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(54) Title: PROCESS FOR THE MANUFACTURE OF A MIXTURE OF 2-METHYL-4-(2,6,6-TRIMETHYL-1-CYCLOHEXEN-1-YL)-2-BUTENAL AND 2-METHYL-4-(2,6,6-TRIMETHYL-2-CYCLOHEXEN-1-YL)-2-BUTENAL

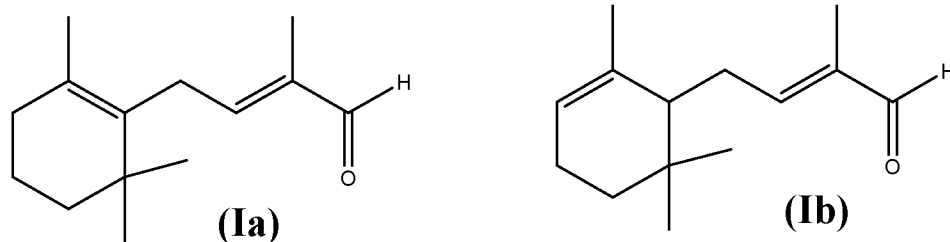
(57) Abstract: The present invention relates to an improved process for the manufacture of a mixture of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-butenal and 2-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-butenal.



PROCESS FOR THE MANUFACTURE OF A MIXTURE OF 2-METHYL-4-(2,6,6-TRIMETHYL-1-CYCLOHEXEN-1-YL)-2-BUTENAL AND 2-METHYL-4-(2,6,6-TRIMETHYL-2-CYCLOHEXEN-1-YL)-2-BUTENAL

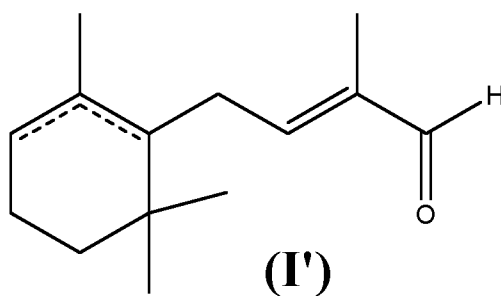
- 5 The present invention relates to an improved process for the manufacture of a mixture of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-butenal and 2-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-butenal.

- 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-butenal (compound of formula
10 (Ia)) and 2-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-butenal (compound of formula (Ib))



- 15 are a colorless to pale yellow clear liquid.
The odor of this mixture is described mainly as having a long-lasting berry accent used notably in chypre composition.

- In the context of the present invention the mixture of the compound of formula
20 (Ia) and the compound of formula (Ib) is symbolized by the following formula (I')

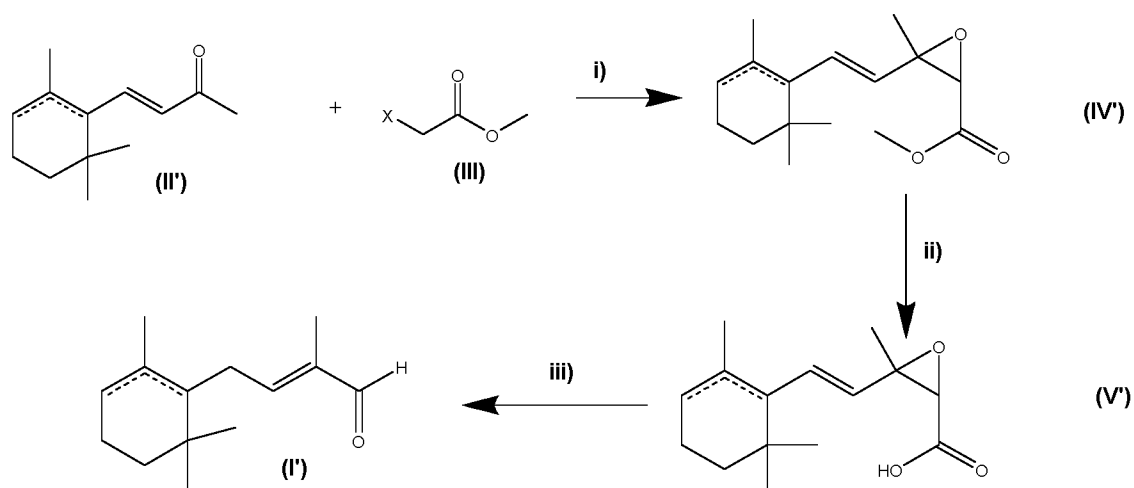


- 2 -

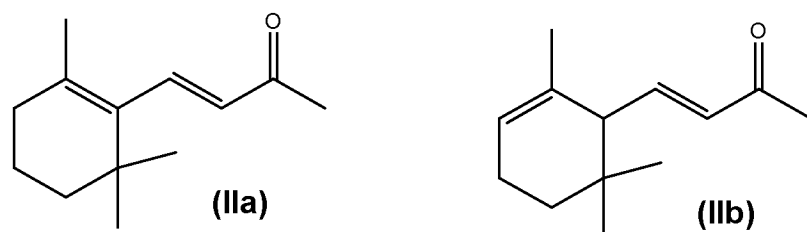
The mixture can have any ratio of compound of formula (Ia) to compound of formula (Ib).

Due to the importance of the mixture of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-butenal and 2-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-butenal the objective of the invention was to provide an improved process for the manufacture of this mixture.

The synthesis of the mixture of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-butenal and 2-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-butenal is carried out according to the following reaction scheme:

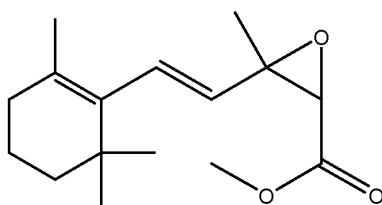


The compound of formula (II') stands for a mixture of

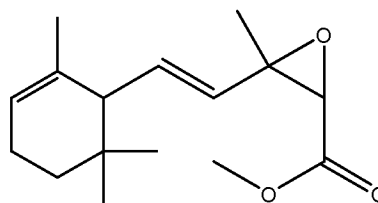


The compound of formula (IV') stands for a mixture of

- 3 -

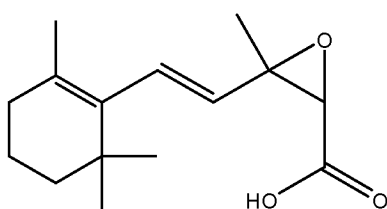


(IVa)

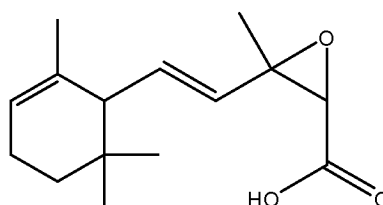


(IVb)

The compound of formula (V') stands for a mixture of



(Va)



(Vb)

5

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.

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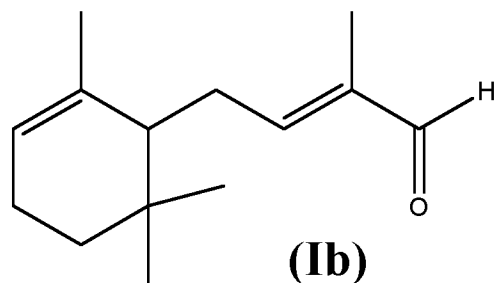
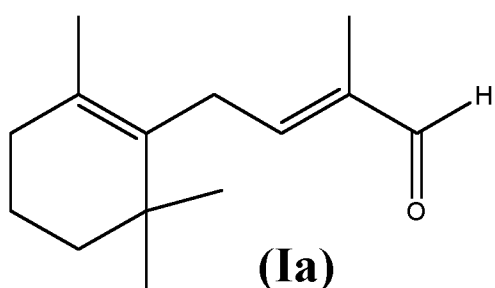
Furthermore, the decarboxylation can be carried out also in a continuous manner. Additionally, the decarboxylation is carried out without any metal powder under very mild conditions.

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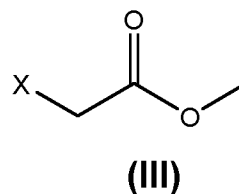
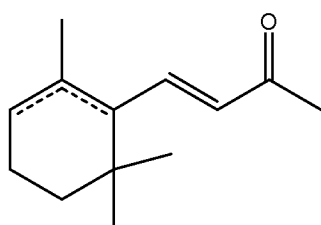
Therefore, the present invention relates to a process (P) for the manufacture of the compound of a mixture of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-butenal (compound of formula (Ia)) and 2-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-butenal (compound of formula (Ib)) comprising the following steps

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- 4 -

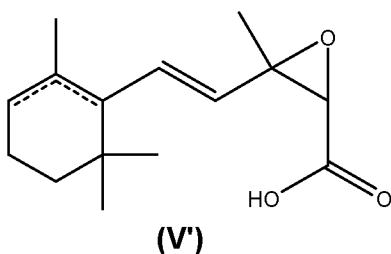


i) a Darzens reaction of a compound of formula (II') and a compound of formula (III)



wherein X is Cl or Br, preferably Cl,
in the presence of NaOR, wherein R is C₁-C₄-alkyl,
followed by

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



and

iii) a decarboxylation reaction of the compound of formula (V') to form the mixture of the compounds of formula (Ia) and formula (Ib).

15

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

Step (i)

- 5 -

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 wherein R is methyl or ethyl, more preferably wherein R is methyl, as a base and methyl chloroacetate or methyl bromoacetate, preferably methyl chloroacetate, as α -haloester at a low temperature, preferably at a temperature $\leq -15^{\circ}\text{C}$.

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

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

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

Step ii)

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

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

- 6 -

hydrocarbons or any mixture thereof. Examples of aliphatic hydrocarbons are straight and branched C₆₋₁₀-alkanes and C₆₋₁₀-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 cyclohexane, n-hexane, n-heptane, benzene, o-xylene, m-xylene, p-xylene and toluene. Preferred are n-hexane, n-heptane and toluene. Most preferred is n-hexane.

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.

10

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 or in at least one aromatic hydrocarbon.

15 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 group consisting of cyclohexane, n-hexane, n-heptane, benzene, o-xylene, m-xylene, p-xylene and toluene.

20 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 .

25 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 $\leq -15^{\circ}\text{C}$.

30 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 in the range of from -45°C to -15°C .

- 7 -

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 in the range of from -30°C to -15°C.

- 5 The starting materials, compound (II) and compound (III), can be added in equimolar amounts with respect to each other. Preferably compound of formula (III) is added in excess, i.e. the molar ratio of the compound of the formula (III) to the compound of formula (II) is in the range of from 1.1:1 to 2:1.
- 10 Step ii) is usually carried out at slightly elevated temperature, preferably up to 60°C. More preferably the reaction temperature is in the range of from 30 to 60°C.

Therefore, the present invention relates to a process (P3), which is either process
15 (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
20 out at a reaction temperature in the range of from 30°C to 60°C.

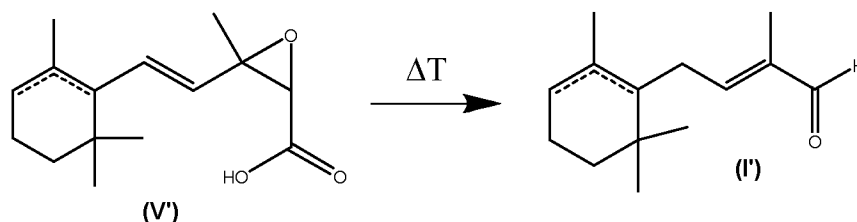
The reaction product of step ii), which is the compound of formula (V) is extracted from the reaction mixture with an aliphatic hydrocarbon (preferably with n-hexane or n-heptane) or an aromatic hydrocarbon (preferably with benzene or
25 toluene) and it can be washed with an aqueous phase. Advantageously the solvent is used wherein the reaction has been taken place.

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

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Step iii)

- 8 -



The reaction product of step ii), which is the compound of formula (V') in at least one aliphatic hydrocarbon or in at least one aromatic hydrocarbon, is decarboxylated in step iii) to the compound of formula (I').

This is done by heating up the reaction mixture to a temperature $\geq 140^\circ\text{C}$, preferably to a temperature $\geq 160^\circ\text{C}$, more preferably to a temperature in the range of from 160 - 300°C . The by-products can be 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 use of metal powders such as copper also creates additional waste. The disposal of such waste is expensive and adds to the overall costs of the process.

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

- 9 -

Example

In a 250-ml glass reactor 20 g (104 mmol) of a mixture (compound of formula (II')) comprising α -ionone (compound of formula (IIb)) and β -ionone (compound of formula (IIa)) (30 % IIb, 70 % IIb), 2 ml of methanol, 2 ml of n-hexane and 17.9 g (163 mmol) of methyl chloroacetate (2) are charged. The mixture is stirred at 800 rpm (rotations per minute) and cooled to -20°C (internal temperature). 11.3 g (199 mmol) of sodium methoxide are added in a powder dropping funnel. The base is added to the reaction mixture in 1 g portions within 4 hours (the internal temperature varied between -20°C and -12°C). The mixture is held at -20°C for 1 hour, then at 0°C for 1 hour.

After heating to 25°C 109 ml (218 mmol) of methanolic sodium hydroxyde (2M) are added in 30 minutes. The mixture is rigorously stirred (1000 RPM) during 4 hours at 25°C. 200 ml water are added, the mixture is warmed up to 40°C and stirred for 20 hours. 150 ml n-hexane is added and the layers are separated in a separation funnel. The organic layer is filtered over 20 g of Dicalite in order to remove the remaining inorganic impurities. To the brownish solution is added 10 g of charcoal Norit SX1 and the solution is stirred at ambient temperature (ca. 20°C) for 30 minutes. The solution is filtered and dried over 20 g of anhydrous sodium sulfate. The solvent is evaporated under reduced pressure (20 mbar, 50°C). A yellowish liquid is obtained.

To this yellowish liquid n-hexane is added and this solution is fed through a tube reactor heated at a temperature in the range of 140 to 300°C.

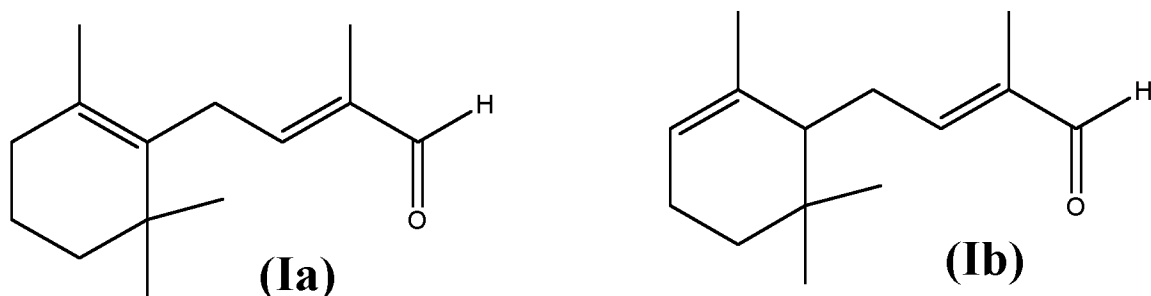
The same decarboxylation temperature (range given above) may also be applied when a different reactor or a different solvent is used.

The crude product is distilled to give the product in an overall yield of 51%.

- 10 -

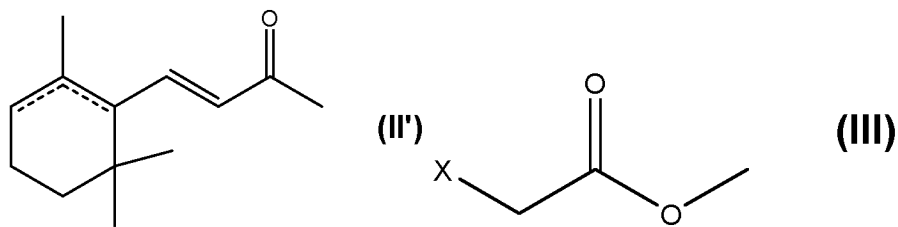
Claims

1. A process for the manufacture of a mixture of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-butenal (compound of formula (Ia)) and 2-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-butenal (compound of formula (Ib))



comprising the following steps:

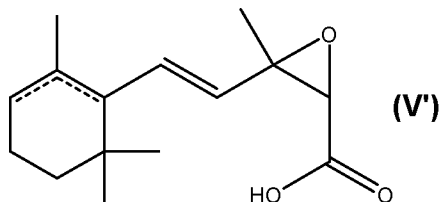
- 10 i) a Darzens reaction of a compound of formula (II) and a compound of formula (III)



wherein X is Cl or Br,

- 15 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

- 20 iii) a decarboxylation reaction of the compound of formula (V') to form the mixture of the compounds of formula (Ia) and formula (Ib).

- 11 -

2. The process according to claim 1, wherein steps i) and ii) are carried out in at least one solvent.
- 5 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.
4. The process according to claim 3, wherein the solvent is at least one
10 aromatic hydrocarbon chosen from the group consisting of benzene, toluene, o-xylene, m-xylene and p-xylene.
5. The process according to claim 2, wherein the solvent is at least one aliphatic solvent.
- 15 6. The process according to claim 5, wherein the at least one aliphatic hydrocarbon is chosen from the group consisting of cyclohexane, n-hexane and n-heptane.
- 20 7. 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 .
8. The process according to anyone of the preceding claims, wherein step ii) is
25 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 step iii) is carried out at a reaction temperature of $\geq 140^{\circ}\text{C}$.
- 30 10. The process according to anyone of the preceding claims, wherein step iii) is carried out in the absence of any metal powder.

- 12 -

11. The process according to anyone of the preceding claims, wherein step iii) is carried out in the absence of any copper powder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/076083

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C403/14
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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IGLESIAS B ET AL: "A PERICYCLIC CASCADE TO THE STEREOCONTROLLED SYNTHESIS OF 9-CIS-RETINOIDS", THE JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 65, no. 9, 5 May 2000 (2000-05-05), pages 2696-2705, XP000911995, ISSN: 0022-3263, DOI: 10.1021/J0991757F the whole document	1-11
Y	EP 1 764 359 A1 (DSM IP ASSETS BV [NL]) 21 March 2007 (2007-03-21) the whole document	1-11



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

15 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/EP2017/076083

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1764359	A1	21-03-2007	AT 455757 T 15-02-2010
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