy-2,6-dimethylheptanal can be prepared by oxidation of 7-methoxy-3,7-dimethyloctan-1,2–diol in the presence of copper chromite followed by basification with anhydrous potassium carbonate (see reaction scheme below). This reaction is described in US 4,311,617. The yields of this process to obtain methoxy melonal are low (between 11 and 29 %, based on the starting material).



Due to the importance of 6-methoxy-2,6-dimethylheptanal the objective of the invention was to provide an improved process for the manufacture of 6-methoxy-2,6-dimethylheptanal, especially with the aim of achieving a higher yield of 6-methoxy-2,6-dimethylheptanal. Furthermore, the use of an ecological questionable reagent such as copper chromite should be avoided.

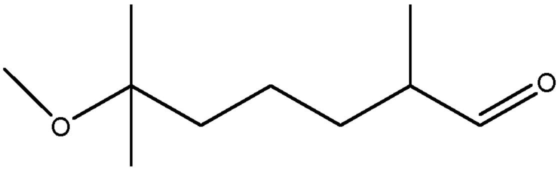
It was found that the following improved synthesis of 6-methoxy-2,6-dimethylheptanal (see reaction scheme below) allows to produce it with better yields (more than 40%) than according to the process of the prior art.



,

wherein X is Cl or Br and R is C_1-C_4-alkyl. Preferably R is methyl or ethyl.

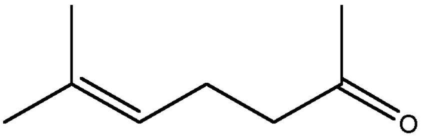
Therefore, the present invention relates to a process (P) for the manufacture of the compound of formula (I)



(I)

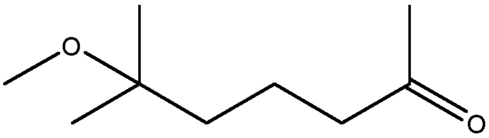
,

wherein in a first step i) the compound of formula (II)



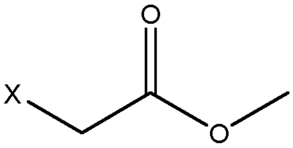
(II)

is methoxylated to the compound of formula (III)



(III)

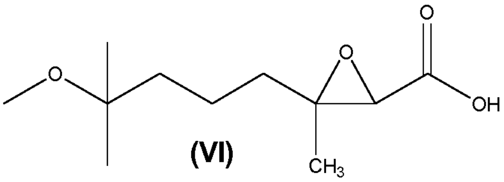
and wherein in a second step ii) a Darzens reaction is carried out with a compound of formula (III) and a compound of formula (IV)



(IV)

wherein X is Cl or Br, preferably wherein X is Cl,

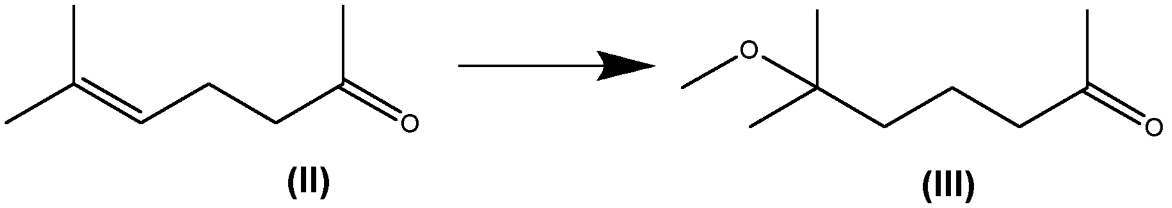
in the presence of NaOR with R being C_1-C_4-alkyl, preferably with R being methyl or ethyl, (step (ia)) followed by a saponification reaction (step (ib)) to form the compound of formula (VI)



(VI)

and wherein in a third step iii) the compound of formula (VI) is undergoing a decarboxylation reaction to form the compound of formula (I).

The first reaction step (step i)) is the methoxylation of 6-methyl-5-hepten-2-one (compound of formula (II)) to 6-methoxy-6-methylheptan-2-one (compound of formula (III)):



This can be done by commonly known methoxylation processes.

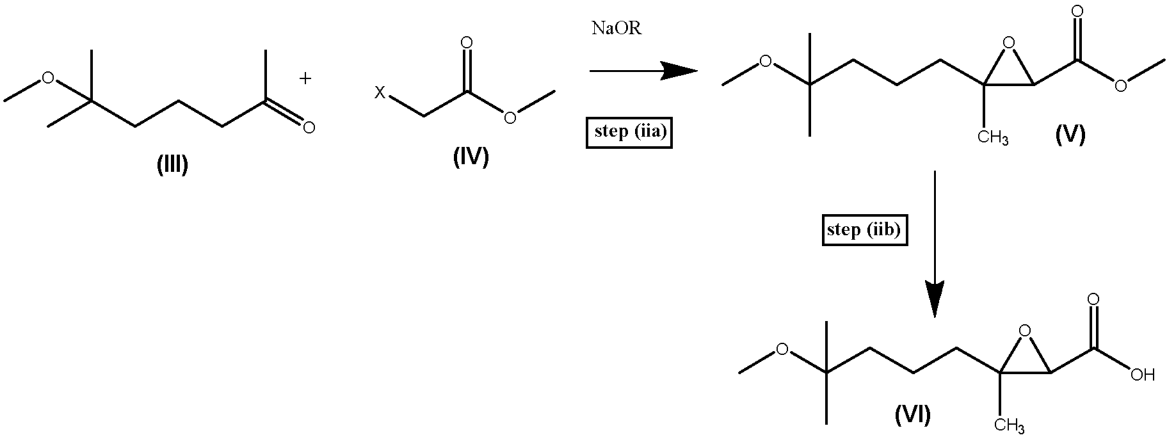
In a preferred embodiment of the process of the present invention the methoxylation is achieved by use of methanol and a strong Brønsted acid (such as H_2SO_4). Methanol serves here also as solvent.

Step (i) is usually carried out at elevated temperature. Preferably the reaction temperature is in the range of from 30°C to 80°C. The reaction is preferably carried out at ambient pressure.

The product (compound of formula (III)) is isolated in good yield and quality. The isolation can be carried out by extraction.

Step (ii)

Step ii) is in fact two steps (step (iia) and step (iib)) which are done in sequence without isolating the reaction product of the first reaction step (compound of formula (V)):



Step (iia) is a glycidic ester condensation, whereby an α,β-epoxy ester (= glycidic ester) is formed and then (step (iib)) saponified into the corresponding acid.

It was found that it is very advantageous to use NaOR with R being C_1-C_4-alkyl (preferably R is methyl or ethyl) as a base and methyl chloroacetate or methyl bromoaceate (preferably methyl chloroacetate) as α-haloester at a low temperature, preferably at a temperature ≤ -15°C.

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

Step iib) is the saponification of the glycidic ester (the α,β-epoxy ester of formula (V)) into the corresponding acid (compound of formula (VI)). 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 such as HCl or H_2SO_4.

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

The reaction of step (ii) (step (iia) and step (iib)) is usually carried out in a solvent (or a mixture of solvents). Suitable solvents are aliphatic hydrocarbons or aromatic hydrocarbons. Examples of aliphatic hydrocarbons are straight and branched $C_{6\text{-}10}$-alkanes and $C_{6\text{-}10}$-cylcoalkanes such as cyclohexane, n-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. Especially preferred is toluene.

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

Therefore, the present invention relates to a process (P1’), which is process (P1), wherein step (ii) is carried out in at least one aliphatic hydrocarbon or in at least one aromatic hydrocarbon.

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

The reaction temperature of step (iia) is preferably ≤ -15°C, more preferably in the range of from -45°C to -15°C, most preferably in the range of from -30°C to -15°C.

Therefore, the present invention relates to a process (P2), which is process (P), (P1), (P1’) or (P1’’), wherein step (iia) is carried out at a reaction temperature ≤-15°C.

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

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

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

Step (iib) is usually carried out at slightly elevated temperature; preferably up to 60°C.

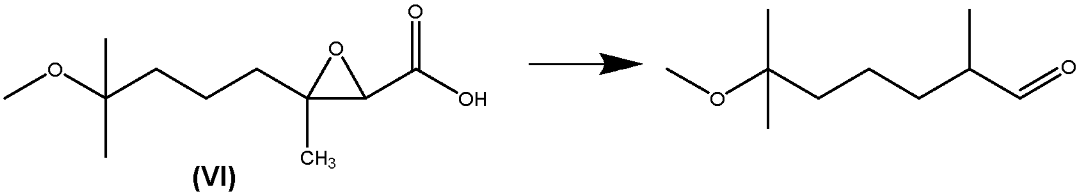
Therefore, the present invention relates to a process (P3), which is process (P), (P1), (P1’), (P1’’), (P2), (P2’) or (P2’’), wherein step (iib) is carried out at elevated temperature.

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

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

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

Step (iii)



(VI) **(I)**

The reaction product of step (ii), which is the compound of formula (VI) in at least one aliphatic hydrocarbon or in at least one aromatic hydrocarbon, is heated up, preferably to a temperature ≥ 160°C, whereby the decarboxylation takes place.

More preferably a temperature in the range of from 160 to 300°C is applied.

After the decarboxylation the side products are removed by distillation.

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, it is an ecological process.

The invention is illustrated by the following Examples. All percentages are related to the weight and the temperature is given in °C.

Example 1

Step (i)

Into a 1000-ml glass reactor 220 g (1743 mmol) of 6-methyl-5-hepten-2-one and 548 g (17.1 mol) of methanol are added. 36 g (0.349 mmol) of sulfuric acid (95 - 97 %) are added to the reaction mixture. The mixture is stirred at 50°C for 20 hours. The reaction mixture is cooled down to 20°C, 37.2 g (0.349 mol) of sodium carbonate are added and the reaction mixture is stirred at 20°C for 1 hour. Methanol is evaporated and afterwards 200 g of water are added.
The aqueous layer is extracted two times with 100 ml of tert-butyl methyl ether. Afterwards the organic layers are combined and dried over 20 g of sodium sulfate and the solvent is evaporated under reduced pressure (20 mbar, 50°C). A brownish liquid (267.68 g) is obtained. The yield is 62.9 %, based on 6-methyl-5-hepten-2-one.

Step (ii)

Into a 1000-ml glass reactor 100 g (632 mmol) of 6-methoxy-6-methylheptan-2-one, which is obtained by the reaction of step (i), 250 ml of toluene and 84.0 ml (948 mmol) of methyl chloroacetate are added. The mixture is stirred and cooled to -20°C (internal temperature). In a powder dropping funnel is added 51.2 g (948 mmol) of sodium methoxide. The base is added to the reaction mixture within 2 hours. The mixture is held at -20°C for 1 hour. After heating to ambient temperature (ca. 20°C), 200 ml of sulfuric acid (5 %; ca. 105 mmol) are added and the reaction mixture is stirred for 1 hour at 20°C. Afterwards 100 ml of toluene and 284.4 ml of sodium hydroxide (4 M; 1138 mmol) are added. The mixture is stirred at 40°C for 20 hours.
After cooling to ambient temperature (ca. 20°C) the toluene layer is separated and dried over 10 g of anhydrous sodium sulfate. The solvent is evaporated under reduced pressure (20 mbar, 50°C).

Afterwards sulfuric acid (40 % w/w) is added at 10°C under argon atmosphere to the aqueous layer until the pH reached pH = 2. 250 ml of toluene are charged and the mixture is stirred for 30 minutes at 10°C. The toluene layer is separated, dried over 20 g of anhydrous sodium sulfate and diluted with toluene. The compound of formula (VI) is obtained in a yield of 72.3%.

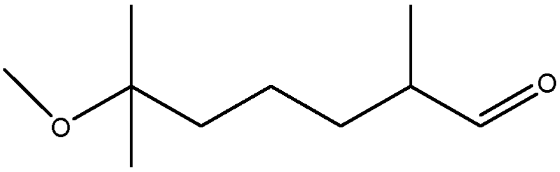
<u>Step (iii)</u>

In a 1000-ml glass bottle 520 g of the compound of formula (VI) (=glycidic acid) in toluene are charged under argon atmosphere. The solution is fed at 5 ml/min through a tube reactor heated at 240°C. The reaction mixture is cooled down to 10°C after the decarboxylation and collected under argon atmosphere in a glass bottle. The solvent is evaporated under reduced pressure (20 mbar, 50°C).
The overall yield of methoxy melonal based on the starting material (compound of formula (II)) is 45.9 %.

The yield obtained by the process according to the present invention is significantly higher than that of the prior art.

Claims

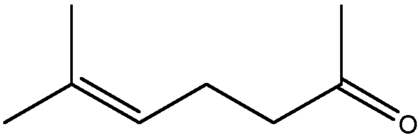
1. A process for the manufacture of the compound of formula (I)



(I)

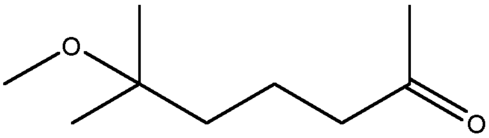
,

wherein in a first step i) the compound of formula (II)



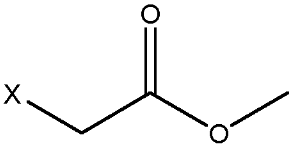
(II)

is methoxylated to the compound of formula (III)



(III)

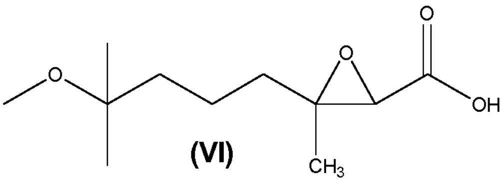
and wherein in a second step ii) a Darzens reaction is carried out with a compound of formula (III) and a compound of formula (IV)



(IV)

wherein X is Cl or Br,

in the presence of NaOR with R being C_1-C_4-alkyl followed by a saponification reaction to form the compound of formula (VI)



(VI)

and wherein in a third step iii) the compound of formula (VI) is undergoing a decarboxylation reaction to form the compound of formula (I).

2. The process according to claim 1, wherein X is Cl and R is methyl or ethyl.

3. The process according to claim 1 and/or 2, wherein step i) is done by use of methanol and a strong Brønsted acid.

4. The process according to anyone of the preceding claims, wherein the reaction of step i) is carried out at a reaction temperature in the range of from 30°C to 80°C.

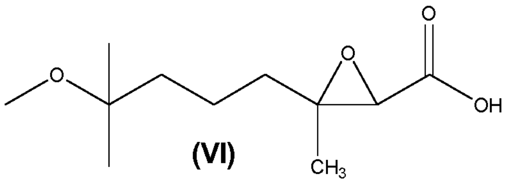
5. The process according to anyone of the preceding claims, wherein step ii) is carried out in at least one solvent.

6. The process according to claim 5, wherein the solvent is at least one aliphatic hydrocarbon or at least one aromatic hydrocarbon.

7. The process according to anyone of the preceding claims, wherein the Darzens reaction is carried out at a temperature in the range of from -45°C to -15°C.

8. The process according to anyone of the preceding claims, wherein the saponification reaction is carried out at a reaction temperature in the range of from 30°C to 60°C.

9. The process according to anyone of the preceding claims, wherein the compound of formula (VI)



(VI)

is heated to a temperature of at least 160°C to form the compound of formula (I).

10. The process according to anyone of the preceding claims, wherein no metal is present in the decarboxylation reaction.

11. The process according to anyone of the preceding claims, wherein no copper is present in the decarboxylation reaction.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/076089

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C45/58 C07C45/64 C07D301/02 C07C49/175 C07C47/198
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	XIAODAN GUO: "Synthesis of Novel Fragrant Molecules 6-Methoxy-2,6-dimethyl Heptanol Derivatives", ASIAN JOURNAL OF CHEMISTRY, vol. 26, no. 13, 2014, pages 3958-3962, XP055330720, IN ISSN: 0970-7077, DOI: 10.14233/ajchem.2014.16089 page 3959, column 1, paragraph 1-3 page 3959, column 2, last paragraph - page 3960, column 1, paragraph 1 page 3960; figures 1,2 -----	1-11
A	EP 1 764 355 A1 (GIVAUDAN SA [CH]) 21 March 2007 (2007-03-21) example 1 ----- -/--	1-11

☒ 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

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"&" document member of the same patent family

Date of the actual completion of the international search

4 January 2018

Date of mailing of the international search report

11/01/2018

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INTERNATIONAL SEARCH REPORT

International application No	PCT/EP2017/076089

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WILLIAM S. JOHNSON ET AL: "Studies Relating to the Formation and Reactions of Glycidic Esters", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 75, no. 20, 1953, pages 4995-5001, XP055437789, US ISSN: 0002-7863, DOI: 10.1021/ja01116a033 page 4999, column 1, lines 48-70 -----	1-11

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/076089

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1764355 A1	21-03-2007	AT 420846 T	15-01-2009
		BR PI0616232 A2	14-06-2011
		CN 101277919 A	01-10-2008
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		US 2008261860 A1	23-10-2008
		WO 2007030967 A1	22-03-2007