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(71) Applicant *(for all designated States except US)*: **CHORISIS S.R.L.** [IT/IT]; Via Mons. Colombo, 30/32, I-22066 Mariano Comense (CO) (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GALLIANI, Guido** [IT/IT]; Via Santa Liberata, 60, I-20033 Desio (Milano) (IT). **RADAELLI, Vincenzo** [IT/IT]; Via Trento, 17, I-22066 Mariano Comense (CO) (IT). **TERRANEO, Alberto** [IT/IT]; Via Fogazzaro, 5 C, I-22066 Mariano Comense (CO) (IT).

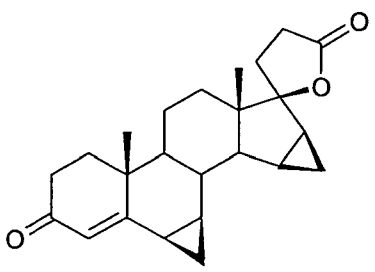
(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Plinio, 63, I-20129 Milano (IT).

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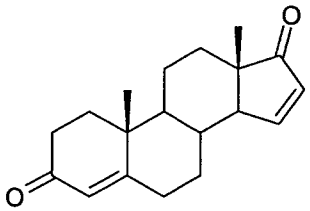
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(54) **Title:** PROCESS FOR THE PREPARATION OF DROSPIRENONE



(I)



(V)

(57) **Abstract:** The present invention describes a process for the preparation of drospirenone (I) using androstendione as a starting material. In particular, androstendione protected on carbonyl group in position 3 as an enol-ether is functionalized in position 16 with a sulfoxide group and the derivative thus obtained undergoes thermal elimination in alkaline to give androsta-4,15- diene-3, 17-dione (V) which is further transformed into Drospirenone (I).

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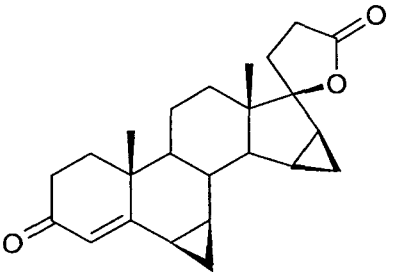
PROCESS FOR THE PREPARATION OF DROSPIRENONE

Field of the invention

The present invention discloses a process for the preparation of drospirenone.

Basis for the invention

Drospirenone (**I**) [chemical name 6β,7β,15β,16β-dimethylene-3-oxo-17α-pregn-4-en-21,17-carbolactone] is a steroid endowed with progestinic activity used as a birth control agent.



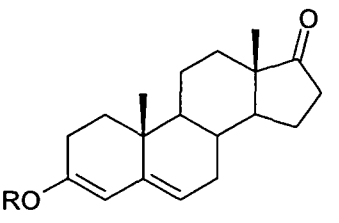
(I)

The synthesis of this compound is described for example in WO 2006/061309, WO 2006/059167, WO 2006/059168, EP 1571153, EP 0918791, DE 3626838 and DE 2652761.

Description of the invention

The present invention discloses a process for the preparation of drospirenone (**I**) comprising the following steps:

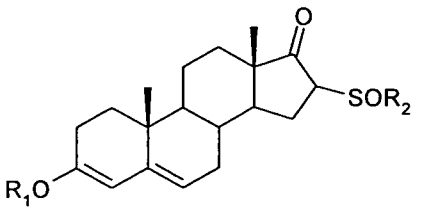
a) reaction of a derivative protected at the carbonyl at the 3-position of androstenedione, of formula (**II**):



(II)

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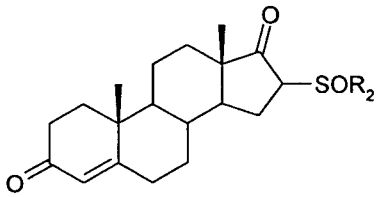
where R represents a linear or branched C_1-C_5 alkyl group, , preferably ethyl, with a sulfinic acid ester, preferably methyl benzenesulfinate, in alkaline conditions to give a compound of formula (**III**):



(III)

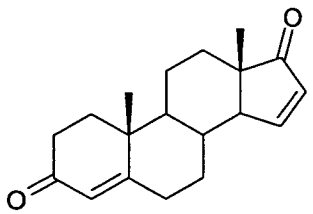
where R^1 is as previously defined and R^2 represents an alkyl or aryl group, preferably phenyl;

b) deprotection of the carbonyl at the 3-position 3 give a compound of formula (**IV**):



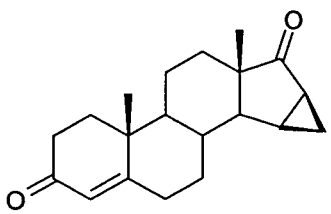
(IV)

c) thermal elimination of the compound of formula (**IV**) to give androsta-4,15-diene-3,17-dione (**V**):



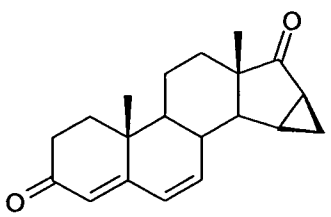
(V)

d) methylenation of androsta-4,15-diene-3,17-dione (**V**) to give 15β,16β-methylenandrosta-4-ene-3,17-dione (**VI**):



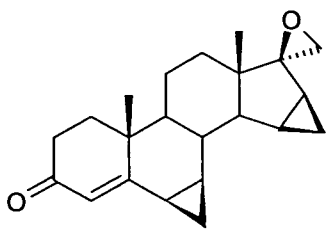
(VI)

e) dehydrogenation of (**VI**) to give 15β,16β-methylenandrosta-4,6-diene-3,17-dione (**VI**)



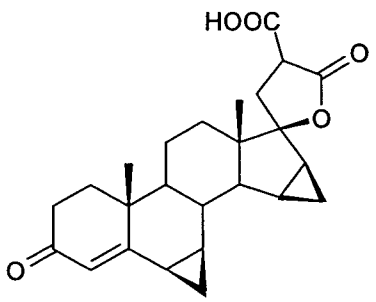
(VII)

f) methylenation of (**VII**) to give 6β,7β,15β,16β-dimethylene-17β-spirooxiraneandrost-4-en-3-one (**VIII**):



(VIII)

g) reaction of (**VIII**) with diethyl malonate in alkaline conditions to give carboxylated drospirenone (**IX**)



(IX)

and

h) decarboxylation of (**IX**) to give drospirenone (**I**).

Step a) is typically performed in an aprotic polar solvent, such as tetrahydrofuran, in alkaline conditions, preferably by using potassium *ter*-butylate. Typically, a solution of the selected base in the selected organic solvent is prepared, into which compound (**II**) and the sulfinylating agent are

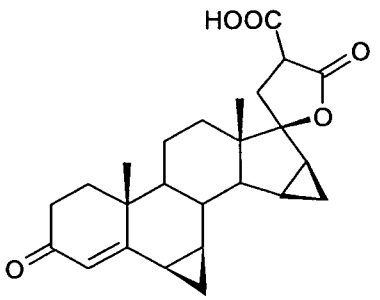
added successively. When the reaction is over, compound (**III**) obtained is not isolated, but treated directly with a mineral acid, typically 35% hydrochloric acid, by pouring the reaction mixture into acidic water and reacting at room temperature, typically between 20 e 30°C. Also the resulting sulfoxide of formula (**IV**) is not isolated, but directly subjected to thermal elimination in alkaline conditions to give androsta-4,15-diene-3,17-dione (**V**).

Typically, the reaction mixture containing sulfoxide (**IV**) is poured into an apolar organic solvent, such as toluene, chlorobenzene or xylene, preferably xylene; the organic phase is separated and the aqueous phase is again extracted one or more times with the same organic solvent. Collected organic phases are treated with an inorganic base, for example sodium carbonate, in a molar ratio of approximately 5:1 as to 3-ethoxy-androsta-3,5-diene-17-one; the mixture is heated to the boiling point of the solvent, approximately two thirds of which are distilled off; heating is then maintained for about four hours, till completion of the reaction. The reaction mixture is then filtered and the residue is washed with some more solvent. The collected filtrates are evaporated and the residue is purified typically through column chromatography on silica gel to give compound (**V**).

Methylenation reactions are usually performed with trimethyl-sulfoxonium iodide as described in the literature. Typically, a solution of trimethylsulfoxonium iodide is treated with sodium hydride, followed by the compound of formula (**V**) or formula (**VII**) in an aprotic polar solvent, for example tetrahydrofuran, and reacted till completion, whereby products are isolated.

Dehydrogenation is usually carried out with chloranil in the presence of p-toluenesulfonic acid, with acetone as a solvent. The reaction is performed at room temperature, preferably between 20 and 25°C, for approximately 20 hours, usually between 20 and 21 hours.

The step leading to drospirenone is performed according to standard methods; usually a solution of ethyl malonate and sodium ethoxide in ethanol is prepared, which is treated with 6β,7β,15β,16β-dimethylene-17β-spirooxiraneandrost-4-en-3-one (**VIII**), and refluxed till completion (in about 2 hours). The reaction mixture is then cooled and treated, in the order, with an inorganic base, for example with sodium hydroxide, and with a mineral acid, for example with hydrochloric acid, to give carboxylated drospirenone (**IV**)



(IX)

from which the alpha isomer is separated by crystallization. Drospirenone is obtained by decarboxylation effected according to standard methods, for example by dissolving the product in dimethylformamide and heating it at 130°C. As an alternative, raw carboxylated drospirenone may be used, and the crystallization may be performed on final drospirenone.

The process of the invention has the advantages of using an inexpensive starting material, being performed in a few steps, and not involving the use of microorganisms.

The following example describes the invention in deeper detail.

EXAMPLE

Step 1: 3-Ethoxy-androsta-3,5-diene-17-one

A suspension of 80 g (0.279 moles) of androstenedione in 144 ml of ethanol, blanketed with nitrogen, is treated with 57.6 g (0.389 moles) of triethyl orthoformate and 2.69 g (0.016 moles) of pyridine hydrobromide.

Stirring is maintained at 25°/30°C for 6 hours. The reaction mixture is

cooled at 0°-5°C and treated with 4 g (0.039 moles) of triethylamine; after stirring for an additional hour at 0°-5°C, the solid is filtered by suction and washed with some ethanol on the filter.

After drying under reduced pressure at 30°C, 76.6 g (0.244 moles) of 3-ethoxy-androsta-3,5-diene-17-one are obtained.

Molar yield: 87.2%.

Step 2: Androsta-4,15-diene-3,17-dione

A solution of 20.28 g (0.172 moles) of potassium *ter*-butylate 95% in 600 ml of tetrahydrofuran, blanketed with nitrogen, is treated with 30 g (0.095 moles) of 3-ethoxy-androsta-3,5-diene-17-one at 20-30°C, whereby a yellow-orange solution is formed. The mixture is stirred at 20-25°C for ten minutes, then treated with 26.34 g (0.165 moles) of 98% methyl benzenesulfinate: temperature rises up to 35°C. After stirring at 0-30°C for 30 minutes, a dark solution is obtained. The solution is then poured into a mixture of 600 ml of water and 60 ml of 35% hydrochloric acid, in about 20 minutes, keeping temperature between 10° and 20°C. Stirring is maintained at such temperature for additional 2.5 hours.

600 ml of xylene are added, and after stirring for 15 minutes, phases are separated. The lower aqueous phase is washed with 300 ml of xylene, and, after stirring for 15 minutes, phases are separated. The organic phases are collected and treated with 50.4 g (0.475 moles) of sodium carbonate; the mixture is heated under nitrogen atmosphere to distil off the solvent until an internal temperature of 130°C is reached (710 ml are distilled off), then maintained at reflux for 4 hours, and finally cooled at 20°/30°C. Solids are removed by filtration, washed with 2 x 120 ml of xylene; the solution is concentrated under vacuum until an oily residue is obtained (45.45 g).

After chromatographic separation, 16 g of androsta-4,15-diene-3,17-dione are obtained.

Molar yield: 59.2%.

Analysis: ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.12 (s, 3H, CH_3); 1.26 (s, 3H, CH_3); 5.77 (s, 1H, CH); 6.01 (m, 1H, CH); 7.52 (d, 1H, CH).

Step 3: 15β,16β-Methylenandrosta-4-ene-3,17-dione

A solution of 11.16 g (0.0497 moles) of 98% trimethylsulfoxonium iodide in 180 ml of dimethylsulfoxide, blanketed with nitrogen, is treated with 2.04 g (0.051 moles) of sodium iodide 60% at 20/25°C. The mixture is stirred at 20°/30°C for 1 hour, then treated with a solution of 12 g (0.042 moles) of androsta-4,15-diene-3,17-dione in 60 ml of tetrahydrofuran.

After stirring the mixture at 20°/25°C for 15 hours, the solution obtained is poured into a mixture of 300 g of water and 400 g of crushed ice.

Stirring is maintained for an additional hour, then 150 ml of methylene chloride are added.

Phases are separated; the aqueous phase is extracted with 2 x 100 ml of methylene chloride; after separation of phases, the organic ones are collected, washed with 3 x 100 ml of water, and evaporated under reduced pressure. 13.7 g of a yellow solid are obtained, which is dissolved in methylene chloride. The solution is filtered on silica gel; after evaporation, 8.55 g of 15β,16β-methylenandrosta-4-ene-3,17-dione are obtained.

Molar yield: 68,2%.

Analysis: ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.02 (s, 3H, CH_3); 1.22 (s, 3H, CH_3); 5.78 (s, 1H, CH).

Step 4: 15β,16β-Methylenandrosta-4,6-diene-3,17-dione

A solution of 13.3 g (0.04457 moles) of 15β,16β-methylenandrosta-4-ene-3,17-dione, 133 ml of acetone, 5.3 g of water and 3.46 g (0.01781 moles) of 98% para-toluenesulfonic acid is treated at 20°/25°C with 16.89 g (0.06663 moles) of 97% chloranil, whereby a yellow suspension is obtained, which is stirred at 20°-25°C for 20-21 hours, then dropped into 519 g of water

and 11.94 g (0.298 moles) of sodium hydroxide at 0°C. Temperature is maintained at 0/5°C during dropping; when this is over, the mixture is stirred at 0/5°C for 1 hour and filtered. The solid is washed with 2 x 50 ml of water and dried under vacuum at 50°C.

10.1 g (0.034 moles) of 15β,16β-methylenandrosta-4,6-diene-3,17-dione are obtained.

Molar yield: 76.4%.

Analysis ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.07 (s, 3H, CH_3); 1.15 (s, 3H, CH_3); 5.73 (s, 1H, CH); 6.23 (d,d, 1H, J=8,6 -2,1 H_Z, CH); 6.38 (d,d, 1H, J=8.6 - 1.1 H_Z, CH).

Step 5: 6β,7β,15β,16β-Dimethylene-17β-spirooxiranoandrost-4-en-3-one

A solution of 18.59 g (0.828 moles) of 98% trimethylsulfoxonium iodide in 180 ml of dimethylsulfoxide is treated with 3.37 g (0.843 moles) of 60% sodium hydride, maintained under stirring at room temperature for 1 hour, and finally treated with a solution of 5 g (0.169 moles) of 15β,16β-methyleneandrosta-4,6-diene-3,17-dione in 60 ml of tetrahydrofuran. The mixture is stirred at room temperature for 24 hours, then it is poured into 600 g of ice/water, treated with 230 ml of methylene chloride. Phases are separated; the aqueous layer is extracted with 115 ml of methylene chloride; phases are again separated and the organic phases are collected and washed with 3 x 115 ml of 5% aqueous sodium hydrogen carbonate. After phase separation, the organic phase is evaporated under reduced pressure, whereby 5.9 g of raw 6β,7β,15β,16β-dimethylene-17β-spirooxiraneandrost-4-en-3-one are obtained which is used in the next step without any further purification.

Step 6: Drospirenone

A solution of 9.5 g (0.293 moles) of 21% sodium ethoxide and 10.2 g (0.637 moles) of diethyl malonate in 40 ml of ethanol is refluxed for 1 hour;

after cooling at 40°C, a solution of 5.9 g of raw 6β,7β,15β,16β-dimethylene-17β-spirooxiraneandrost-4-en-3-one and 20 ml of ethanol is added. The reaction mixture is refluxed for 2 hours; when the reaction is over, the mixture is evaporated under reduced pressure and the residue is taken up in 18 ml of ethanol. The solution thus obtained is dropped into a solution of 9.5 g of sodium hydroxide in 161 ml of water, cooled at 0°C under stirring. The mixture is then stirred at room temperature for additional 15-20 hours. The solution is cooled at 0°C and treated dropwise with 25 ml of 35% hydrochloric acid; after stirring at 0°C for 2 hours, the suspension is filtered and the solid is washed with water.

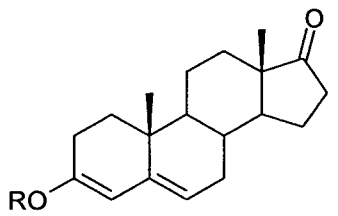
After drying under reduced pressure, 5.8 g of carboxylated drospirenone are obtained. The alpha isomer is separated by crystallization.

Carboxylated drospirenone is dissolved in 45 ml of dimethylformamide and the solution is heated at 130°C for 2 hours. After cooling at room temperature, the solution is poured into 400 g of water, then extracted with 2 x 100 ml of ethyl acetate, phases are separated and the organc phase is dried under reduced pressure. After purification by crystallization, 1.1 g of drospirenone is obtained.

CLAIMS

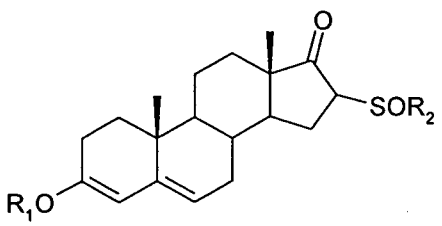
1. A process for the preparation of drospirenone (**I**) comprising the following steps:

a) reaction of a derivative protected at the carbonyl at the 3-position of androstenedione of formula (**II**):



(II)

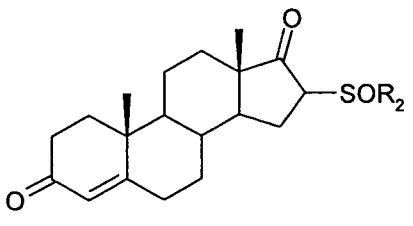
where R represents a linear or branched C_1-C_5 alkyl group, preferably ethyl, with a sulfinic acid ester, preferably methyl benzensulfinate, in alkaline conditions to give a compound of formula (**III**):



(III)

where R^1 is as previously defined and R^2 represents an alkyl or aryl group, preferably phenyl;

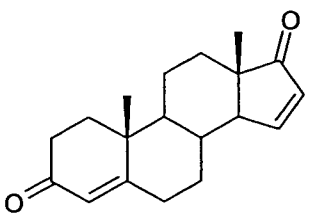
b) deprotection of the carbonyl at the 3-position to give a compound of formula (**IV**):



(IV)

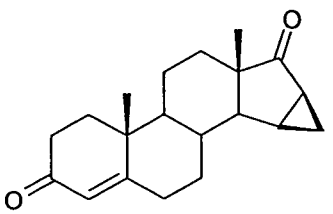
c) thermal elimination of the compound of formula (**IV**) to give

androsta-4,15-diene-3,17-dione (**V**):



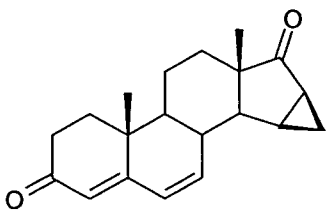
(V)

d) methylenation of androsta-4,15-diene-3,17-dione (**V**) to give 15β,16β-methylenandrosta-4-ene-3,17-dione (**VI**):



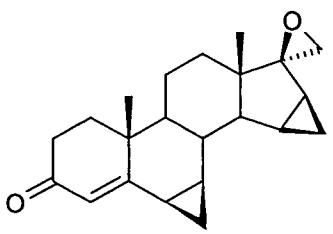
(VI)

e) dehydrogenation of (**VI**) to give 15β,16β-methylenandrosta-4,6-diene-3,17-dione (**VI**)



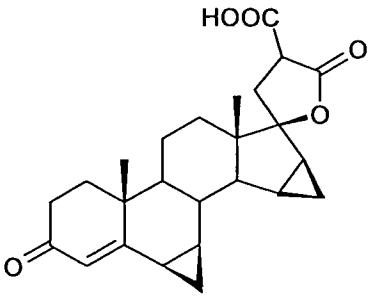
(VII)

f) methylenation of (**VII**) to give 6β,7β,15β,16β-dimethylene-17β-spirooxiraneandrost-4-en-3-one (**VIII**):



(VIII)

g) reaction of (**VIII**) with diethyl malonate in alkaline conditions to give carboxylated drospirenone (**IX**)



(IX)

and

h) decarboxylation of (**IX**) to give drospirenone (**I**).

2. The process according to claim 1 wherein R^1 is ethyl and R^2 is phenyl.

3. The process according to claim 1 or 2 wherein step a) is performed in acetone in the presence of potassium *ter*-butylate as a base and where the sulfinic acid ester is methyl benzenesulfinate.

4. The process according to any one of claims 1 to 3 wherein step b) is performed without isolating compound (**III**), by using hydrochloric acid at room temperature.

5. The process according to any one of claims 1 to 4 wherein step c) is performed without isolating compound (**IV**) in xylene in the presence of sodium carbonate as a base.