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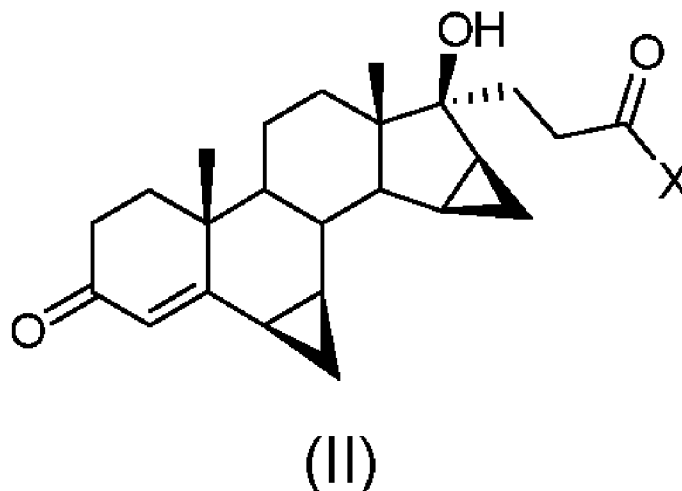
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(54) Title: PROCESS FOR OBTAINING DROSPIRENONE

(57) Abstract: The invention relates to processes for obtaining 6 β ,7 β ; 15 β , 16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, commonly known as Drospirenone, as well as to intermediate compounds of formula (II) useful in said process.

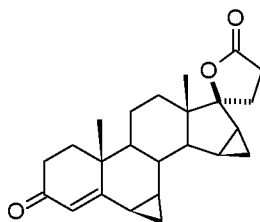
PROCESS FOR OBTAINING DROSPIRENONE

Field of the Invention

The invention relates to processes for obtaining 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, commonly known as Drospirenone, as well as to intermediates useful in said process.

Background of the Invention

Drospirenone has progestogenic, antimineralocorticoid and antiandrogenic activity; it is therefore being used in pharmaceutical compositions for its use as a contraceptive.



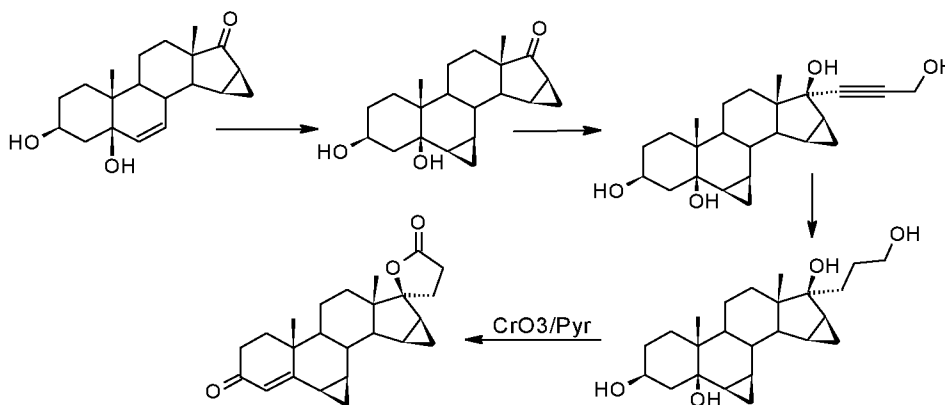
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The lactone group in position 17 in Drospirenone is prone to isomerization, particularly in acid medium, as has been described in *Steroids*, 71, 745-50, 2006 and in US 6,933,395, giving rise to the isolactone, which is one of the main impurities associated to the end product.

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In particular, to prevent the isomerization of the lactone and the appearance of the isolactone as an associated impurity, it is desirable to use a synthetic route in which the lactone group is introduced as a final step of the synthesis and, furthermore, in which the reaction conditions when the lactone is formed are controlled.

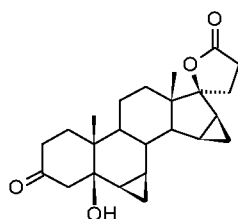
US 4,416,985 describes a process in which the diastereoselective introduction of cyclopropyl in position 6,7 is resolved and the lactone is obtained in the last synthesis steps:



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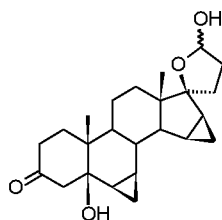
wherein the lactone is introduced simultaneously by means of adding a propargyl alcohol which is subjected to a hydrogenation and subsequent oxidation of the tetraol formed to yield the desired product. However, the oxidation conditions of the final step, in the presence of a toxic oxidant such as CrO_3 , give rise to a product which is purified by chromatographic column and in which the partial isomerization of the lactone formed occurs both due to the acid medium used and due to the presence of chromium salts aiding in the isomerization.

US 6,933,395 shows the drawbacks set forth above and proposes as a solution mitigating the final oxidation conditions of the tetraol intermediate by means of using catalytic amounts of ruthenium trichloride in the presence of sodium bromate. Under these conditions, the 5- β -hydroxy derivative:



is isolated as an intermediate, which gives rise to the final Drospirenone by means of eliminating the hydroxyl group in acid medium under controlled conditions, thus preventing the appearance of the isolactone. However, despite disclosing the tendency of the lactone group to isomerize in acid medium, a strong acid such as p-toluenesulfonic acid is used in the last dehydration step. Under these conditions, Drospirenone is obtained with a chromatographic purity of only 93% and further chromatographic techniques are needed if a product with a higher purity is to be obtained.

US 2005/192450 also uses the tetraol intermediate to, by means of its oxidation, directly obtain final Drospirenone or by previously isolating the lactol derivative:

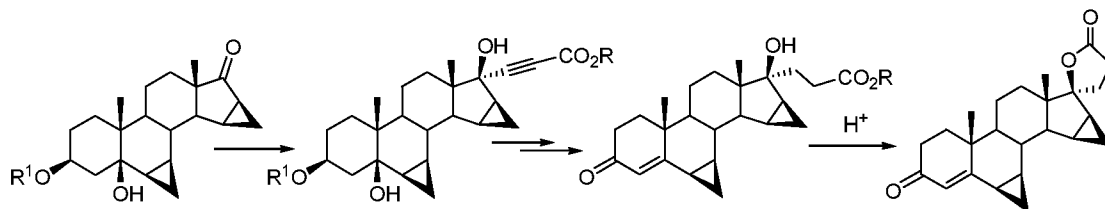


Various oxidation conditions are described, such as for example the use of MnO_2 , Oppenauer oxidation conditions, NaClO in the presence of TEMPO, etc. In this case, the Drospirenone obtained is also purified by column chromatography.

Other patents or patent applications following the same strategy of partial or

complete oxidation of the tetraol intermediate under oxidizing conditions are, for example: EP 1828222 B1 and EP 1746101 B1.

Finally, patent applications WO 2010/118023 and WO 2010/146042 refer to synthetic approaches directed to obtain the hydroxyl-acid or hydroxyl-ester precursors of the lactone group by avoiding oxidative conditions, through the introduction of an alkynyl ester or alkynyl acid group.



However, both from the hydroxy-ester and from the hydroxy-carboxylic acid compound, the use of an acid medium is necessary for its cyclization to the lactone. If the use of a strong acid, which favors the isomerization, is avoided by using a weak acid (e.g. acetic acid), then harder reaction conditions are needed such as heating the reaction mixture, which could also favor the isomerization process.

As it can be seen, all the synthetic approaches for introducing the lactone group as a final step of the synthesis require either a complete or partial oxidation reaction of the tetraol intermediate, followed by elimination in acid medium to yield Drospirenone, or a cyclization of a hydroxyl-carboxyl group in an acid medium.

In all the cases, the final conditions of the last step involve oxidation reagents which complicate the purification of the end product, or the use of acid medium which could enable the appearance of impurities derived from the degradation of the lactone, such as for example the isolactone, or both conditions together.

It is therefore necessary to develop an alternative process for obtaining steroid derivatives with a spiro lactone function which overcomes all or part of the problems associated with the known processes belonging to the state of the art.

Summary of the Invention

The invention faces the problem of providing a process for preparing steroids, and particularly Drospirenone, which allows introducing the lactone group in position 17 from a hydroxy-carboxylic or carboxylic derived group, preferably as a last synthesis step, and which prevents using acid conditions that favor the degradation of the end product with the appearance, for example, of the isolactone.

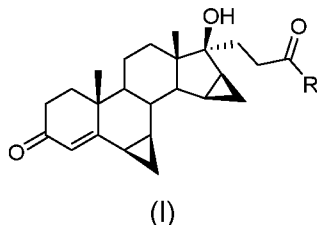
The solution provided by the invention is based on the fact that the inventors have surprisingly observed that it is possible to introduce a lactone group from the

corresponding hydroxy-carboxylic or carboxylic derived group, to obtain steroids while avoiding the use of acid medium. This is particularly interesting for those steroids, such as Drospirenone, wherein the exposure to said acid medium would involve the formation of impurities such as the isolactone, or impurities resulting from the ring opening of the cyclopropyl groups.

The cyclization of a hydroxyl-carboxylic or carboxylic derived group to yield a lactone in non acidic medium is achieved through the introduction of a carbonyl activating moiety that favors the intramolecular attack of the hydroxyl group on the activated carbonyl group. In this way, the lactone group is obtained in the absence of an acid medium and can be further isolated and purified.

These cyclization conditions can be applied to different hydroxy-carboxylic or carboxylic derived groups, such as hydroxy-carboxylic acid compounds or its corresponding salts, hydroxy-ester compounds, hydroxy-amide compounds or hydroxy-thioester compounds.

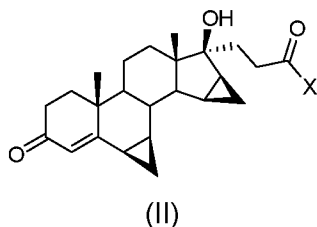
Thus, in a first aspect, the invention is directed to a process for obtaining Drospirenone or a solvate thereof, which comprises reacting a compound of formula (I)



wherein

R is selected from -OM, -OR^a, -SR^b, -NR^cR^d, OSiR^eR^fR^g; wherein M is an alkali metal, and R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently selected from H, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted aryl.

with a carbonyl activating compound, to form a compound of formula (II)



wherein X is a carbonyl activating group, which cyclizes to give Drospirenone.

This reaction proceeds in the absence of an acid medium. Due to the activation of the carbonyl group, the compound of formula (II) cyclizes to give Drospirenone without needing further addition of an acid.

In another aspect, the invention relates to compounds of formula (II) as defined above, which are useful intermediates in the synthesis of Drospirenone or a solvate thereof.

Detailed Description of the Invention

5 In the context of the present invention, the following terms have the meaning detailed below:

 The term "alkyl" refers to a radical derived from a linear or branched alkane, containing from 1 to 12 ("C₁-C₁₂ alkyl"), preferably from 1 to 6 carbon atoms ("C₁-C₆ alkyl"), and which is attached to the rest of the molecule by a single bond. Examples of
10 alkyl groups include methyl, ethyl, propyl, butyl, pentyl and hexyl.

 As used herein, the term "cycloalkyl" refers to a radical derived from a cycloalkane, containing from 3 to 7 ("C₃-C₇ cycloalkyl"), preferably from 3 to 6 ("C₃-C₆ cycloalkyl") carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

15 The term "aryl" refers to an aromatic group having between 6 and 18, preferably between 6 and 10, even more preferably 6 or 10 carbon atoms, comprising 1, 2 or 3 aromatic nuclei, bound by means of a carbon-carbon bond or fused, including for example and in a non-limiting sense, phenyl, naphthyl, diphenyl, indenyl, phenanthryl, etc.

20 "Heterocyclyl" refers to a stable 3- to 10-membered ring radical, preferably a 5- or 6-membered ring, which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur and which can be partially or fully saturated. For the purposes of this invention, the heterocycle can be a monocyclyl, bicyclyl or tricyclyl ring system, which can include systems of fused rings.
25 Examples of such heterocycles include, but are not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydrofuran.

 "Heteroaryl" refers to a stable 3- to 10-membered aromatic ring radical, preferably a 5- or 6-membered aromatic ring, which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen, and
30 sulphur. For the purposes of this invention, the heteroaryl can be a monocyclyl, bicyclyl or tricyclyl ring system, which can include systems of fused rings. Examples of such heteroaryl include, but are not limited to, benzimidazole, benzothiazole, furan, pyrrole, pyridine, pyrimidine, isothiazole, imidazole, indole, purine, quinoline, thiadiazole. The term "nitrogen containing heteroaryl" refers to a heteroaryl group as defined above,

which contains at least a nitrogen atom, such as e.g. benzimidazole, pyrrole, pyridine, pyrimidine, imidazole, indole, quinoline.

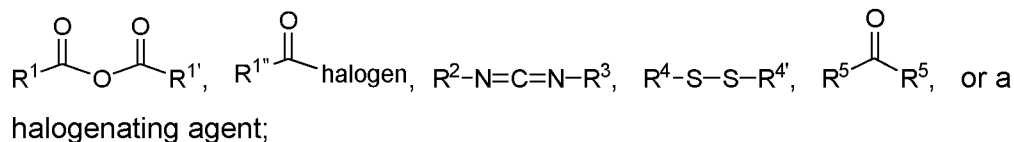
The term "halogen" refers to bromo, chloro, iodo or fluoro.

As understood in this technical area, there can be a certain degree of substitution on the previously defined radicals. Thus, there can be substitution in any of the groups of the present invention. The references of the present document to substituted groups in the groups of the present invention indicate that the specified radical can be substituted in one or more available positions by one or more substituents. Said substituents include, for example and in a non limiting sense, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, cyano, nitro, trifluoromethyl, -N(R_a)(R_b), -OR_c, -SR_d, -C(O)R_e, -C(O)OR_f, -C(O)N(R_g)(R_h), -OC(O)R_i; wherein R_a, R_b, R_c, R_d, R_e, R_f, R_g, R_h and R_i are independently selected from hydrogen, C₁-C₆ alkyl, aryl, heterocyclyl, heteroaryl and trifluoromethyl.

Alkali metals are the chemical elements forming Group 1 of the periodic table: lithium (Li), sodium (Na), potassium (K), rubidium (Rb), cesium (Cs), and francium (Fr). Preferably, the alkali metal in the present invention is selected from Li, Na and K, more preferably K.

An "alkali metal alkoxide" is a compound of formula R⁷O-M, wherein M is an alkali metal and R⁷ is an alkyl group as defined above, e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium ethoxide.

The term "carbonyl activating compound" refers to a compound that converts the carbonyl of a carboxylic acid group to one that is more prone to nucleophilic addition, such as e.g. anhydrides, carboxylic acid halides, carbodiimides, halogenating agents, di(nitrogen-containing heteroaryl) disulfides, etc. In a particular embodiment, the carbonyl activating compound is selected from a compound of formula:



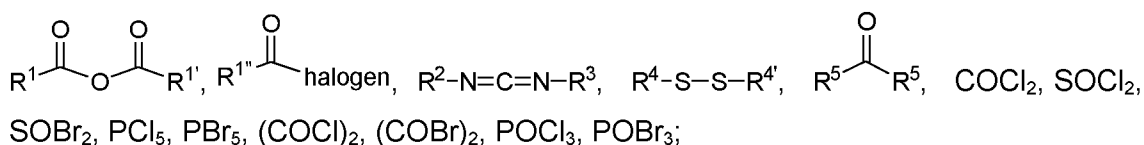
wherein

R¹, R^{1'}, R^{1''}, R² and R³ are independently selected from substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₃-C₇ cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R⁴, R^{4'}, and R⁵ are independently selected from a substituted or unsubstituted nitrogen-containing heteroaryl.

According to the present invention, the halogenating agent may include a fluorinating agent, a chlorinating agent, a brominating agent or an iodinating agent. It is preferably selected from the group consisting of Cl_2 , Br_2 , I_2 , COCl_2 , SOCl_2 , SOBr_2 , PCl_5 , PBr_5 , PCl_3 , PBr_3 , $(\text{COCl})_2$, $(\text{COBr})_2$, POCl_3 , POBr_3 , N-bromosuccinimide, N-chlorosuccinimide and N-iodosuccinimide.

More preferably, the carbonyl activating compound is selected from a compound of formula:



wherein

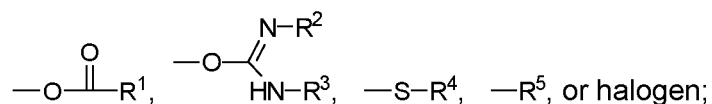
R^1 , $\text{R}^{1'}$ and $\text{R}^{1''}$ are independently selected from substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, and substituted or unsubstituted phenyl;

R^2 and R^3 are independently selected from substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted C_3 - C_7 cycloalkyl;

R^4 , $\text{R}^{4'}$, and R^5 are independently selected from pyridine and imidazol.

In another particular embodiment, the carbonyl activating compound is selected from acetic anhydride, propionic anhydride, trifluoroacetic anhydride, 2,4,6-trichlorobenzoyl chloride, 1,3-dicyclohexylcarbodiimide (DCC), 1,3-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 2,2'-dipyridyl-disulfide, 2,2'-diimidazolyl-disulfide, carbonyldiimidazole, SOCl_2 , SOBr_2 , PCl_5 , PBr_5 , $(\text{COCl})_2$, $(\text{COBr})_2$, POCl_3 and POBr_3 .

The term "carbonyl activating group" refers to a substituent of a carbonyl that renders that carbonyl prone to nucleophilic addition, such as e.g. acyloxy, aryloxy, 1,3-disubstituted isoureido group, halogen, heteroarylsulfide, etc. In a particular embodiment, the carbonyl activating group is selected from a compound of formula:



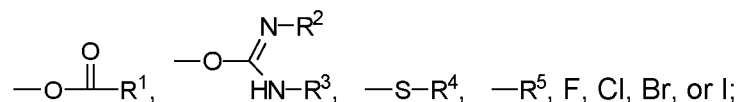
wherein

R^1 , R^2 and R^3 are independently selected from substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted

heteroaryl;

R⁴ and R⁵ are independently selected from a substituted or unsubstituted nitrogen-containing heteroaryl.

More preferably, the carbonyl activating group is selected from a compound of
5 formula:



wherein

R¹ is selected from substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₃-C₇ cycloalkyl, and substituted or unsubstituted phenyl;

10 R² and R³ are independently selected from substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted C₃-C₇ cycloalkyl;

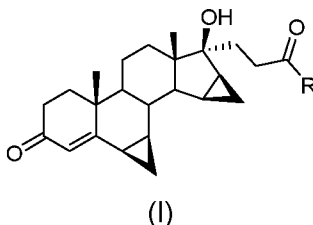
R⁴ and R⁵ are independently selected from pyridine and imidazol.

In another particular embodiment, the carbonyl activating group is selected from acetyloxy, propionyloxy, trifluoroacetyloxy, 2,4,6-trichlorobenzoyloxy, 1,3-dicyclohexyl-
15 2-isoureido, 1,3-diisopropyl-2-isoureido, 1-ethyl-3-(3-dimethylaminopropyl)-2-isoureido, 2-pyridylthio, 2-imidazolthio, 1-imidazol, Cl, Br and I.

The term “solvate” according to this invention is to be understood as meaning any form of the active compound according to the invention which has another molecule (most likely a polar solvent) attached to it via non-covalent bonding.
20 Examples of solvates include hydrates and alcoholates, e.g. methanolate.

Process for preparing Drospirenone

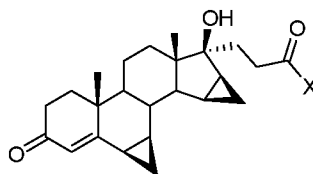
In an aspect, the invention relates to a process for preparing Drospirenone or a solvate thereof, which comprises reacting a compound of formula (I)



wherein

R is selected from -OM, -OR^a, -SR^b, -NR^cR^d, OSiR^eR^fR^g; wherein M is an alkali metal, and R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently selected from H,
30 substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted aryl;
with a carbonyl activating compound, to form a compound of formula (II)

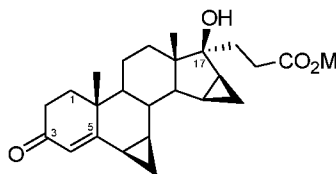
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(II)

wherein X is a carbonyl activating group,
which cyclizes to give Drospirenone.

- 5 In a preferred embodiment, the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein M is an alkali metal.

- 10 In a particular embodiment of the invention, M represents Li, Na or K, more preferably K.

In a particular embodiment, the compound of formula (II) cyclizes under the reaction conditions employed for its preparation, directly giving rise to Drospirenone or a solvate thereof.

- 15 Preferred carbonyl activating compounds and carbonyl activating groups are as defined above. In a further preferred embodiment, the carbonyl activating compound is an anhydride or a carboxylic acid halide, thus giving rise to a compound of formula (II)

- wherein X is a group —O—C(=O)—R^1 , wherein R^1 is selected from substituted or unsubstituted $\text{C}_1\text{—C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_3\text{—C}_7$ cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. More preferably, R^1 is selected from substituted or unsubstituted $\text{C}_1\text{—C}_6$ alkyl, substituted or unsubstituted $\text{C}_3\text{—C}_7$ cycloalkyl, and substituted or unsubstituted phenyl. Even more preferably, it is selected from unsubstituted $\text{C}_1\text{—C}_3$ alkyl, halogen substituted $\text{C}_1\text{—C}_3$ alkyl, phenyl substituted $\text{C}_1\text{—C}_3$ alkyl, phenyl, halogen substituted phenyl, and $\text{C}_1\text{—C}_3$ substituted phenyl; such as acetyloxy, propionyloxy, trifluoroacetyloxy, 2,4,6-trichlorobenzoyloxy, benzoyloxy and p-toluyloxy.
- 20
25

The reaction can be carried out in the presence or in the absence of a base. Suitable bases include organic and inorganic bases, such as for example, metal carbonates and bicarbonates, carboxylate salts, tertiary and secondary amines,

pyridines, etc.

In a particular embodiment, the reaction of the compound of formula (I) with the carbonyl activating compound is carried out in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et₂O, iPr₂O, dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an ester (e.g. EtOAc) or mixtures thereof. In a particular embodiment, the solvent is selected from ethyl acetate and methylene chloride.

The amount of the carbonyl activating compound can vary within a broad range, typically between 1 and 10 equivalents, preferably between 1.1 and 5 equivalents, with respect to the compound of formula (I).

The reaction rate depends on the amount of carbonyl activating compound, the temperature and the solvent. In a particular embodiment, the reaction is carried out at a temperature between -20°C and 100°C, preferably between 0°C and 80°C, more preferably between 10°C and 50°C.

In a particular embodiment, the reaction is carried out between a compound of formula (Ia) and an anhydride or a carboxylic acid halide, in the presence of an organic solvent, giving rise to a compound of formula (II) wherein X is a group $\text{—O—}\overset{\text{O}}{\parallel}\text{R}^1$, as defined above. In a further embodiment, the carbonyl activating compound is acetic anhydride or trifluoroacetic anhydride. Preferably M is Na or K.

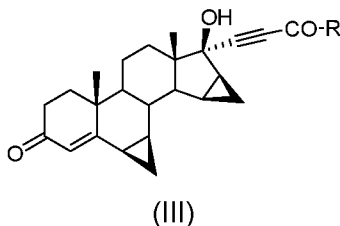
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Process for preparing Compounds of formula (I)

Compounds of formula (I) can be obtained by methods known in the state of the art, as mentioned for example in WO 2010/118023 and WO 2010/146042.

In an embodiment, the compound of formula (I) of the present invention is obtained through route (a) or (b):

(a) by subjecting a compound of formula (III)

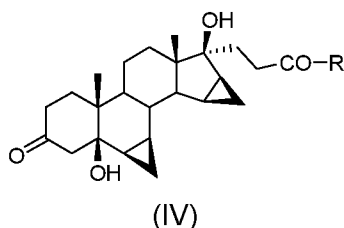


to a hydrogenation reaction in the presence of a Pt or Pd catalyst; or

(b) by subjecting a compound of formula (IV)

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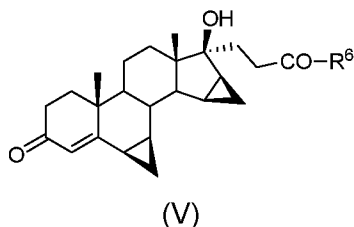
to a dehydration reaction;

wherein R is as defined previously.

5 The hydrogenation reaction (route (a)) is performed using Pt or Pd as catalyst, preferably Pd/C or Pt/C. Preferably, the reaction is performed at atmospheric pressure and in the presence of water, an organic solvent, such as an acyclic or cyclic ether (e.g. Et₂O, iPr₂O, dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an ester (e.g. EtOAc), or mixtures thereof; preferably tetrahydrofuran, ethanol, ethyl acetate, or mixtures thereof. The reaction is preferably carried out between 0°C and 40°C. In a particular embodiment the reaction is carried out in the presence of water.

15 The dehydration reaction (route (b)) can be performed in the presence of a base, such as e.g. alkali metal alkoxides (e.g. sodium methoxide), alkali metal hydroxides, tertiary amines (e.g. triethylamine, pyridine) or carbonate bases (e.g. K₂CO₃). The reaction can be carried in the presence of an organic solvent, water or mixtures thereof.

20 If the compound of formula (I) is a compound of formula (Ia), it can be also obtained by reacting a compound of formula (V)



25 wherein R⁶ is selected from -OR', -SR' and -NR'R'', wherein each R' and R'' is independently selected from H, substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted aryl;

with an alkali metal hydroxide or an alkali metal alkoxide.

30 In a particular embodiment, the alkali metal hydroxide or alkali metal alkoxide is selected from NaOH, KOH, MeONa, MeOK, EtONa, EtOK, tBuONa and tBuOK. The reaction can be performed in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et₂O, iPr₂O, dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g.

pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an alcohol (e.g. methanol, ethanol) or an ester (e.g. EtOAc). In a particular embodiment, the organic solvent is selected from methanol, tetrahydrofuran, toluene and mixtures thereof.

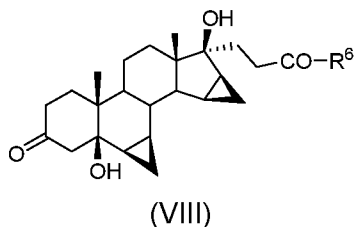
- 5 In an embodiment of the invention, R^6 is a group $-OR'$, wherein R' is selected from H and substituted or unsubstituted C_1-C_6 alkyl. More preferably, R' is selected from H, methyl and ethyl.

In a particular embodiment, the reaction is carried out using KOH in the presence of a mixture of tetrahydrofuran and methanol.

- 10 In another embodiment, the reaction is carried out using MeONa in the presence of a mixture of tetrahydrofuran and methanol.

In another embodiment, the reaction is carried out using tBuOK in the presence of toluene or tetrahydrofuran.

- 15 Alternatively, the compound of formula (Ia) can be obtained by reacting a compound of formula (VIII)



- 20 wherein R^6 is selected from $-OR'$, $-SR'$, $-NR'R''$, wherein each R' and R'' is independently selected from H, substituted or unsubstituted C_1-C_6 alkyl and substituted or unsubstituted aryl;

with an alkali metal hydroxide or an alkali metal alkoxide.

In this way, both dehydration of the hydroxyl group at position 5 and formation of the alkali metal caboxylate salt take place, leading to a compound of formula (Ia).

- 25 In a particular embodiment, the alkali metal hydroxide or alkali metal alkoxide is selected from NaOH, KOH, MeONa, MeOK, EtONa, EtOK, tBuONa and tBuOK. The reaction can be performed in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et_2O , iPr_2O , dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), and alcohol (e.g. methanol, ethanol) or an ester (e.g. EtOAc) or mixtures thereof. In a particular embodiment, the organic solvent is selected from methanol, tetrahydrofuran, toluene and mixtures thereof.
- 30

In an embodiment of the invention, R^6 is a group $-OR'$, wherein R' is selected

from H and substituted or unsubstituted C₁-C₆ alkyl. More preferably, R' is selected from H, methyl and ethyl.

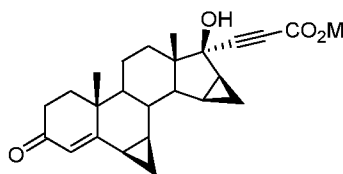
In a particular embodiment, the reaction is carried out using KOH in the presence of a mixture of tetrahydrofuran and methanol.

- 5 In another embodiment, the reaction is carried out using MeONa in the presence of a mixture of tetrahydrofuran and methanol.

In another embodiment, the reaction is carried out using tBuOK in the presence of toluene or tetrahydrofuran.

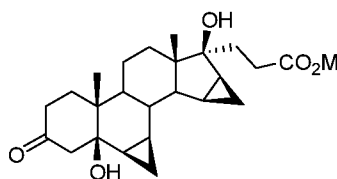
- 10 In another embodiment, the compound of formula (Ia) is obtained through route (a) or (b):

(a) by subjecting a compound of formula (IIIa)



(IIIa)

- 15 to a hydrogenation reaction in the presence of a Pt or Pd catalyst; or
(b) by subjecting a compound of formula (IVa)



(IVa)

to a dehydration reaction;

- 20 wherein M is as defined previously.

The hydrogenation reaction (route (a)) is performed using Pt or Pd as catalyst, preferably Pd/C or Pt/C. Preferably, the reaction is performed at atmospheric pressure and in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et₂O, iPr₂O, dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an ester (e.g. EtOAc) or mixtures thereof; preferably tetrahydrofuran, ethanol, ethyl acetate or mixtures thereof. The reaction is preferably carried out between 0°C and 40°C. In a particular embodiment the reaction is carried out in the presence of water.

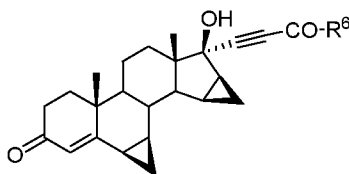
The dehydration reaction (route (b)) can be performed in the presence of a
30 base, such as e.g. alkali metal alkoxides (e.g. sodium methoxide), alkali metal

hydroxides, tertiary amines (e.g. triethylamine, pyridine) or carbonate bases (e.g. K_2CO_3). The reaction can be carried in the presence of an organic solvent, water or mixtures thereof.

5 Process for preparing Compounds of formula (V)

In a particular embodiment, compounds of formula (V) of the present invention are obtained through route (a) or (b):

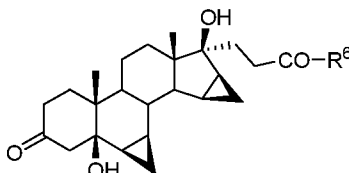
(a) by subjecting a compound of formula (VI)



(VI)

to a hydrogenation reaction in the presence of a Pt or Pd catalyst; or

(b) by subjecting a compound of formula (VII)



(VII)

to a dehydration reaction;

wherein R^6 is as defined previously.

The hydrogenation reaction (route (a)) is performed using Pt or Pd as catalyst, preferably Pd/C or Pt/C. Preferably, the reaction is performed at atmospheric pressure and in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et_2O , iPr_2O , dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an ester (e.g. EtOAc) or mixtures thereof; preferably tetrahydrofuran, ethanol, ethyl acetate or mixtures thereof. The reaction is preferably carried out between 0°C and 40°C.

The dehydration reaction (route (b)) is preferably performed by heating the compound of formula (VII) in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et_2O , iPr_2O , dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an alcohol (e.g. methanol, ethanol), an ester (e.g. EtOAc) or mixtures thereof; or by reaction in the presence of a base, such as e.g. alkali metal alkoxides

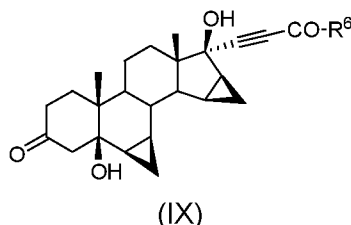
(e.g. sodium methoxide), alkali metal hydroxides, tertiary amines (e.g. triethylamine, pyridine) or carbonate bases (e.g. K_2CO_3), preferably in absence of water.

Processes for preparing compounds of formula (VI) and (VII) are known in the state of the art as disclosed, for example, in WO 2010/118023 and WO 2010/146042.

5

Process for preparing Compounds of formula (VIII)

In a particular embodiment, compounds of formula (VIII) of the present invention are obtained by subjecting a compound of formula (IX)



10

wherein R^6 is as defined previously,

to a hydrogenation reaction in the presence of a Pt or Pd catalyst.

The hydrogenation reaction is performed using Pt or Pd as catalyst, preferably Pd/C or Pt/C. Preferably, the reaction is performed at atmospheric pressure or at a hydrogen overpressure, and in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et_2O , iPr_2O , dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an ester (e.g. EtOAc) or mixtures thereof; preferably tetrahydrofuran, ethanol, ethyl acetate or mixtures thereof. The reaction is preferably carried out between 0°C and 40°C.

In a particular embodiment, the hydrogenation reaction of the compound of formula (IX) is performed using Pt/C as catalyst, tetrahydrofuran as solvent and a hydrogen overpressure of 0.1 bar. Preferably, R^6 is a group $-OR'$, wherein R' is selected from H and substituted or unsubstituted C_1-C_6 alkyl. More preferably, R' is selected from H, methyl and ethyl.

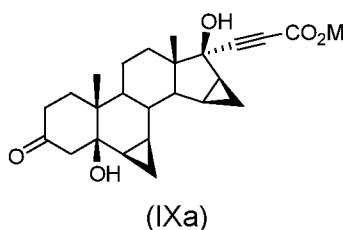
Processes for preparing compounds of formula (IX) are known in the state of the art as disclosed, for example, in WO 2010/118023 and WO 2010/146042.

Process for preparing Compounds of formula (IIIa) and (IVa)

In a particular embodiment, compounds of formula (IIIa) of the present invention are obtained by subjecting a compound of formula (IXa)

30

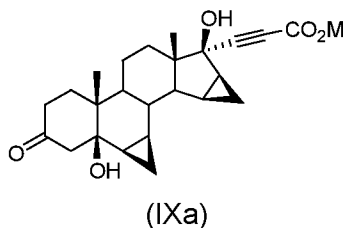
16



wherein M is as defined previously,
to a dehydration reaction.

- 5 The dehydration reaction (route (b)) is preferably performed by heating the compound of formula (VII) in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et₂O, iPr₂O, dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an alcohol (e.g. methanol, ethanol), an ester (e.g. EtOAc) or mixtures
10 thereof; or by reaction in the presence of a base, such as e.g. alkali metal alkoxides (e.g. sodium methoxide), alkali metal hydroxides, tertiary amines (e.g. triethylamine, pyridine) or carbonate bases (e.g. K₂CO₃).

- In a particular embodiment, compounds of formula (IVa) of the present invention
15 are obtained by subjecting a compound of formula (IXa)

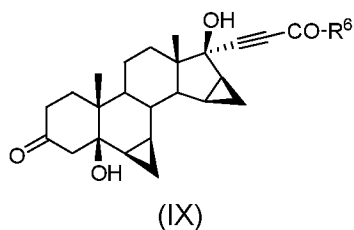


wherein M is as defined previously,
to a hydrogenation reaction in the presence of a Pt or Pd catalyst.

- 20 The hydrogenation reaction is performed using Pt or Pd as catalyst, preferably Pd/C or Pt/C. Preferably, the reaction is performed at atmospheric pressure or at a hydrogen overpressure, and in the presence of an organic solvent, such as an acyclic or cyclic ether (e.g. Et₂O, iPr₂O, dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an ester (e.g. EtOAc) or mixtures thereof; preferably tetrahydrofuran,
25 ethanol, ethyl acetate or mixtures thereof. The reaction is preferably carried out between 0°C and 40°C.

- Compounds of formula (IXa) can be obtained by reacting a compound of
30 formula (IX)

17



wherein R⁶ is as defined previously,

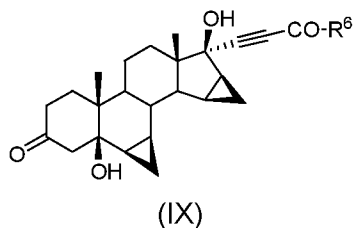
with an alkali metal hydroxide or an alkali metal alkoxide.

- 5 In a particular embodiment, the alkali metal hydroxide or alkali metal alkoxide is selected from NaOH, KOH, MeONa, MeOK, EtONa, EtOK, tBuONa and tBuOK. The reaction can be performed in the presence of water, an organic solvent, such as an acyclic or cyclic ether (e.g. Et₂O, iPr₂O, dioxane, tetrahydrofuran), a hydrocarbon solvent (e.g. pentane, hexane), a halogenated solvent (e.g. methylene chloride), an aromatic solvent (e.g. toluene), an alcohol (e.g. methanol, ethanol) or an ester (e.g. EtOAc), or mixtures thereof. In a particular embodiment, the organic solvent is selected from methanol, tetrahydrofuran, toluene and mixtures thereof.
- 10

In a particular embodiment of the invention, Drospirenone is obtained by a process comprising:

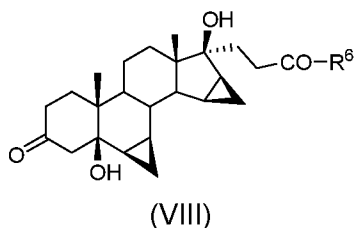
15

- (i) subjecting a compound of formula (IX)



wherein R⁶ is as defined previously,

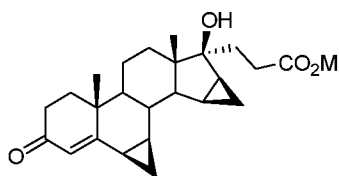
- 20 to a hydrogenation reaction in the presence of a Pt or Pd catalyst, to yield a compound of formula (VIII)



wherein R⁶ is as defined previously;

- 25 (ii) subjecting said compound of formula (VIII) to a reaction with an alkali metal hydroxide or an alkali metal alkoxide, to yield a compound of formula (Ia)

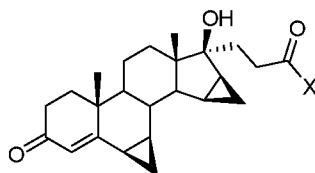
18



(Ia)

wherein M is an alkali metal, and

- (iii) reacting said compound of formula (Ia) with a carbonyl activating compound, to
5 form a compound of formula (II)



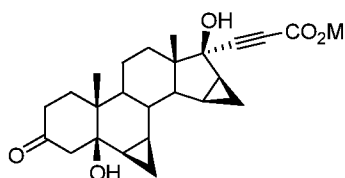
(II)

wherein X is a carbonyl activating group, which cyclizes to give Drospirenone.

- Preferred embodiments for R⁶, M, X, carbonyl activating group and reaction
10 conditions are as defined previously in this document. In a particular embodiment, the above mentioned synthetic sequence is carried out to obtain Drospirenone from a compound of formula (IX) without isolation of the corresponding intermediate compounds (VIII), (Ia) and (II).

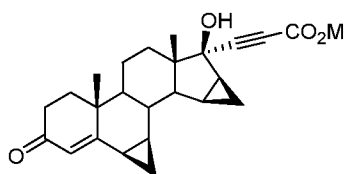
- 15 In another embodiment of the invention, Drospirenone is obtained by a process comprising:

- (i) subjecting a compound of formula (IXa)



(IXa)

- 20 wherein M is as defined previously,
to a reaction with an alkali metal hydroxide or an alkali metal alkoxide, to yield a compound of formula (IIIa)

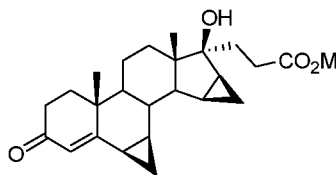


(IIIa)

19

wherein M is as defined previously,

(ii) subjecting said compound of formula (IIIa) to a hydrogenation reaction in the presence of a Pt or Pd catalyst, to yield a compound of formula (Ia)

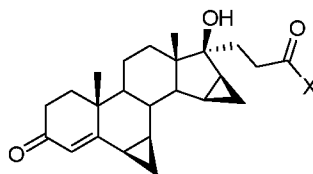


5

(Ia)

wherein M is an alkali metal, and

(iii) reacting said compound of formula (Ia) with a carbonyl activating compound, to form a compound of formula (II)



10

(II)

wherein X is a carbonyl activating group, which cyclizes to give Drospirenone.

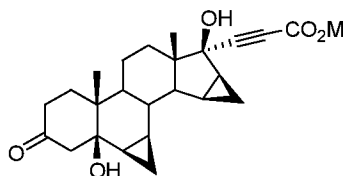
Preferred embodiments for M, X, carbonyl activating group and reaction conditions are as defined previously in this document. In a particular embodiment, the above mentioned synthetic sequence is carried out to obtain Drospirenone from a compound of formula (IXa) without isolation of the corresponding intermediate compounds (IIIa), (Ia) and (II).

15

In another embodiment of the invention, Drospirenone is obtained by a process comprising:

(i) subjecting a compound of formula (IXa)

20



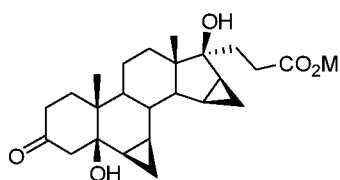
(IXa)

wherein M is as defined previously,

to a hydrogenation reaction in the presence of a Pt or Pd catalyst, to yield a compound of formula (IVa)

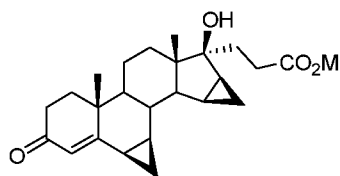
25

20



(IVa)

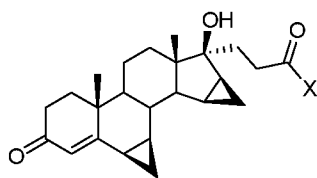
(ii) subjecting said compound of formula (IVa) to a dehydration reaction, to yield a compound of formula (Ia)



(Ia)

wherein M is an alkali metal, and

(iii) reacting said compound of formula (Ia) with a carbonyl activating compound, to form a compound of formula (II)



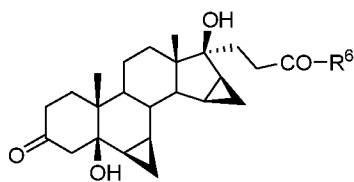
(II)

wherein X is a carbonyl activating group, which cyclizes to give Drospirenone.

Preferred embodiments for M, X, carbonyl activating group and reaction conditions are as defined previously in this document. In a particular embodiment, the above mentioned synthetic sequence is carried out to obtain Drospirenone from a compound of formula (IXa) without isolation of the corresponding intermediate compounds (IVa), (Ia) and (II).

In a particular embodiment of the invention, Drospirenone is obtained by a process comprising:

(i) subjecting a compound of formula (VII)

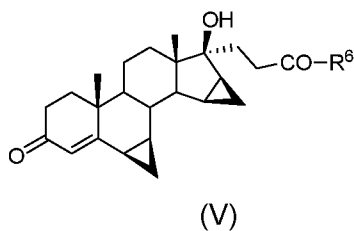


(VII)

wherein R⁶ is as defined previously,

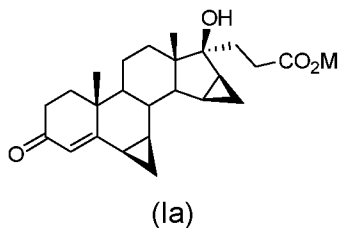
21

to a dehydration reaction, to yield a compound of formula (V)



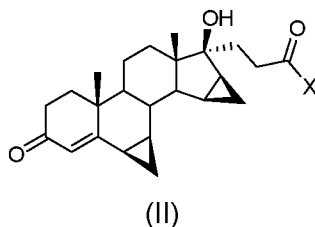
wherein R^6 is as defined previously;

- 5 (ii) subjecting said compound of formula (V) to a reaction with an alkali metal hydroxide or an alkali metal alkoxide, to yield a compound of formula (Ia)



wherein M is an alkali metal, and

- 10 (iii) reacting said compound of formula (Ia) with a carbonyl activating compound, to form a compound of formula (II)



wherein X is a carbonyl activating group, which cyclizes to give Drospirenone.

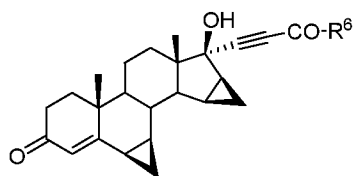
- 15 Preferred embodiments for R^6 , M, X, carbonyl activating group and reaction conditions are as defined previously in this document. In a particular embodiment, the above mentioned synthetic sequence is carried out to obtain Drospirenone from a compound of formula (VII) without isolation of the corresponding intermediate compounds (V), (Ia) and (II).

20

In a particular embodiment of the invention, Drospirenone is obtained by a process comprising:

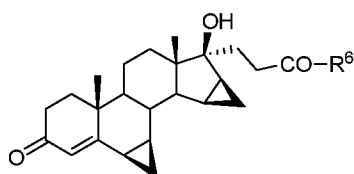
- (i) subjecting a compound of formula (VI)

22



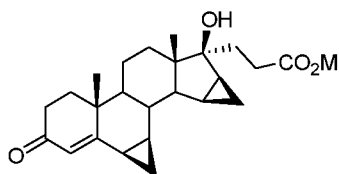
(VI)

wherein R^6 is as defined previously,
 to a hydrogenation reaction in the presence of a Pt or Pd catalyst; to yield a
 5 compound of formula (V)



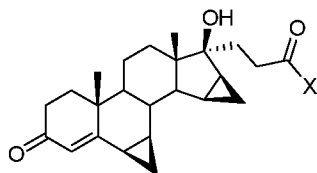
(V)

wherein R^6 is as defined previously;
 (ii) subjecting said compound of formula (V) to a reaction with an alkali metal
 10 hydroxide or an alkali metal alkoxide, to yield a compound of formula (Ia)



(Ia)

wherein M is an alkali metal, and
 (iii) reacting said compound of formula (Ia) with a carbonyl activating compound, to
 15 form a compound of formula (II)



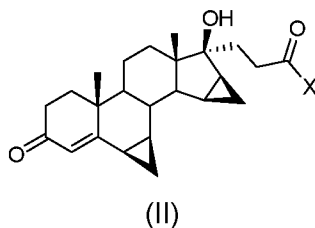
(II)

wherein X is a carbonyl activating group, which cyclizes to give Drospirenone.

Preferred embodiments for R^6 , M, X, carbonyl activating group and reaction
 20 conditions are as defined previously in this document. In a particular embodiment, the
 above mentioned synthetic sequence is carried out to obtain Drospirenone from a
 compound of formula (VI) without isolation of the corresponding intermediate
 compounds (V), (Ia) and (II).

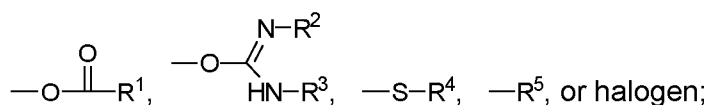
Compounds of formula (II)

In another aspect, the invention is directed to a compound of formula (II)



- 5 wherein X is a carbonyl activating group,
or a solvate thereof.

In a particular embodiment, the carbonyl activating group X is selected from a compound of formula:

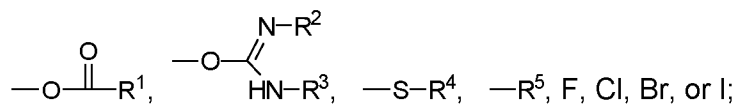


- 10 wherein

R¹, R² and R³ are independently selected from substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₃-C₇ cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

- 15 R⁴ and R⁵ are independently selected from a substituted or unsubstituted nitrogen-containing heteroaryl.

More preferably, X is selected from a compound of formula:



wherein

- 20 R¹ is selected from substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₃-C₇ cycloalkyl, and substituted or unsubstituted phenyl;

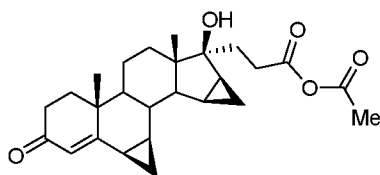
R² and R³ are independently selected from substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted C₃-C₇ cycloalkyl;

R⁴ and R⁵ are independently selected from pyridine and imidazol.

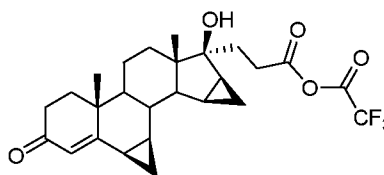
- 25 In another particular embodiment, X is selected from acetyloxy, propionyloxy, trifluoroacetyloxy, 2,4,6-trichlorobenzoyloxy, 1,3-dicyclohexyl-2-isoureido, 1,3-diisopropyl-2-isoureido, 1-ethyl-3-(3-dimethylaminopropyl)-2-isoureido, 2-pyridylthio, 2-imidazolthio, 1-imidazol, Cl, Br and I.

In a further embodiment, the compound of formula (II) is selected from a

compound of formula (IIa) and (IIb):



(IIa)



(IIb)

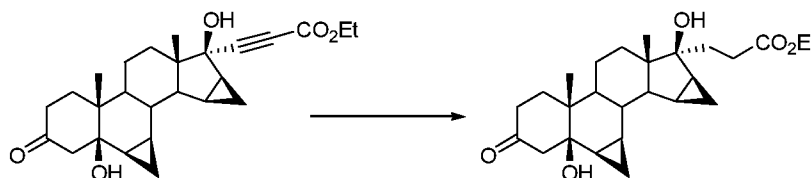
or a solvate thereof.

5

The following examples illustrate the invention and should not be considered as limitative of the invention.

EXAMPLES

- 10 **Example 1. Synthesis of 6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 β -dihydroxy-17 α -(2-ethoxycarbonyl)-ethyl-androstan-3-one**



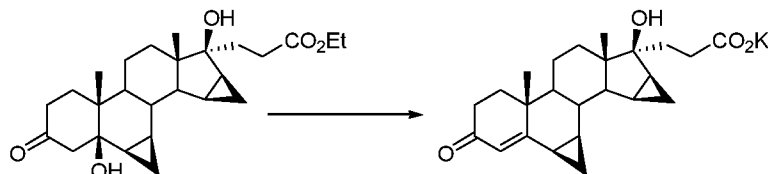
- 0.05 g of Pt/C (50% moisture) were added to a solution of 5 g (11.7 mmol) of 6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 β -dihydroxy-17 α -(2-ethoxy-carbonyl)-ethynyl-androstan-3-one in 25 ml of tetrahydrofuran at 5/10°C. The system was first purged with nitrogen and then with hydrogen and stirred under a hydrogen atmosphere at an overpressure of 0.1 bar for 6 hours. The catalyst was eliminated by filtration and the solid was washed with 5 ml of tetrahydrofuran. The solvent was eliminated under reduced pressure and methylene chloride (15 ml) was added. The mixture was stirred at 0/5°C and filtered. 4.95 g of 6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 β -dihydroxy-17 α -(2-ethoxycarbonyl)-ethyl-androstan-3-one were obtained.

- ¹H-NMR (400 MHz, CDCl₃, δ): 0.28 (1H, q, J=8.0 Hz), 0.60-0.70 (2H, m), 0.70-0.90 (3H, m), 0.87 (3H, s, CH₃ 18), 1.00-1.10 (3H, m), 1.20 (3H, s, CH₃ 19), 1.22 (3H, t, J=8.0 Hz, CH₃ Et), 1.10-1.40 (5 H, m), 1.45-2.00 (4 H, m), 2.00-2.30 (3H, m), 2.43 (1H, d, J=12.0 Hz, H4), 2.50-2.70 (2H, m), 2.92 (1H, d, J=12.0 Hz, H4), 4.10 (2H, q, J=8.0 Hz, CH₂ Et).

- ¹³C-NMR (100 MHz, CDCl₃, δ): 8.0 (CH₂), 11.8 (CH₂), 14.3 (CH₃), 16.2 (CH), 16.9 (CH), 17.4 (CH₃), 19.4 (CH₃), 22.1 (CH₂), 22.8 (CH), 24.8 (CH), 29.4 (CH₂), 29.7 (CH₂), 31.9 (CH₂), 34.4 (CH₂), 34.5 (CH), 36.4 (CH₂), 36.7 (CH₂), 40.3 (C), 42.8 (C), 47.7 (CH), 52.9 (CH), 53.6 (CH₂, C4), 75.9 (C), 81.9 (C), 175.0 (O-C=O), 211.0 (C=O, C3).

30

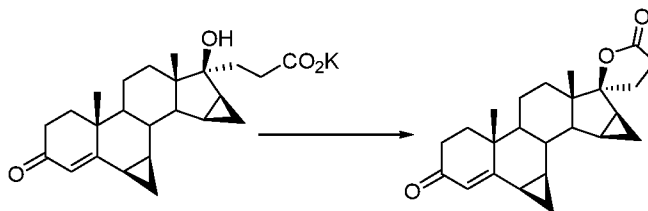
Example 2. Synthesis of 6 β ,7 β ;15 β ,16 β -dimethylene-17 β -hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid potassium salt



5 A solution was formed by 5 g (11.6 mmol) of 6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 β -dihydroxy-17 α -(2-ethoxycarbonyl)-ethyl-androstan-3-one in 30 ml of tetrahydrofuran and 7.5 ml of methanol at 20/25°C. 1.2 g (0.043 mol) of potassium hydroxide were added and the mixture was stirred for 16 hours. Diisopropyl ether (30 ml) was then added, the mixture was cooled to 0/5°C, filtered and washed with
10 diisopropyl ether (5 ml) at 0/5°C, to yield 4,38 g of the title compound.

Similar results were obtained by using potassium tert-butoxide in toluene or in THF; and also by using sodium methoxide in methanol and THF as solvent.

Example 3. Synthesis of Drospirenone

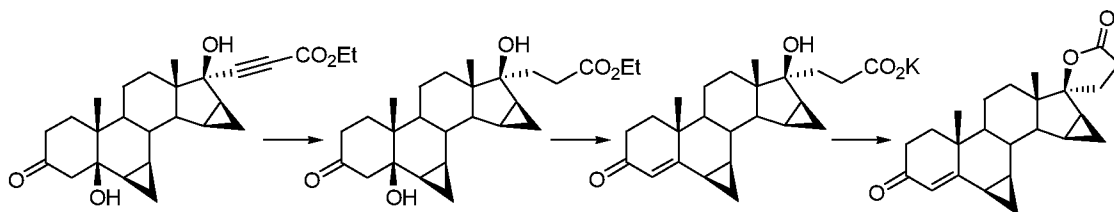


15 5.75 ml of acetic anhydride (59.0 mmol) were added to a suspension of 5 g (11.8 mmol) of 6 β ,7 β ;15 β ,16 β -dimethylene-17 β -hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid potassium salt in ethyl acetate at 20/25°C and the mixture was stirred for 1 hour. 25 ml of a 7% solution of sodium carbonate were added following by stirring.
20 The phases were separated. The organic layer was washed with water and evaporated under reduced pressure. Isopropanol was added, the mixture was cooled to 0/5°C, filtered and washed with isopropanol at 0/5°C. 4.0 g of drospirenone with a 99.6% purity were obtained.

Similar results were obtained by using trifluoroacetic anhydride instead of acetic
25 anhydride.

Similar results were obtained also by using ethyl acetate or methylene chloride as solvent.

Example 4. Synthesis of Drospirenone without isolation of intermediate compounds

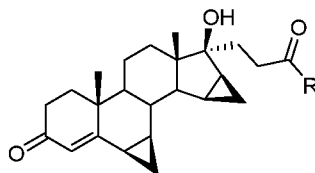


- 0.05 g of Pt/C (50% moisture) were added to a solution of 5 g (11.7 mmol) of
- 5 6β,7β;15β,16β-dimethylene-5β,17β-dihydroxy-17α-(2-ethoxy-carbonyl)-ethynyl-androstan-3-one in 25 ml of tetrahydrofuran at 5/10°C. The system was first purged with nitrogen and then with hydrogen and stirred under a hydrogen atmosphere at an overpressure of 0.1 bar for 6 hours. The catalyst was eliminated by filtration, the solid was washed with tetrahydrofuran (5 ml) and the temperature was adjusted to 20/25°C.
- 10 1.2 g (0.043 mol) of sodium hydroxide were added to the above solution and the mixture was stirred for 16 hours. Solvent was then evaporated and ethyl acetate was added until a final volume of 30 ml.

- 5.75 ml of acetic anhydride (59.0 mmol) were added to the resulting suspension and the mixture was stirred for 1 hour. 25 ml of a 7% solution of sodium carbonate
- 15 were added following by stirring. The phases were separated. The organic layer was washed with water and evaporated under reduced pressure. Isopropanol was added, the mixture was cooled to 0/5°C, filtered and washed with isopropanol at 0/5°C. 3.0 g of drospirenone were obtained.

CLAIMS

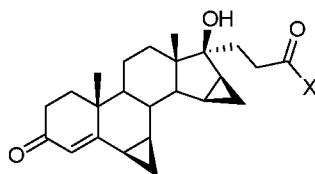
1. A process for obtaining Drospirenone or a solvate thereof, which comprises reacting a compound of formula (I)



(I)

wherein

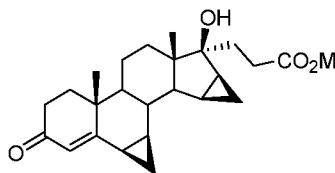
- R is selected from -OM, -OR^a, -SR^b, -NR^cR^d, OSiR^eR^fR^g; wherein M is an alkali metal, and R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently selected from H, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted aryl, with a carbonyl activating compound, to form a compound of formula (II)



(II)

- wherein X is a carbonyl activating group, which cyclizes to give Drospirenone.

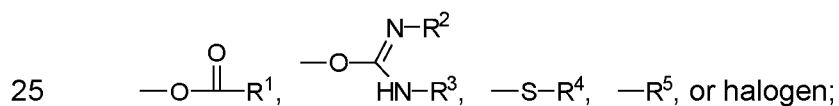
2. Process according to claim 1, wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein M is an alkali metal.

3. Process according to any previous claim, wherein X is selected from a group of formula:

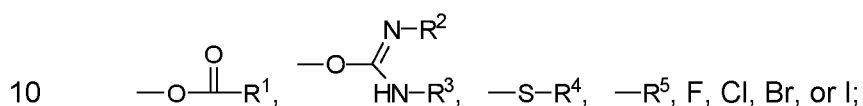


wherein

R^1 , R^2 and R^3 are independently selected from substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^4 and R^5 are independently selected from a substituted or unsubstituted nitrogen-containing heteroaryl.

4. Process according to claim 3, wherein X is selected from:



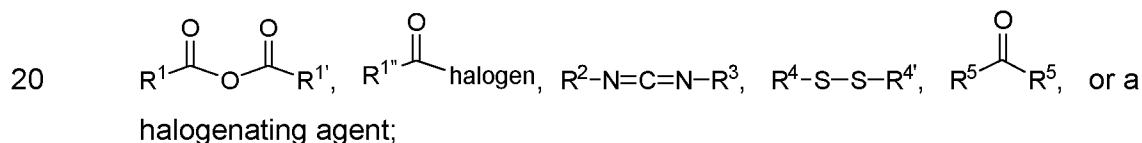
wherein

R^1 is selected from substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, and substituted or unsubstituted phenyl;

R^2 and R^3 are independently selected from substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted C_3 - C_7 cycloalkyl;

R^4 and R^5 are independently selected from pyridine and imidazol.

5. Process according to any previous claims, wherein the carbonyl activating compound is selected from a compound of formula:

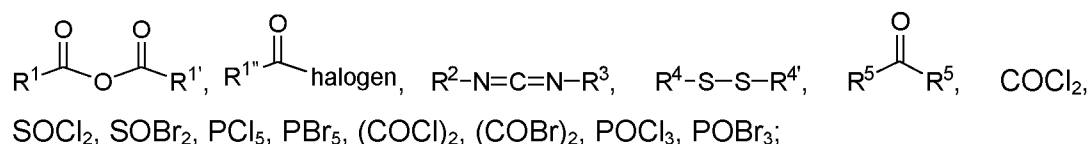


wherein

R^1 , $R^{1'}$, $R^{1''}$, R^2 and R^3 are independently selected from substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^4 , R^4' , and R^5 are independently selected from a substituted or unsubstituted nitrogen-containing heteroaryl.

6. Process according to claim 5, wherein the carbonyl activating compound is selected from a compound of formula:



wherein

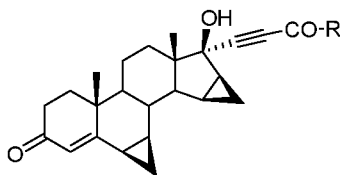
R^1 , $R^{1'}$ and $R^{1''}$ are independently selected from substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, and substituted or unsubstituted phenyl;

R^2 and R^3 are independently selected from substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted C_3 - C_7 cycloalkyl;

R^4 , R^4' , and R^5 are independently selected from pyridine and imidazol.

7. Process according to any of claims 1 to 6, wherein the compound of formula (I) is obtained:

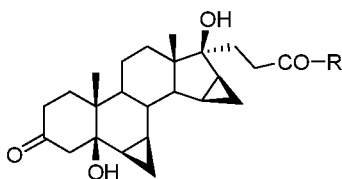
(a) by subjecting a compound of formula (III)



(III)

to a hydrogenation reaction in the presence of a Pt or Pd catalyst; or

(b) by subjecting a compound of formula (IV)

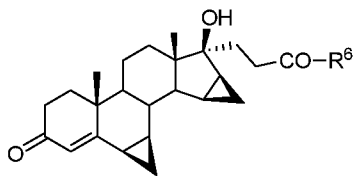


(IV)

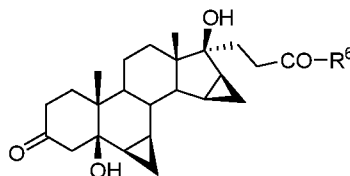
to a dehydration reaction;

wherein R is as defined previously.

8. Process according to any of claims 2 to 6, wherein the compound of formula (Ia) is obtained by reacting a compound of formula (V) or (VIII)



(V)



(VIII)

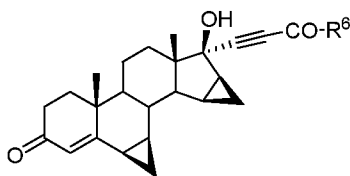
wherein R^6 is selected from $-OR'$, $-SR'$ and $-NR'R''$, wherein each R' and R'' is independently selected from H, substituted or unsubstituted C_1-C_6 alkyl and substituted or unsubstituted aryl,

with an alkali metal hydroxide or an alkali metal alkoxide.

5

9. Process according to claim 8, wherein the compound of formula (V) is obtained:

(a) by subjecting a compound of formula (VI)

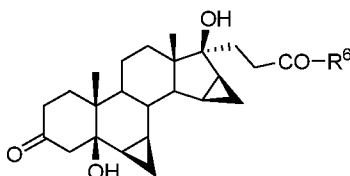


(VI)

10

to a hydrogenation reaction in the presence of a Pt or Pd catalyst; or

(b) by subjecting a compound of formula (VII)



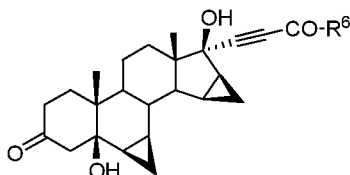
(VII)

to a dehydration reaction;

15

wherein R^6 is as defined in claim 8.

10. Process according to claim 8, wherein the compound of formula (VIII) is obtained by subjecting a compound of formula (IX)



(IX)

20

wherein R^6 is as defined in claim 8,

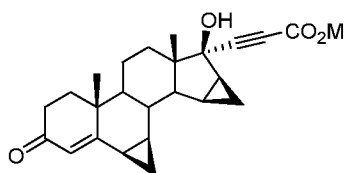
to a hydrogenation reaction in the presence of a Pt or Pd catalyst.

11. Process according to any of claims 2 to 6, wherein the compound of formula (Ia) is obtained:

25

a) by subjecting a compound of formula (IIIa)

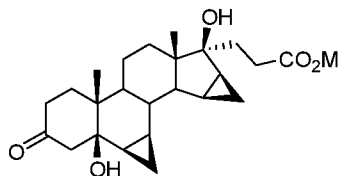
31



(IIIa)

to a hydrogenation reaction in the presence of a Pt or Pd catalyst; or

(b) by subjecting a compound of formula (IVa)



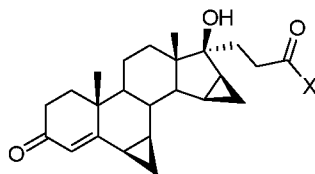
(IVa)

to a dehydration reaction;

wherein M is as defined previously.

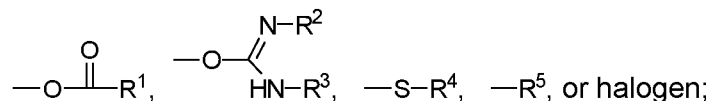
12. Process according to any previous claim, wherein M is selected from Li, Na and K.

13. A compound of formula (II)



(II)

wherein X is selected from a group of formula:



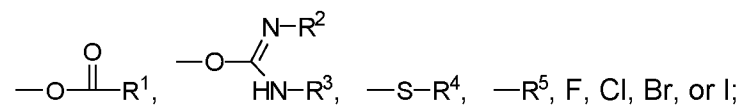
wherein

R^1 , R^2 and R^3 are independently selected from substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_3 - C_7 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^4 and R^5 are independently selected from a substituted or unsubstituted nitrogen-containing heteroaryl;

or a solvate thereof.

14. Compound according to claim 13, wherein X is selected from:



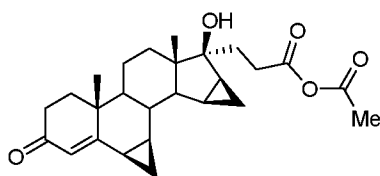
wherein

R^1 is selected from substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, substituted or unsubstituted $\text{C}_3\text{-C}_7$ cycloalkyl, and substituted or unsubstituted phenyl;

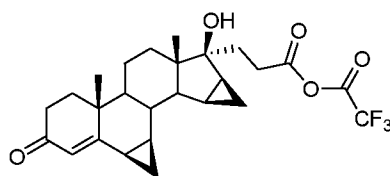
R^2 and R^3 are independently selected from substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl and substituted or unsubstituted $\text{C}_3\text{-C}_7$ cycloalkyl;

R^4 and R^5 are independently selected from pyridine and imidazol; or a solvate thereof.

15. Compound according to claim 14, which is selected from a compound of formula (IIa) and (IIb):



(IIa)



(IIb)

or a solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/052180

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07J53/00
 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)
 C07J

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, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 2010/261896 A1 (NICKISCH KLAUS [DE] ET AL) 14 October 2010 (2010-10-14) page 13, paragraph [0102] - page 14, paragraph [0103] -----	1-15
Y	EP 0 122 232 A1 (CIBA GEIGY AG [CH]) 17 October 1984 (1984-10-17) page 17, last paragraph - page 18, paragraph 1 -----	1-15
Y	US 4 150 127 A (ANNER GEORG ET AL) 17 April 1979 (1979-04-17) column 12, lines 32-40 -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

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"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

9 May 2012

Date of mailing of the international search report

18/05/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/052180

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/052180

Patent document cited in search report	Publication date	Patent family member(s)	Publication date