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(54) PROCESS FOR THE PREPARATION OF DROSPIRENONE

VERFAHREN ZUR HERSTELLUNG VON DROSPIRENON

PROCEDEZ DE PREPARATION DE LA DROSPIRENONE

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- **ANELLI P L ET AL: "OXIDATION OF DIOLS WITH ALKALI HYPOCHLORITES CATALYZED BY OXAMMONIUM SALTS UNDER TWO-PHASE CONDITIONS" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 54, no. 12, 9 June 1989 (1989-06-09), pages 2970-2972, XP000025425 ISSN: 0022-3263**

EP 1 828 222 B9

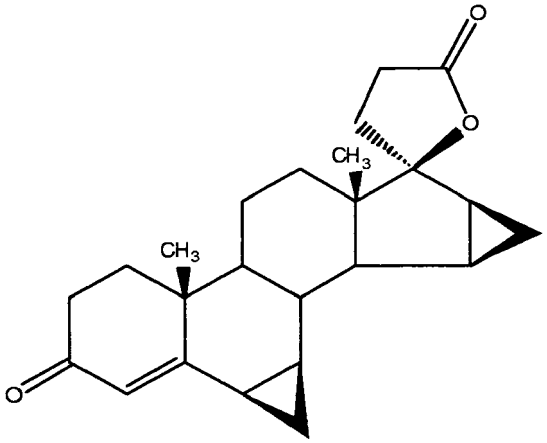
Description

FIELD OF THE INVENTION

[0001] The present invention relates to the field of processes for synthesising steroids, and in particular to a process for the industrial scale preparation of drospirenone.

STATE OF THE ART

[0002] The compound of formula (I) given hereinafter, whose chemical name is 6β,7β;15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, is commonly known as drospirenone:



(I)

[0003] It is a synthetic steroid with progestogenic, antimineralocorticoid and antiandrogenic activity; by virtue of these characteristics drospirenone has long been used for preparing pharmaceutical compositions with contraceptive action for oral administration.

[0004] Many processes are known in the literature for preparing drospirenone, for example the process described in European Patent No. 0 075 189, starting from 3β,7α,15α-trihydroxy-5-androsten-17-one passing via the intermediate 5,6β-epoxy-7β-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one.

[0005] As described in EP 0 075 189, this intermediate is then transformed into 7α-chloro-5,6β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one by a reaction that uses tetrachloromethane both as reagent and reaction solvent. The use of this highly toxic solvent in relatively large quantities is one of the unfavourable aspects of this process.

[0006] In the process described in EP 0 075 189 the intermediate 17α-(3-hydroxypropyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol is arrived at from the intermediate 7α-chloro-5,6 β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one by way of several steps, from which the final product drospirenone is obtained by oxidising with a pyridine/water/chromic anhydride mixture under hot conditions. This step constitutes a further disadvantage of the known process: chromic anhydride, as all Cr (VI) compounds, is actually a known carcinogen whose use is subject to legislative restrictions such that the precautions required during the use and disposal of these products render them practically unusable.

[0007] Another process for preparing drospirenone is described in European Patent No. 0 918 791 B8 wherein the drospirenone is produced in two distinct phases starting from 17α-(3-hydroxypropyl)-6β,7β,15β,16β-dimethylene-5β-androstane-3β,5,17β-triol, using a ruthenium salt as oxidant; in the examples given in said patent crude drospirenone is obtained with a chromatographic purity of 93% which is then improved by chromatography.

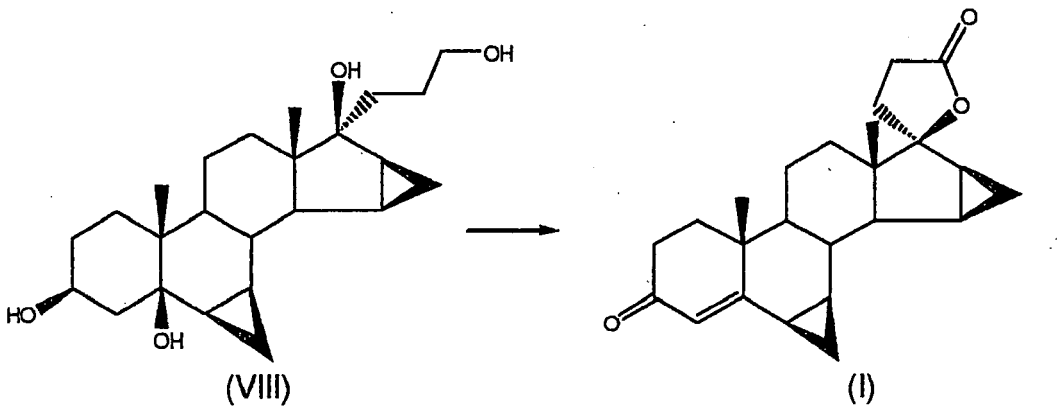
[0008] At this point it is worth noting that a possible technique is the systematic chromatographic purification of industrial batches of steroids, requiring however dedicated equipment and working environments and consequently a considerable logistic and economic involvement.

[0009] There is therefore still a need for a process which enables high purity drospirenone to be prepared, but without presenting the aforestated disadvantages of processes of the known art.

SUMMARY OF THE INVENTION

[0010] The Applicant has now developed a process that enables drospirenone with a high degree of purity to be obtained, suitable for use in the preparation of pharmaceutical compositions, and which overcomes the aforestated disadvantages connected to the use of toxic and carcinogenic reagents and the need for chromatographic purifications of crude drospirenone to obtain a high final purity.

[0011] Subject of the present invention is therefore a process for the preparation of drospirenone, comprising the oxidation of 17α-(3-hydroxypropyl)-6β,7β,15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VIII) with a suitable oxidising agent in an organic solvent in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl radical or a derivative thereof, said oxidation being followed by the addition of a protic acid directly into the same reactor in which the oxidation took place, to obtain the drospirenone of formula (I)



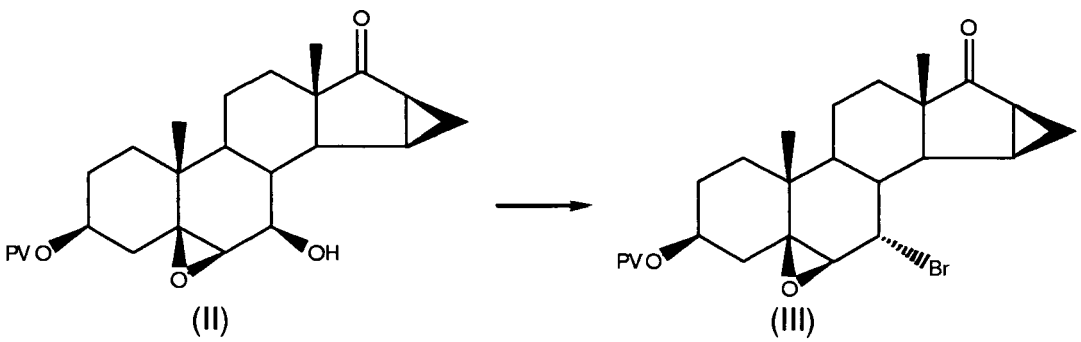
(VIII) (I)

[0012] The characteristics and advantages of the present process will be illustrated in detail in the description which follows.

DETAILED DESCRIPTION OF THE INVENTION

[0013] The oxidation substrate of the present process, i.e. 17α-(3-hydroxypropyl)-6β,7β,15β,16β-dimethylene-5β-androstane-3β,5,17β-triol, can be obtained starting from commercial products by procedures known to any expert of the art. Preferably this product is obtained from 5,6β-epoxy-7β-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one, in accordance with the procedure comprising the following steps:

a) bromination in position 7α of 5,6β-epoxy-7β-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one of formula (II) to obtain 7α-bromo-5,6β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one of formula (III) by reacting the compound of formula (II) with mesyl chloride to obtain the corresponding mesylate which is not isolated and from which the compound of formula (III) is obtained by the addition of lithium bromide:

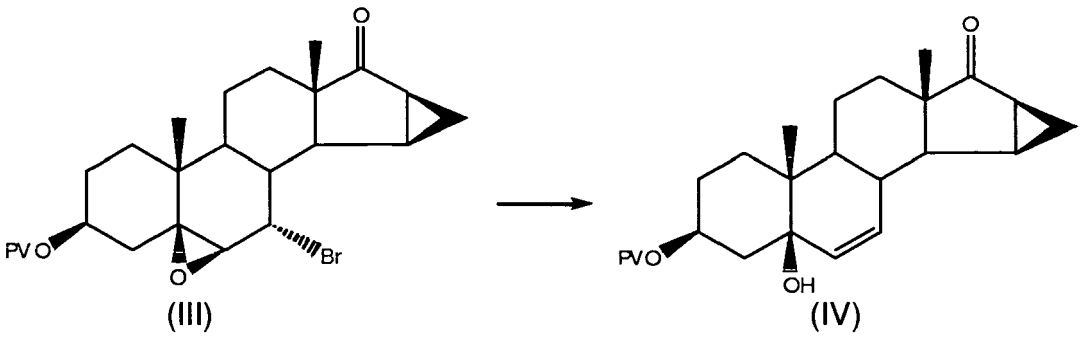


(II) (III)

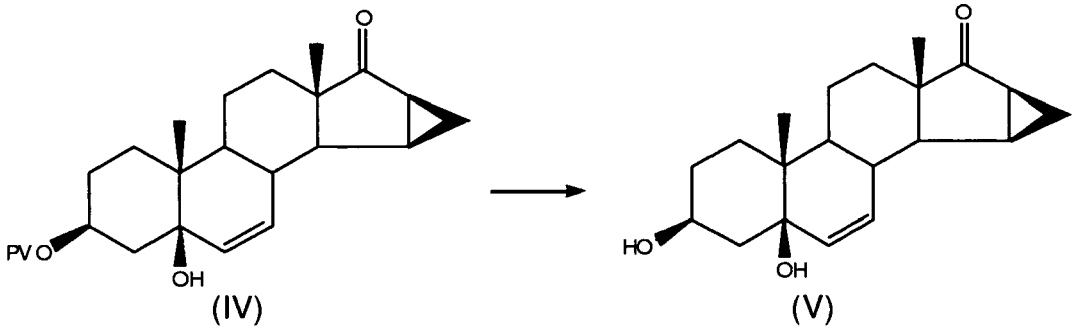
in which the symbol PV indicates a pivaloyl group, i.e. atrimethylacetyl group;

b) opening the epoxy ring and removing the bromine from 7α-bromo-5,6β-epoxy-15β,16β-methylene-3β-pivaloyloxy-

5β-androstan-17-one of formula (III) coming from step a) to obtain 5-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androst-6-en-17-one of formula (IV):

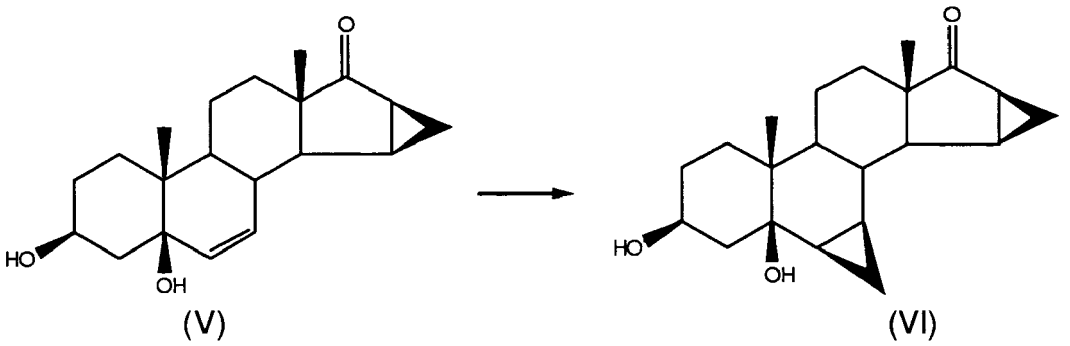


c) hydrolysis of the pivaloyl group of 5-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androst-6-en-17-one of formula (IV) coming from step b) to obtain 3β,5-dihydroxy-15β,16β-methylene-5β-androst-6-en-17-one of formula (V):

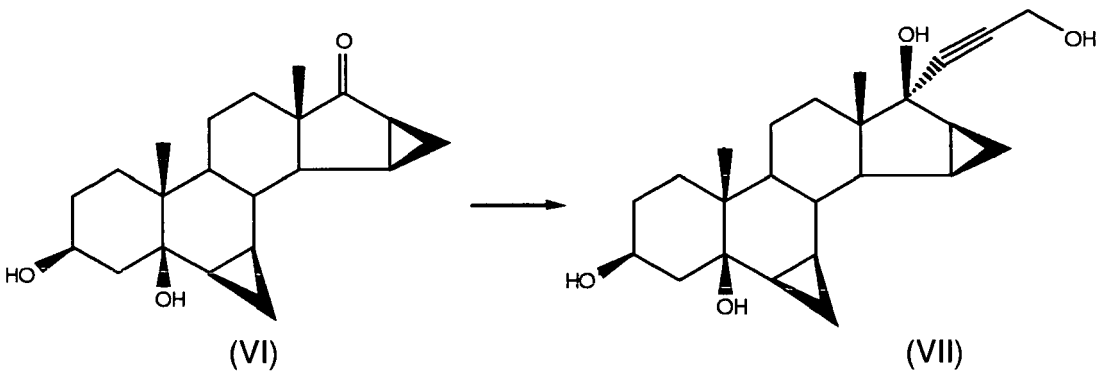


in which PV is defined as above,

d) methylenation at the Δ^6 double bond of 3β,5-dihydroxy-15β,16β-methylene-5β-androst-6-en-17-one of formula (V) coming from step c), to obtain 3β,5-dihydroxy-6β,7β;15β,16β-dimethylene-5β-androst-17-one of formula (VI)

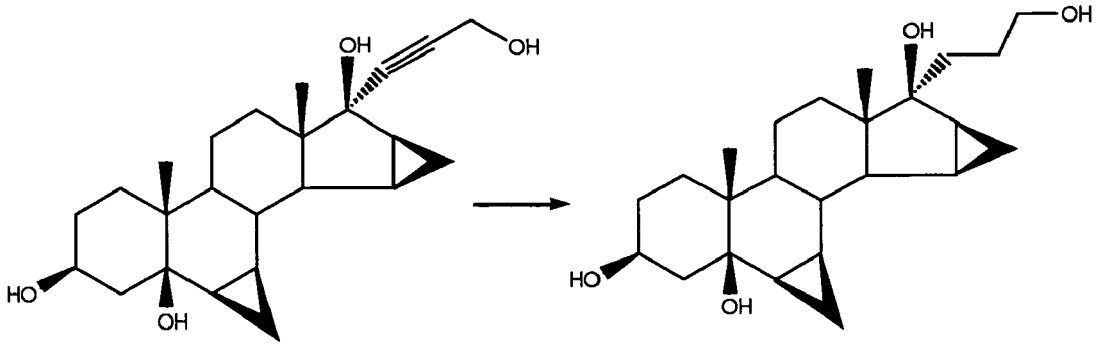


e) reacting 3β,5-dihydroxy-6β,7β;15β,16β-dimethylene-5β-androst-17-one of formula (VI) coming from step d) with propargyl alcohol to obtain 17α-(3-hydroxy-1-propinyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VII)



(VI) (VII)

f) hydrogenating 17α-(3-hydroxy-1-propinyl)-6β,7 β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VII) coming from step e) to obtain 17α-(3-hydroxypropyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VIII)



(VII) (VIII)

[0014] The starting 5,6 β-epoxy-7β-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one of formula (I) can be in its turn obtained from 3β-hydroxy-5-androsten-17-one as described in European Patent No. 0 075 189.

[0015] The bromination reaction in step a) is preferably carried out by adding mesyl chloride and pyridine to the starting compound at room temperature with the formation of the corresponding mesylate, then adding lithium bromide dissolved in water and bringing the temperature to values between 70 and 75°C.

[0016] The successive steps a) to f) can be carried out in accordance with procedures commonly utilised and known to any skilled person.

[0017] The term "suitable oxidising agent" in accordance with the invention means a product chosen from the group consisting of hypohalides of alkali and alkaline-earth metals, preferably calcium and sodium hypochlorite, iodine, oxygen in the presence of CuCl, potassium peroxymonosulfate $KHSO_5$ known commercially as Oxone®, and 1,3,5-trichloro-2,4,6-triazinetrione.

[0018] Derivatives of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical of possible use in the present process are chosen for example from the 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical, the 4-methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical and the 4-(benzoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl radical. As organic solvent for the oxidation reaction a solvent chosen from the group consisting of ethers such as acetone, methyl t-butyl ether and tetrahydrofuran, esters such as ethyl acetate, hydrocarbons such as toluene, halogenated hydrocarbons, such as methylene chloride, and mixtures thereof, can be used. The oxidation reaction and subsequent dehydration can be carried out for example at a temperature between 0 and 40°C, preferably at a temperature between 20 and 25°C.

[0019] Preferred reaction conditions are those in which the oxidation is carried out with calcium hypochlorite using as organic solvent a methylene chloride/tetrahydrofuran mixture, preferably in a 8.5/1 ratio, at a temperature between 20 and 25°C in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl radical and in the presence of an aqueous sodium bicarbonate solution.

[0020] At the end of the oxidation reaction a protic acid is added directly to the organic solution in which the oxidation reaction took place. Alternatively, the organic solution in which the oxidation reaction took place is distilled until a semi-solid residue is obtained which is then redissolved in a suitable organic solvent, and to the so obtained solution the protic

acid is then added.

[0021] The aforesaid protic acid is chosen for example from the group consisting of concentrated hydrochloric acid, dilute hydrochloric acid and p-toluenesulfonic acid; preferably the protic acid used is p-toluenesulfonic acid monohydrate.

[0022] The crude drospirenone obtained with the present process as described above has a high degree of purity, being greater than 96.5%, which can nevertheless be increased by subjecting the crude product coming from the oxidation to a purification procedure to obtain drospirenone with a degree of purity greater than 99.5%.

[0023] To obtain drospirenone with said degree of purity no chromatographic procedure is necessary, but a filtration through gel and decolourising carbon is sufficient, followed by crystallisation of the filtrate from solvent, the two steps of filtration and crystallisation possibly being repeated one or more times.

[0024] Preferably the gel utilised in accordance with the invention is silica gel, while the crystallisation solvent can be chosen from the group consisting of ethyl ether, isopropyl ether, ethyl acetate, methyl tertbutyl ether, isopropyl acetate, methyl acetate, dimethoxyethane, methanol, ethanol, isopropanol, methylene chloride, acetone, dimethylacetamide, dimethylformamide and mixtures thereof; the preferred crystallisation solvent is isopropyl acetate.

[0025] In accordance with a particularly preferred embodiment of the invention, the present purification procedure comprises the following steps:

i) dissolving crude drospirenone in a suitable organic solvent, further containing silica gel and decolourising carbon, and filtering the solution thus obtained;
ii) distilling the solution coming from step i) and redissolving the distillate in a second organic solvent;
iii) distilling the solution coming from step ii) and redissolving the distillate in said second organic solvent;
iv) crystallising pure drospirenone from the solution coming from step iii);
v) recovering pure drospirenone by filtering, washing over the filter at least once with a suitable organic solvent, then drying at a pressure lower than atmospheric pressure;
vi) if necessary repeating steps i) to v), starting from the drospirenone coming from step v).

[0026] The amount of silica gel and decolourising carbon employed in step i) is preferably less than 5% by weight with respect of the weight of the crude drospirenone to be purified.

[0027] The distillation steps ii) and iii) are preferably carried out at a distillation temperature between 35 and 45°C, and at a pressure lower than atmospheric pressure.

[0028] In step iv) said crystallisation is carried out at a temperature between 0 and 5°C for a time period between 60 and 180 minutes.

[0029] The organic solvent used in steps i), ii), iii) and v) is chosen for example from the group consisting of ethyl ether, isopropyl ether, ethyl acetate, isopropyl acetate, methyl acetate, dimethoxyethane, methanol, ethanol, isopropanol, methylene chloride, acetone, dimethylacetamide, dimethylformamide, methyl tertbutyl ether and mixtures thereof.

[0030] Preferably the organic solvent in step i) is methylene chloride, the organic solvent in step ii) is isopropyl acetate, and in step v) two washings are undertaken, the first with isopropyl acetate and the second with ethyl ether.

[0031] The present process for drospirenone preparation as described above has proved to be advantageous in that it enables preparation of the intermediate 7α-bromo-5,6 β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one, useful for drospirenone synthesis, while avoiding toxic solvents and reagents such as tetrachloromethane as used in the process given in EP 0 075 189. Furthermore, though preparation of this brominated intermediate passes via the formation of a mesylated intermediate, it does not involve an additional process step because the mesylate is not isolated but brominated directly.

[0032] The use of carcinogenic reagents is also avoided in the oxidation step which, as well as not requiring carcinogenic reagents, is just as efficient as the oxidation with chromic anhydride described in EP 0 075 189.

[0033] Finally, the purification process described above enables the inverted lactone fraction that is present in the crude product and identified as ZK35096 in US Patent 6,121,465, to be completely eliminated without the use of chromatographic techniques. This purification process is applicable and useful for the purification not only of drospirenone prepared in accordance with the present process, but also of products obtained with other processes and in which the aforementioned inverted lactone is present as impurity.

[0034] The following examples are given as non-limiting illustrations of the present invention.

EXAMPLE 1

Preparation of 7α-bromo-5,6β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one-Step a)

[0035] 67.5 g of 5,6β-epoxy-7β-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one are dissolved in 205 ml of pyridine in a 2 litre flask, under nitrogen.

[0036] 17.5 ml of mesyl chloride are added from a dropping funnel, maintaining a temperature of 20/25°C.

[0037] The mixture is stirred for 1 hour at 20°C to obtain a thick orange suspension.

[0038] The progress of the reaction is checked by TLC. Once the reaction is completed, 83.2 g of lithium bromide dissolved in 54 ml of water are added and the temperature is brought to 70/75°C. After 3 hours another 8 g of lithium bromide dissolved in water and 50 ml of pyridine are added.

[0039] At the end of the reaction (checked by TLC) the temperature is brought to 60°C and 700 ml of water are added; it is left to cool to 15/20°C, maintaining under stirring for 1 hour at this temperature.

[0040] The solid is filtered off and washed with 500 ml of water.

[0041] The solid is dried for 24 hours under reduced pressure at 45°C to obtain 69.5 g of the title compound.

[0042] On the product thus obtained, purified by chromatography, ^{1}H-NMR and mass spectroscopic analyses were carried out, and the following results were obtained:

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 0.92 (18-Me, s, 3H); 1.04 (19-Me, s, 3H); 1.08-1.16 (m, 1 H); 1.16 (t-But, s, 9H); 1.18-1.28 (m, 1 H); 1.36-1.60 (m, 8H); 1.62-1.68 (m, 1 H); 1.72-1.76 (m, 1 H); 1.84-1.96 (m, 3H); 2.04-2.16 (m, 3H); 3.46 (6-H, broad s, 1 H); 4.73 (7-H, broad s, 1 H); 4.76-4.84 (3-H, m, 1 H).

[0043] Electron impact mass spectroscopy: m/z [376] and [378]= M^+-$C(CH_3)_3$-COOH; [297] and [299]= M^+-$C(CH_3)_3$-COOH-Br

EXAMPLE 2

Preparation of 5-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androst-6-en-17-one- Step b)

[0044] 27 g of powdered zinc suspended in 91 ml of THF (tetrahydrofuran) are fed into a 1 litre flask, under nitrogen.

[0045] A solution of 67.5 g of 7α-bromo-5,6β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one, prepared as described in Example 1, in 277 ml of THF is then added; 19.9 ml of glacial acetic acid are slowly added dropwise, maintaining the temperature below 60°C during the addition. The reaction mixture is maintained under stirring for 3 hours at 59/60°C.

[0046] At the end of the reaction (checked by TLC) and after cooling to 50°C, the zinc is filtered off over dicalite and the filter washed with 200 ml of THF.

[0047] The filtered solution is brought to pH 9 with 60 ml of triethylamine.

[0048] The solution is concentrated under reduced pressure at 50°C to obtain about 180 g of a semi-solid product which is dissolved in 500 ml of a 5% acetic acid-water solution (pH=4 with a precipitate).

[0049] It is maintained under stirring for 1 hour at 10/15°C, the solid is filtered off and washed with 500 ml of water then dried under reduced pressure for 12 hours at 50°C, thus obtaining 57 g of crude product.

[0050] The crude product is refluxed for 1 hour in a mixture of 115 ml of t-butyl methyl ether and 114 ml of ethyl acetate (partial dissolution).

[0051] It is cooled for 1 hour at 0/5°C, the solid is filtered off and washed with t-butyl methyl ether and dried under reduced pressure for 1 hour at 60°C.

[0052] 44.6 g of the title compound are obtained.

[0053] The analytical data obtained from a sample purified by chromatography correspond to those given in EP 0 075 189.

EXAMPLE 3

Preparation of 3β,5-dihydroxy-15β,16β-methylene-5β-androst-6-en-17-one - Step c)

[0054] 43 g of 5-hydroxy-15β,16β-methylene-3-β-pivaloyloxy-5-β-androst-6-en-17-one prepared as described above in Example 2, 430 ml of THF, 215 ml of methanol and 12.9 g of potassium hydroxide are fed into a 2 litre flask, under nitrogen at 20°C. The suspension is stirred at 20°C for 3 hours.

[0055] At the end of the reaction (checked by TLC), the reaction mixture is poured into 2 litres of water, brought to pH 7 with 20% sulphuric acid (about 25 ml) then the suspension is stirred for 1 hour at 0/5°C. The solid is filtered off, washed with water and dried for 12 hours under reduced pressure at 50°C to obtain 30.6 g of the title compound.

[0056] The analytical data obtained for a sample purified by chromatography correspond to those given in EP 0 075 189.

EXAMPLE 4

Preparation of 3β,5-dihydroxy-6β,7β;15β,16β-dimethylene-5B-androst-17-one - Step d)

[0057] 29 g of 3β,5-dihydroxy-15β,16β-methylene-5β-androst-6-en-17-one prepared as described above in Example 3 are fed into a 2 litre flask under nitrogen at 20°C with 410 ml of THF.

[0058] 0.6 g of copper (II) acetate hydrate are added and the mixture is maintained under stirring until the solution is clear (green).

[0059] 37.9 g of finely powered zinc are added and, after stirring for 15 minutes, 1.7 ml of acetic acid are further added.

[0060] The mixture is further stirred for 30 minutes at 20°C then heated to 50°C; 32.3 ml of methylene bromide are added and it is refluxed for 2 hours.

[0061] At the end of the reaction (checked by TLC) it is cooled to 20°C and a mixture consisting of 26.8 ml acetic acid in 450 ml water is added slowly while cooling. The mixture is filtered through dicalite and the panel is washed with 600 ml of toluene.

[0062] The phases are separated and the aqueous phase is extracted with 200 ml of toluene. The joined organic phases are washed with 350 ml of water.

[0063] The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure at 60°C until a solid is obtained.

[0064] The solid is dissolved with 50 ml of a 3/1 heptane/ethyl acetate mixture and filtered off, then dried for 12 hours under reduced pressure at 45°C to obtain 25.5 g of the title compound.

[0065] The analytical data obtained from a sample purified by chromatography correspond to those given in EP 0 075 189.

EXAMPLE 5

Preparation of 17α-(3-hydroxy-1-propinyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol - Step e)

[0066] 24 g of 3β,5-dihydroxy-6β,7β;15β,16β-dimethylene-5β-androst-17-one prepared as described above in Example 4 are fed into a 1 litre flask, under nitrogen at 20°C, with 480 ml THF.

[0067] The mixture is cooled to 0/5°C and 72 g of potassium methylate are added (yellow suspension).

[0068] While maintaining the temperature at 0/5°C 48 ml of propargyl alcohol diluted with 90 ml of THF are added slowly (thick orange solution).

[0069] A further 150 ml of THF are added when the solution density renders stirring impossible. The solution is maintained under stirring for 12 hours at 0/5°C.

[0070] At the end of the reaction (checked by TLC) the very thick suspension is poured into 2 litres of water and ice (an orange solid precipitates).

[0071] The solid obtained is extracted with 1.5 litres of isopropyl acetate.

[0072] The organic phase is dried over sodium sulphate, filtered and concentrated under reduced pressure at 50°C to obtain a solid.

[0073] The solid is filtered off from heptane and dried for 12 hours at 45°C under reduced pressure to obtain 27.1 g of the title compound.

[0074] The analytical data obtained from a sample purified by chromatography correspond to those given in EP 0 075 189.

EXAMPLE 6

Preparation of 17α-(3-hydroxypropyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol - Step f)

[0075] A solution of 25.1 g 17α-(3-hydroxy-1-propinyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol prepared as described above in Example 5, in 930 ml of a mixture prepared with 750 ml of THF, 375 ml of methanol and 1.5 ml of pyridine is fed into an autoclave. 5 g of 5% Pd/C catalyst are added and hydrogenation is carried out at atmospheric pressure (20/25°C) for 2 hours.

[0076] At the end of the reaction (checked by TLC) the suspension is filtered through dicalite then the filter is washed with methylene chloride.

[0077] The product is concentrated under reduced pressure at 50°C to obtain 32 g of the title compound.

[0078] The crude title product contained small quantities of the two 6β,7β;15β,16β-dimethylene-3β,5β-dihydroxy-17α-pregn-21,17-carbolactols. It was nevertheless advantageously used for the subsequent reaction, without any further purification. A sample of the title product purified by chromatography gave the following results with ^{1}H-NMR analysis:

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 0.84 (18-Me, s, 3H); 0.88 (19-Me, s, 3H); 1.72 (s, -OH); 2.32-2.40 (m, -OH); 2.6(s,-OH); 3.38-3.40 (m, -OH); 3.64-3.76 (-CH_2OH, m, 2H); 4.0 (3-H, m, 1H).

[0079] The signals of the hydroxyl protons were identified by deuteration.

[0080] The crude reaction product used for the subsequent reaction also presented the following signals:

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 5.50 (17-O-CHOH-21, t, 1 H); 5.58 (17-0-CHOH-21, t, 1H).

EXAMPLE 7

Preparation of 6β,7β;15,6β-dimethylene-3-oxo-17α-pregn-4-en-21,17-carbolactone (DROSPIRENONE) - Oxidation

[0081] 50 g of 17α-(3-hydroxypropyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol prepared as described above in Example 6, 850 ml of methylene chloride and 100 ml of THF are fed into a reactor, and stirred at a temperature of 20°C.

[0082] A solution, prepared by dissolving 75 g of sodium bicarbonate in 750 ml of water, is added to the organic solution thus obtained.

[0083] While maintaining the biphasic solution under vigorous stirring at 20°C, 1.2 g of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) and 35 g of calcium hypochlorite are added in portions, while monitoring oxidation reaction progress by TLC.

[0084] The biphasic solution is filtered, the two phases are left to separate, and the organic phase is washed first with an aqueous sodium bisulfate monohydrate solution then with water.

[0085] The organic phase is concentrated at 40°C under vacuum until a semi-solid residue is obtained, which is then dissolved with 560 ml THF; 4.9 g of p-toluenesulfonic acid monohydrate are added to the solution thus obtained and maintained under stirring for 1 hour at 20°C, while monitoring the formation of drospirenone by means of TLC.

[0086] Once the reaction is completed the product is neutralised with an aqueous 10% sodium bicarbonate solution and extracted with 800 ml of isopropyl acetate. The organic phase is washed with water and concentrated under vacuum at 40°C. The residue is firstly dissolved with isopropyl acetate then concentrated again under vacuum at 40°C and dissolved once more with isopropyl acetate at 0/5°C, to obtain a suspension.

[0087] By filtering this suspension, washing the solid with ethyl ether and drying it under vacuum at 40°C, 31.3 g of crude drospirenone are obtained which are then fed into a container with 150 ml of methylene chloride. 2 g of decolourising carbon and 1.45 g of silica gel are then added. The suspension is then filtered and concentrated to a small volume by distillation under vacuum at 40°C.

[0088] The residue is then dissolved with isopropyl acetate, concentrated to a small volume by distillation under vacuum at 40°C, again dissolved with 25 ml of isopropyl acetate and maintained under stirring at 30°C for 15 minutes, then at 0/2°C for 2 hours.

[0089] After filtering, the solid obtained is washed first with cold isopropyl acetate then with ethyl ether. After drying under vacuum at 40°C until a constant weight is achieved, 28.9 g of drospirenone are obtained whose analytical data correspond with those given in the literature.

EXAMPLE 8

Preparation of 6β,7β;15β,16β-dimethylene-3-oxo-17α-pregn-4-en-21,17-carbolactone (DROSPIRENONE) - Oxidation

[0090] 12 g of 17α-(3-hydroxypropyl)-6β,7β,15β,16β-dimethylene-5β-androstane-3β,5,17β-triol prepared as described above in Example 6, 170 ml of methylene chloride and 20 ml of THF are fed into a reactor. The mixture is stirred at 20°C until a homogeneous solution is obtained.

[0091] A solution, prepared by dissolving 15 g of sodium bicarbonate in 150 ml of water, is added to the organic solution thus obtained.

[0092] While maintaining the biphasic solution under vigorous stirring at 20°C, 0.54 g of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) and 8.6 g of calcium hypochlorite are added in portions, while monitoring oxidation reaction progress by TLC.

[0093] On completion of the oxidation, the biphasic solution is filtered and the two phases are left to separate. 1.5 g of p-toluenesulfonic acid monohydrate are added to the organic phase.

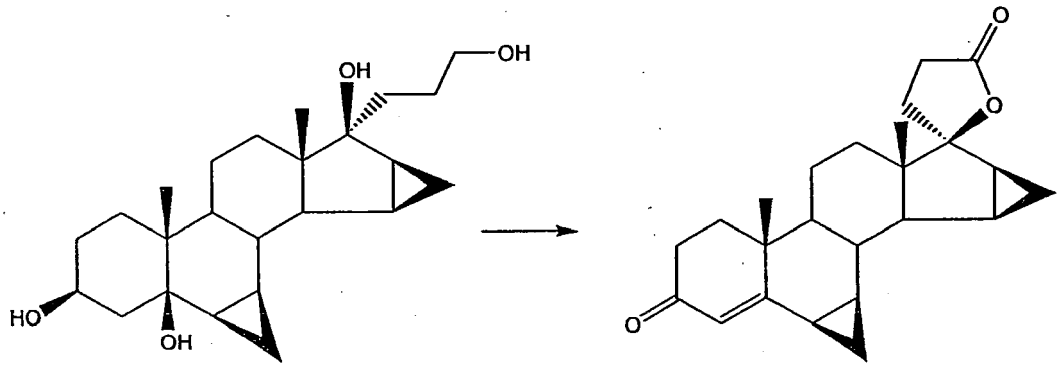
[0094] The mixture is maintained under stirring for about 3 hours at 20°C, while monitoring the reaction by TLC.

[0095] When the reaction is complete, neutralisation is carried out with an 1% aqueous sodium bicarbonate solution.

[0096] The reaction proceeds as described above in Example 7 to finally obtain 6.5 g of drospirenone whose analytical data correspond to those given in the literature and those obtained for the product in Example 7.

Claims

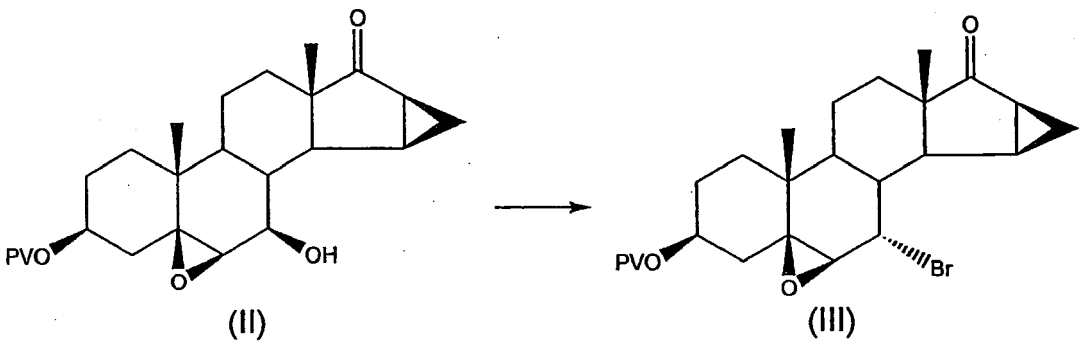
1. Process for the preparation of drospirenone, comprising the oxidation of 17α-(3-hydroxypropyl)-6β,7β,11 5β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VIII) with a suitable oxidising agent in an organic solvent in the presence of a catalytic amount of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical or a derivative thereof, said oxidation being followed by the addition of a protic acid directly into the same container in which the oxidation took place, to obtain the drospirenone of formula (I)



(VIII) (I)

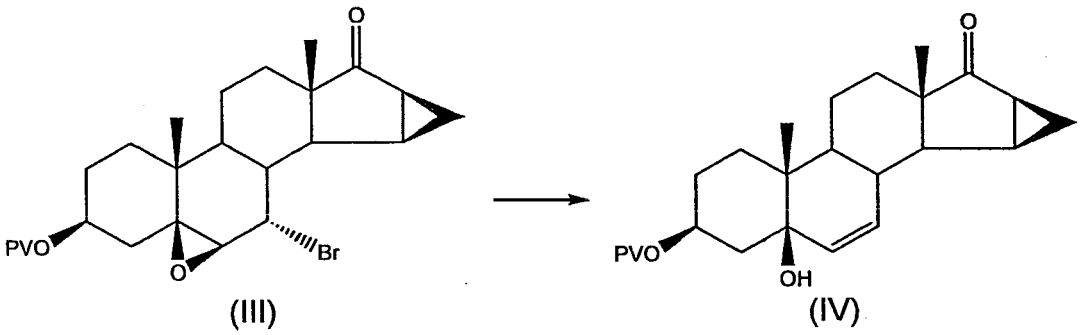
2. The process according to claim 1, wherein said 17α-(3-hydroxypropyl)-6β,7β,15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VIII) is prepared starting from 5,6β-epoxy-7β-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one of formula (II) in accordance with the following steps:

a) bromination in position 7α of 5,6β-epoxy-7β-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one of formula (II) to obtain 7α-bromo-5,6β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one of formula (III) by reacting the compound of formula (II) with mesyl chloride to obtain the corresponding mesylate which is not isolated and from which the compound of formula (III) is obtained by adding lithium bromide:

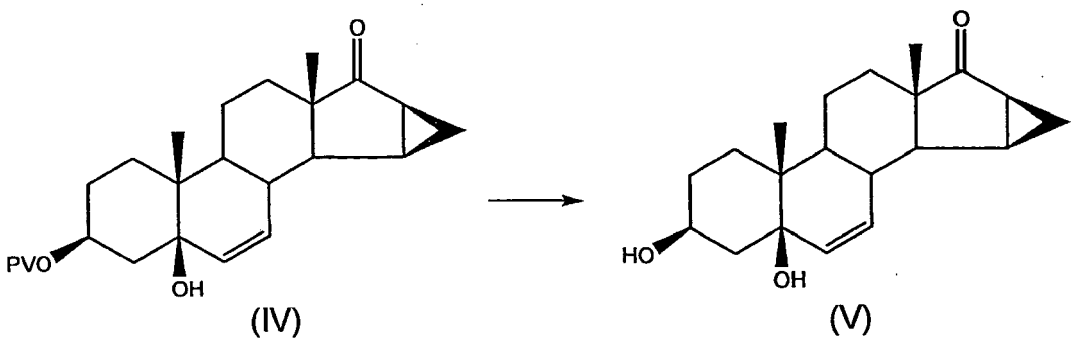


(II) (III)

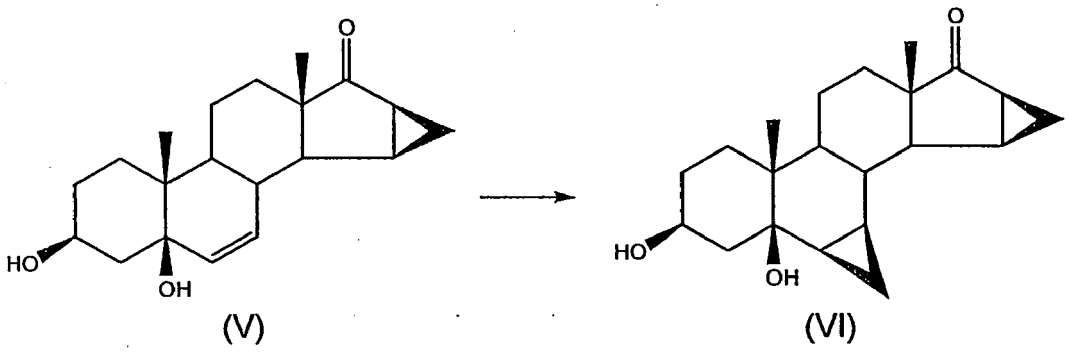
in which the symbol PV indicates a pivaloyl group, i.e. a trimethylacetyl group;
b) opening the epoxy ring and removing the bromine from 7α-bromo-5,6β-epoxy-15β,16β-methylene-3β-pivaloyloxy-5β-androstan-17-one of formula (III) derived from step a) to obtain the 5-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androst-6-en-17-one of formula (IV):



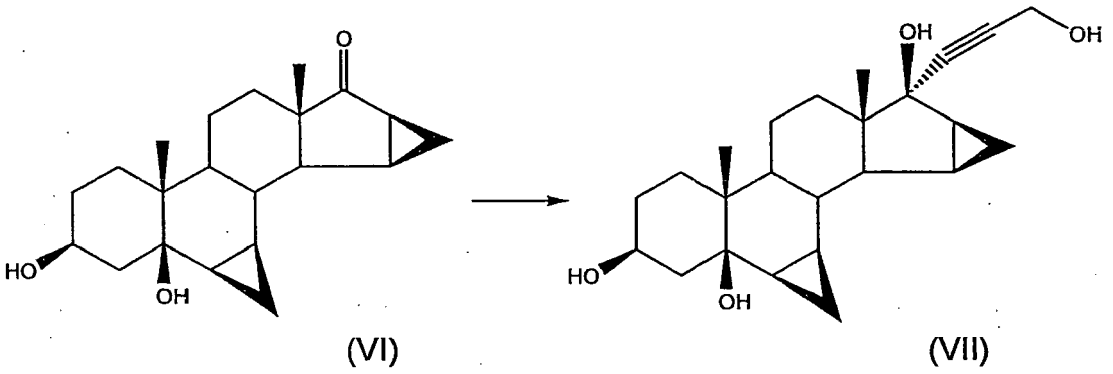
c) hydrolysis of the pivaloyl group of 5-hydroxy-15β,16β-methylene-3β-pivaloyloxy-5β-androst-6-en-17-one of formula (IV) coming from step b) to obtain the 3β,5-dihydroxy-15β,16β-methylene-5β-androst-6-en-17-one of formula (V):



in which PV is defined as above,
d) methylenation at the Δ^6 double bond of 3β,5-dihydroxy-15β,16β-methylene-5β-androst-6-en-17-one of formula (V) coming from step c) to obtain the 3β,5-dihydroxy-6β,7β;15β,16β-dimethylene-5β-androst-17-one of formula (VI)

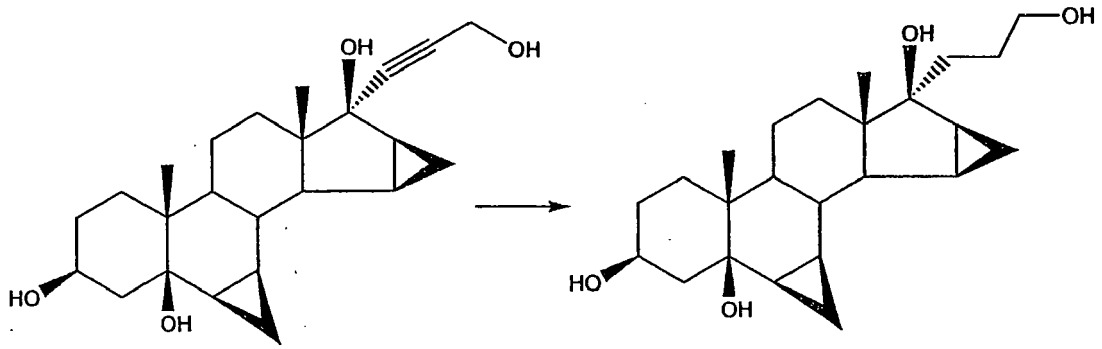


e) reacting the 3β,5-dihydroxy-6β,7β;15β,16β-dimethylene-5β-androst-17-one of formula (VI) coming from step d) with propargyl alcohol to obtain the 17α-(3-hydroxy-1-propinyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VII)



(VI) (VII)

f) hydrogenating the 17α-(3-hydroxy-1-propinyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VII) coming from step e) to obtain the 17α-(3-hydroxypropyl)-6β,7β;15β,16β-dimethylene-5β-androstane-3β,5,17β-triol of formula (VIII)



(VII) (VIII)

3. The process according to claim 1, wherein said oxidising agent is selected from the group consisting of alkali metal and alkaline-earth metal hypohalides, iodine, oxygen in the presence of CuCl, potassium peroxymonosulphate and 1,3,5-trichloro-2,4,6-triazinetrione.

4. The process according to claim 3, wherein said oxidising agent is selected from sodium hypochlorite and calcium hypochlorite.

5. The process according to claim 1, wherein said derivative of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical is selected from the group consisting of the 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical, the 4-methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical and the 4-(benzoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl radical.

6. The process according to claim 1, wherein said organic solvent is selected from the group consisting of ethers, esters, hydrocarbons, halogenated hydrocarbons and mixtures thereof.

7. The process according to claim 1, wherein said organic solvent is selected from the group consisting of acetone, toluene, methyl t-butyl ether, ethyl acetate, methylene chloride, tetrahydrofuran and mixtures thereof.

8. The process according to claim 1, wherein said oxidation is carried out at a temperature between 0 and 40°C.

9. The process according to claim 1, wherein said oxidation is carried out with calcium hypochlorite using as organic solvent a methylene chloride/tetrahydrofuran mixture at a temperature between 20 and 25°C in the presence of a catalytic amount of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical and in the presence of an aqueous sodium bicarbonate solution.

10. The process according to claim 9, wherein said methylene chloride/tetrahydrofuran mixture is used in a ratio of 8.5/1.

11. The process according to claim 1, wherein said protic acid is selected from the group consisting of concentrated hydrochloric acid, dilute hydrochloric acid and p-toluenesulfonic acid.

12. The process according to claim 11, wherein said protic acid is p-toluenesulfonic acid monohydrate.

13. The process according to claim 1, wherein said protic acid addition is carried out at a temperature between 0 and 40°C.

14. The process according to claim 13, wherein said protic acid addition is carried out at a temperature between 20 and 25°C.

15. The process according to claim 1, wherein said protic acid is added directly to the organic solution in which the oxidation reaction took place.

16. The process according to claim 1, wherein said protic acid is added to the solution obtained by dissolving in a suitable organic solvent the semi-solid residue coming from the distillation of the organic solution in which the oxidation reaction took place.

17. The process according to claim 2, wherein said bromination reaction in step a) is carried out by adding mesyl chloride and pyridine to the starting compound at room temperature with the formation of the corresponding mesylate, then adding lithium bromide dissolved in water and bringing the temperature to values between 70 and 75°C.

18. The process according to claim 1, further comprising purification of the crude drospirenone by a procedure comprising gel filtration and filtrate crystallisation from organic solvent, said procedure possibly being repeated one or more times.

19. The process according to claim 18, wherein said purification comprises the following steps:

i) dissolving crude drospirenone in a suitable organic solvent, further containing silica gel and decolourising carbon, and filtering the solution thus obtained;
ii) distilling the solution coming from step i) and redissolving the distillate in a second organic solvent;
iii) distilling the solution coming from step ii) and redissolving the distillate in said second organic solvent;
iv) crystallising pure drospirenone from the solution coming from step iii);
v) recovering pure drospirenone by filtering, washing over the filter at least once with a suitable organic solvent, and drying at a pressure lower than atmospheric pressure;
vi) optionally repeating steps i) to v), starting from the drospirenone coming from step v).

20. The process according to claim 19, wherein the amount of silica gel and decolourising carbon utilised is less than 5% by weight with respect to the weight of the crude drospirenone to be purified.

21. The process according to claim 19, wherein the distillation temperature in steps ii) and iii) is between 35 and 45°C.

22. The process according to claim 19, wherein said distillation in steps ii) and iii) is carried out at a pressure lower than atmospheric pressure.

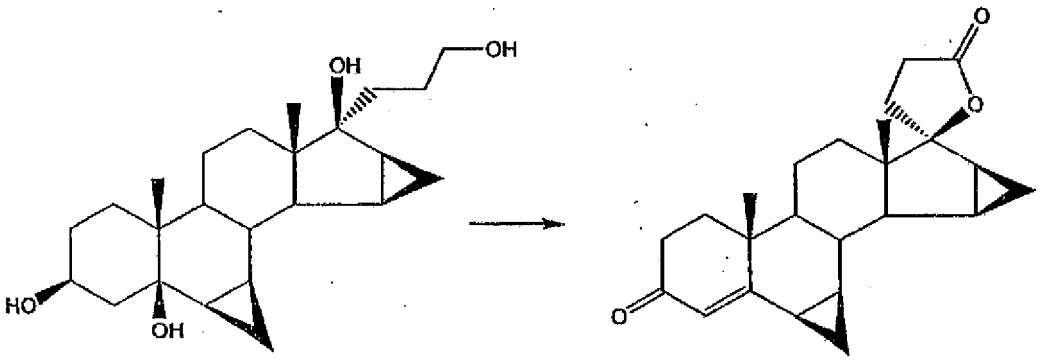
23. The process according to claim 19, wherein said crystallisation in step iv) is carried out at a temperature between 0 and 5°C for a time period between 60 and 180 minutes.

24. The process according to claim 19, wherein said organic solvent in steps i), ii), iii) and v) is selected from the group consisting of ethyl ether, isopropyl ether, ethyl acetate, methyl tertbutyl ether, isopropyl acetate, methyl acetate, dimethoxyethane, methanol, ethanol, isopropanol, methylene chloride, acetone, dimethylacetamide, dimethylformamide and mixtures thereof.

25. The process according to claim 19, wherein said organic solvent in step i) is methylene chloride, said organic solvent in step ii) is isopropyl acetate, and in step v) two washings are carried out, the first with isopropyl acetate and the second with ethyl ether.

Patentansprüche

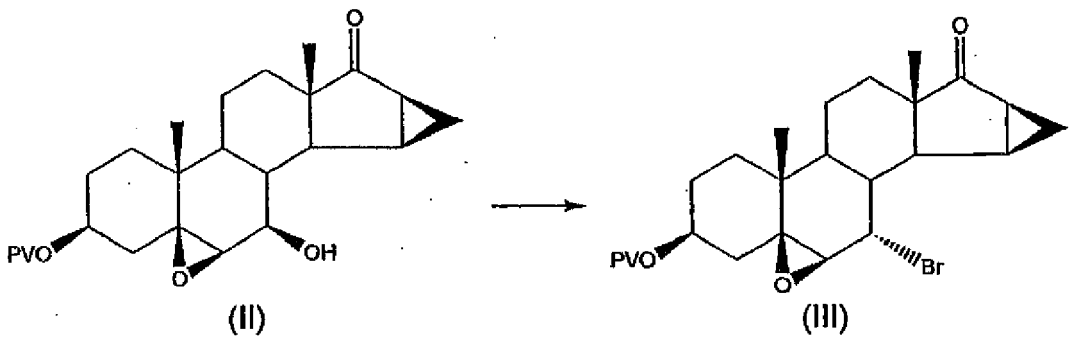
1. Verfahren zur Herstellung von Drospirenon, umfassend die Oxidation von 17α-(3-Hydroxypropyl)-6β,7β,15β,16β-dimethylen-5β-androstan-3β-5,17β-triol der Formel (VIII) mit einem geeigneten Oxidationsmittel in einem organischen Lösungsmittel in Gegenwart einer katalytischen Menge des 2,2,6,6-Tetramethylpiperidin-1-oxylradikals oder eines Derivats davon, wobei auf die genannte Oxidation eine Addition einer protischen Säure direkt im gleichen Gefäß erfolgt, in dem die Oxidation stattgefunden hat, um das Drospirenon der Formel (I) zu erhalten



(VIII) (I)

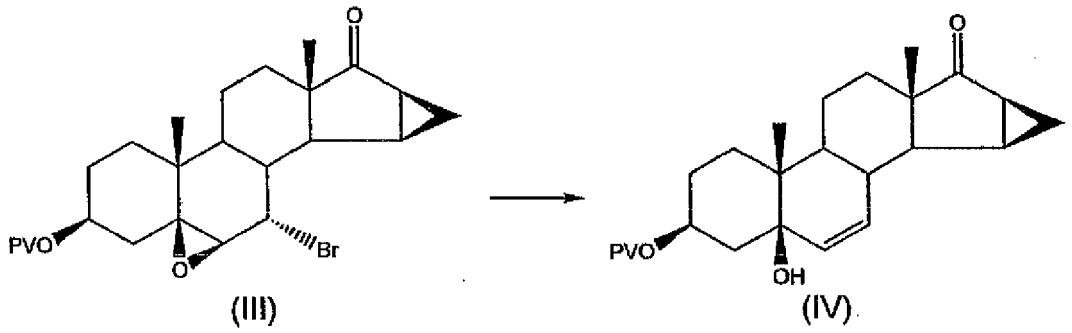
2. Verfahren gemäß Anspruch 1, wobei genanntes 17α-(3-Hydroxypropyl)-6β,7β,15β,16β-dimethylen-5β-androstan-3β-5,17β-triol der Formel (VIII) ausgehend von 5,6β-Epoxy-7β-hydroxy-15β,16β-methylen-3β-pivaloyloxy-5β-androstan-17-on der Formel (II) gemäß der folgenden Schritte hergestellt wird:

   a) Bromierung von 5,6β-Epoxy-7β-hydroxy-15β,16β-methylen-3β-pivaloyloxy-5β-androstan-17-on der Formel (II) in Position 7α, um 7α-Brom-5,6β-epoxy-15β,16β-methylen-3β-pivaloyloxy-5β-androstan-17-on der Formel (III) zu erhalten, indem die Verbindung der Formel (II) mit Mesylchlorid zur Reaktion gebracht wird, um das korrespondierende Mesylat zu erhalten, das nicht isoliert wird und aus dem die Verbindung der Formel (III) durch Zugabe von Lithiumbromid erhalten wird:

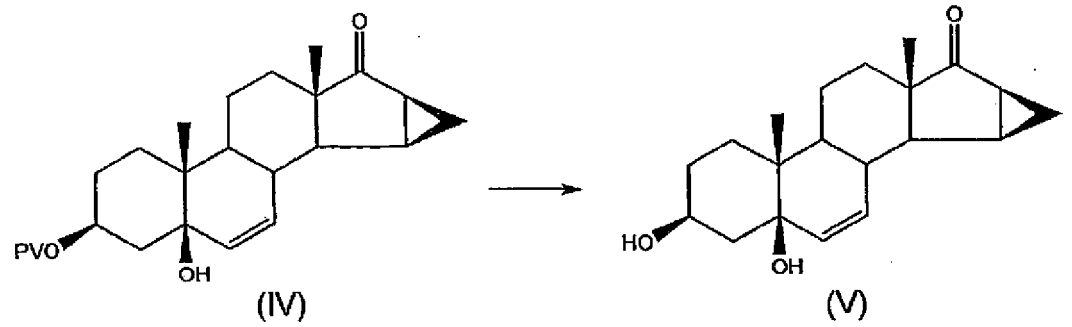


(II) (III)

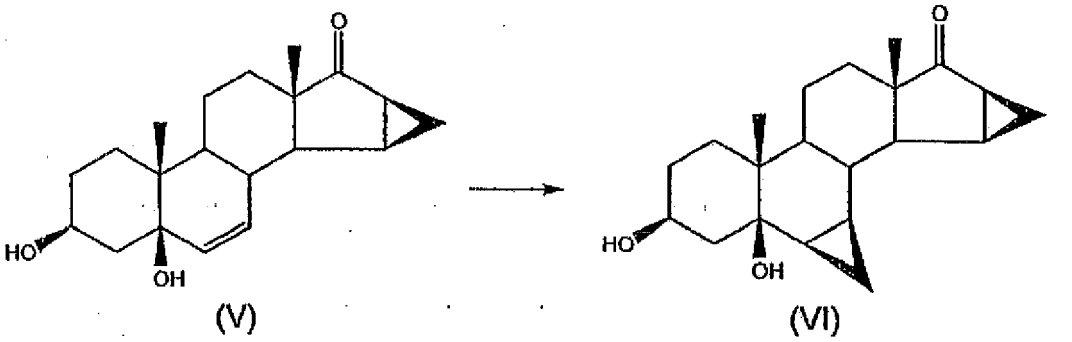
   in der das Symbol PV für eine Pivaloylgruppe steht, d. h. für eine Trimethylacetylgruppe;
   b) Öffnen des Epoxyrings und Entfernen des Broms aus dem aus Schritt a) stammenden 7α-Brom-5,6β-epoxy-15β,16β-methylen-3β-pivaloyloxy-5β-androstan-17-on der Formel (III), um das 5-Hydroxy-15β,16β-methylen-3β-pivaloyloxy-5β-androst-6-en-17-on der Formel (IV) zu erhalten:



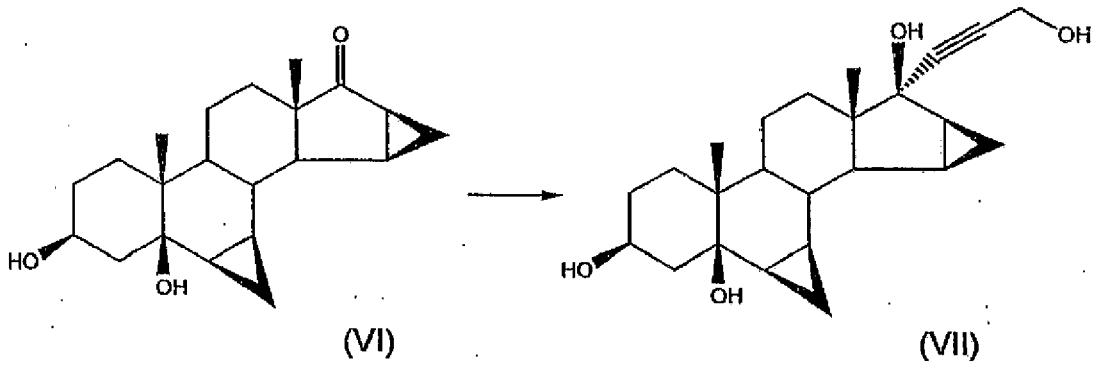
c) Hydrolyse der Pivaloylgruppe von aus Schritt b) stammendem 5-Hydroxy-15β,16β-methylen-3β-pivaloyloxy-5β-androst-6-en-17-on der Formel (IV), um das 3β,5-Dihydroxy-15β,16β-methylen-5β-androst-6-en-17-on der Formel (V) zu erhalten:



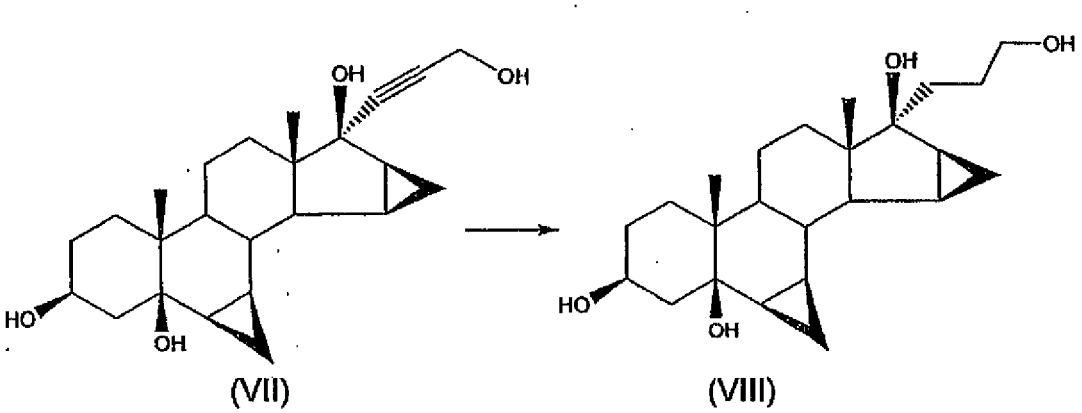
in der PV wie oben definiert ist,
d) Methylenierung an der Δ^6-Doppelbindung von aus Schritt c) stammendem 3β,5-Dihydroxy-15β,16β-methylen-5β-androst-6-en-17-on der Formel (V), um das 3β,5-Dihydroxy-6β,7β,15β,16β-dimethylen-5β-androst-17-on der Formel (VI) zu erhalten:



e) Reaktion von aus Schritt d) stammendem 3β,5-Dihydroxy-6β,7β;15β,16β-dimethylen-5β-androst-17-on der Formel (VI) mit Propargylalkohol, um das 17α-(3-Hydroxy-1-propinyl)-6β,7β,15β,16β-dimethylen-5β-androstan-3β,5,17β-triol der Formel (VII) zu erhalten:



f) Hydrierung von aus Schritt e) stammendem 17α-(3-Hydroxy-1-propinyl)-6β,7β,15β,16β-dimethylen-5β-androstan-3β,5,17β-triol der Formel (VII), um das 17α-(3-Hydroxypropyl)-6β,7β,15β,16β-dimethylen-5β-androstan-3β,5,17β-triol der Formel (VIII) zu erhalten:



3. Verfahren gemäß Anspruch 1, wobei genanntes Oxidationsmittel aus der Gruppe bestehend aus Alkalimetall- und Erdalkalimetallhypohalogeniten, lod, Sauerstoff in Gegenwart von CuCl, Kaliumperoxymonosulfat und 1,3,5-Trichlor-2,4,6-triazintrion ausgewählt wird.

4. Verfahren gemäß Anspruch 3, wobei genanntes Oxidationsmittel aus Natriumhypochlorit und Calciumhypochlorit ausgewählt wird.

5. Verfahren gemäß Anspruch 1, wobei das genannte Derivat des 2,2,6,6-Tetramethylpiperidin-1-oxylradikals aus der Gruppe bestehend aus dem 4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-oxylradikal, dem 4-Methoxy-2,2,6,6-tetramethylpiperidin-1-oxylradikal und dem 4-(Benzoyloxy)-2,2,6,6-tetramethylpiperidin-1-oxylradikal ausgewählt wird.

6. Verfahren gemäß Anspruch 1, wobei genanntes organisches Lösungsmittel aus der Gruppe bestehend aus Ethern, Estern, Kohlenwasserstoffen, halogenierten Kohlenwasserstoffen und Mischungen daraus ausgewählt wird.

7. Verfahren gemäß Anspruch 1, wobei genanntes organisches Lösungsmittel aus der Gruppe bestehend aus Aceton, Toluol, Methyl-*tert*-butylether, Ethylacetat, Methylenchlorid, Tetrahydrofuran und Mischungen davon ausgewählt wird.

8. Verfahren gemäß Anspruch 1, worin genannte Oxidation bei einer Temperatur zwischen 0 und 40°C durchgeführt wird.

9. Verfahren gemäß Anspruch 1, wobei genannte Oxidation mit Calciumhypochlorit unter Verwendung einer Methylenchlorid/Tetrahydrofuran-Mischung als organisches Lösungsmittel bei einer Temperatur zwischen 20 und 25 °C in Gegenwart einer katalytischen Menge des 2,2,6,6-Tetramethylpiperidin-1-oxylradikals und in Gegenwart einer wässrigen Natriumhydrogencarbonatlösung durchgeführt wird.

10. Verfahren gemäß Anspruch 9, wobei genannte Methylenchlorid/Tetrahydrofuran-Mischung in einem Verhältnis von 8,5:1 eingesetzt wird.

11. Verfahren gemäß Anspruch 1, wobei genannte protische Säure aus der Gruppe bestehend aus konzentrierter Salzsäure, verdünnter Salzsäure und p-Toluolsulfonsäure ausgewählt wird.

12. Verfahren gemäß Anspruch 11, wobei genannte protische Säure p-Toluolsulfonsäure-Monohydrat ist.

13. Verfahren gemäß Anspruch 1, worin genannte Zugabe von protischer Säure bei einer Temperatur zwischen 0 und 40 °C durchgeführt wird.

14. Verfahren gemäß Anspruch 13, worin genannte Zugabe einer protischen Säure bei einer Temperatur zwischen 20 und 25 °C durchgeführt wird.

15. Verfahren gemäß Anspruch 1, wobei genannte protische Säure direkt zu der organischen Lösung gegeben wird, in der die Oxidationsreaktion stattgefunden hat.

16. Verfahren gemäß Anspruch 1, wobei genannte protische Säure zu der Lösung gegeben wird, die durch Lösen des halbfesten Rückstands, der aus der Destillation der organischen Lösung stammt, in der die Oxidationsreaktion stattgefunden hat, in einem geeigneten organischen Lösungsmittel erhalten wird.

17. Verfahren gemäß Anspruch 2, wobei genannte Bromierungsreaktion in Schritt a) durch Zugabe von Mesylchlorid und Pyridin zur Startverbindung bei Raumtemperatur unter Bildung des korrespondierenden Mesylats und anschließender Zugabe von in Wasser gelöstem Lithiumbromid und Erhöhen der Temperatur auf Werte zwischen 70 und 75 °C durchgeführt wird.

18. Verfahren gemäß Anspruch 1, des Weiteren umfassend die Reinigung des rohen Drospirenon durch ein Verfahren, das eine Gelfiltration und Filtratkristallisation aus einem organischen Lösungsmittel umfasst, wobei genanntes Verfahren gegebenenfalls einmal oder mehrmals wiederholt wird.

19. Verfahren gemäß Anspruch 18, wobei genannte Reinigung die folgenden Schritte umfasst:

i) Lösen von rohem Drospirenon in einem geeigneten organischen Lösungsmittel, das des Weiteren Silicagel und Entfärbungskohle umfasst, und Filtrieren der so erhaltenen Lösung;
ii) Destillieren der aus Schritt i) stammenden Lösung und erneutes Lösen des Destillats in einem zweiten organischen Lösungsmittel;
iii) Destillieren der aus Schritt ii) stammenden Lösung und erneutes Lösen des Destillats in dem genannten zweiten organischen Lösungsmittel;
iv) Kristallisieren von reinem Drospirenon aus der aus Schritt iii) stammenden Lösung;
v) Rückgewinnung von reinem Drospirenon durch Filtrieren, mindestens einmaliges Waschen des Filters mit einem geeigneten organischen Lösungsmittel und Trocknen bei einem geringeren Druck als Atmosphärendruck;
vi) gegebenenfalls Wiederholen der Schritte i) bis v), ausgehend von dem aus Schritt v) stammenden Drospirenons.

20. Verfahren gemäß Anspruch 19, wobei die eingesetzte Menge an Silicagel und Entfärbungskohle bezogen auf das Gewicht des zur reinigenden, rohen Drospirenons weniger als 5 Gew.-% beträgt.

21. Verfahren gemäß Anspruch 19, wobei die Destillationstemperatur in den Schritten ii) und iii) zwischen 35 und 45°°C liegt.

22. Verfahren gemäß Anspruch 19, wobei genannte Destillation in den Schritten ii) und iii) bei einem geringeren Druck als Atmosphärendruck ausgeführt wird.

23. Verfahren gemäß Anspruch 19, wobei der Kristallisationsschritt von Schritt iv) bei einer Temperatur zwischen 0 und 5 °C über einen Zeitraum zwischen 60 und 180 Minuten durchgeführt wird.

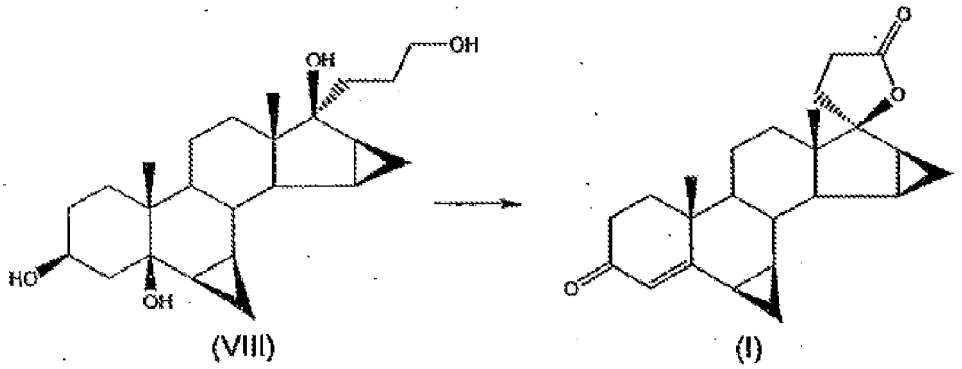
24. Verfahren gemäß Anspruch 19, wobei genanntes organisches Lösungsmittel in den Stufen i), ii) iii) und v) aus der Gruppe bestehend aus Ethylether, Isopropylether, Ethylacetat, Methyl-*tert*-butylether, Isopropylacetat, Methylacetat,

Dimethoxyethan, Methanol, Ethanol, Isopropanol, Methylenchlorid, Aceton, Dimethylacetamid, Dimethylformamid und Mischungen davon ausgewählt wird.

25. Verfahren gemäß Anspruch 19, wobei genanntes organisches Lösungsmittel in Schritt i) Methylenchlorid ist, genanntes organisches Lösungsmittel in Schritt ii) Isopropylacetat ist, und in Schritt v) zweimal gewaschen wird, das erste Mal mit Isopropylacetat und das zweite Mal mit Ethylether.

Revendications

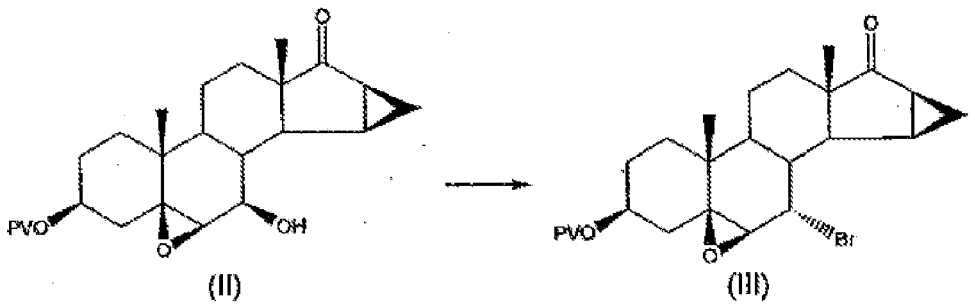
1. Procédé pour la préparation de drospirénone, comportant l'oxydation du 17α-(3-hydroxypropyl)-6β,7β,15β,16β-diméthylène-5β-androstane-3β,5,17β-triol de formule (VIII) avec un agent oxydant adapté dans un solvant organique en présence d'une quantité catalytique du radical 2,2,6,6-tétraméthylpipéridine-1-oxyle ou d'un dérivé de celui-ci, ladite oxydation étant suivie de l'ajout d'un acide protique directement dans le même récipient que celui dans lequel l'oxydation a eu lieu, afin d'obtenir la drospirénone de formule (I)



(VIII) (I)

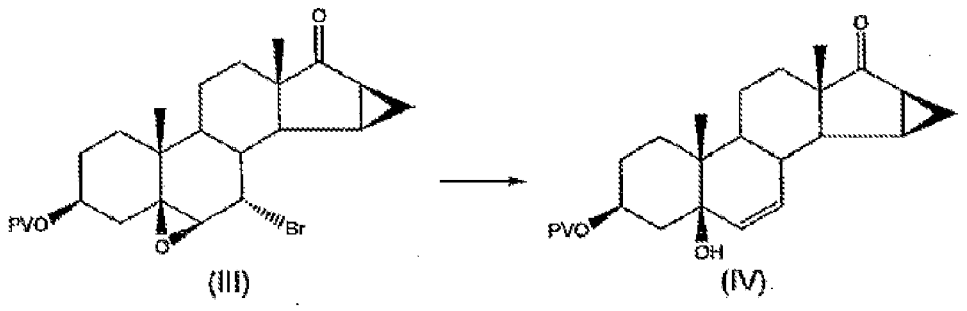
2. Procédé selon la revendication 1, dans lequel ledit 17α-(3-hydroxypropyl)-6β,7β,15β,16β-diméthylène-5β-androstane-3β,5,17β-triol de formule (VIII) est préparé en débutant par la 5,6β-époxy-7β-hydroxy-15β,16β-méthylène-3β-pivaloyloxy-5β-androstan-17-one de formule (II) conformément aux étapes suivantes :

a) bromuration en position 7α de la 5,6β-époxy-7β-hydroxy-15β,16β-méthylène-3β-pivaloyloxy-5β-androstan-17-one de formule (II) pour obtenir la 7α-bromo-5,6β-époxy-15β,16β-méthylène-3β-pivaloyloxy-5β-androstan-17-one de formule (III) en faisant réagir le composé de formule (II) avec du chlorure de mésyle pour obtenir le mésylate correspondant qui n'est pas isolé et à partir duquel le composé de formule (III) est obtenu en ajoutant du bromure de lithium :

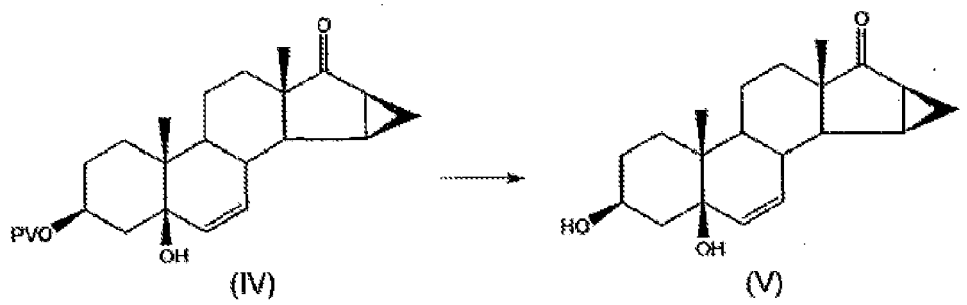


(II) (III)

dans lequel le symbole PV indique un groupe pivaloyle, c'est-à-dire un groupe triméthylacétyle,
b) ouverture du noyau époxy et élimination du brome de la 7α-bromo-5,6β-époxy-15β,16β-méthylène-3β-pivaloyloxy-5β-androstan-17-one de formule (III) obtenue à l'étape a) afin d'obtenir la 5-hydroxy-15β,16β-méthylène-3β-pivaloyloxy-5β-androst-6-èn-17-one de formule (IV) :

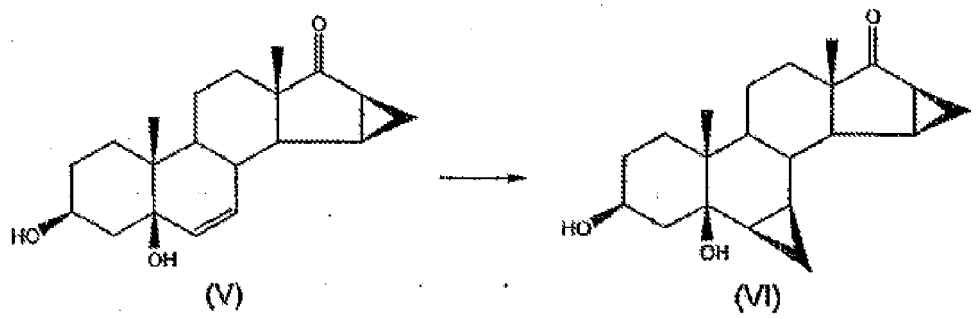


c) hydrolyse du groupe pivaloyle de la 5-hydroxy-15β,16β-méthylène-3β-pivaloyloxy-5β-androst-6-èn-17-one de formule (IV) issue de l'étape b) afin d'obtenir la 3β,5-dihydroxy-15β,16β-méthylène-5β-androst-6-èn-17-one de formule (V) :

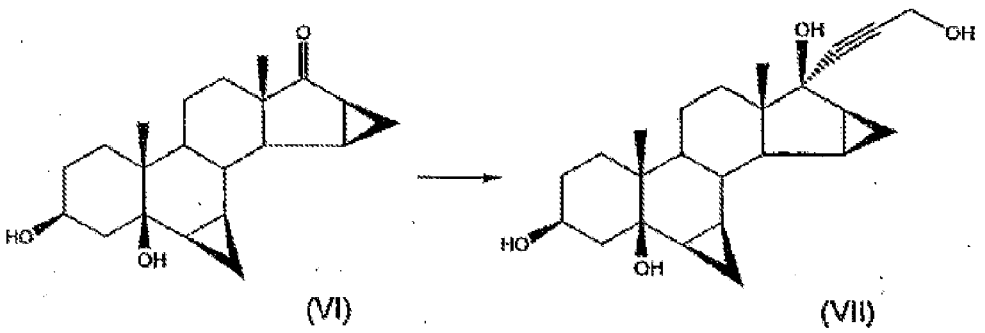


dans laquelle PV est défini comme ci-dessus,

d) méthylénation sur la double liaison Δ^6 de la 3β,5-dihydroxy-15β,16β-méthylène-5β-androst-6-èn-17-one de formule (V) issue de l'étape c) afin d'obtenir la 3β,5-dihydroxy-6β,7β,15β,16β-diméthylène-5β-androst-17-one de formule (VI) :

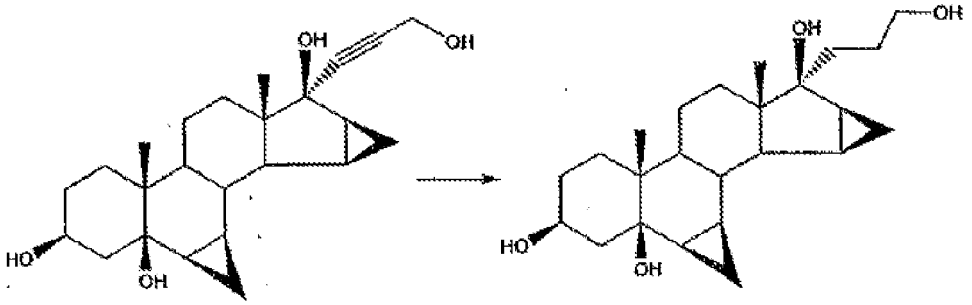


e) réaction de la 3β,5-dihydroxy-6β,7β,15β,16β-diméthylène-5β-androst-17-one de formule (VI) issue de l'étape d) avec de l'alcool propargylique pour obtenir le 17α-(3-hydroxy-1-propinyl)-6β,7β,15β,16β-diméthylène-5β-androstane-3β,5,17β-triol de formule (VII) :



(VI) (VII)

f) hydrogénation du 17α-(3-hydroxy-1-propinyl)-6β,7β;15β,16β-diméthylène-5β-androstane-3β,5,17β-triol de formule (VII) issu de l'étape e) afin d'obtenir le 17α-(3-hydroxypropyl)-6β,7β,15β,16β-diméthylène-5β-androstane-3β,5,17β-triol de formule (VIII) :



(VII) (VIII)

3. Procédé selon la revendication 1, dans lequel ledit agent oxydant est choisi parmi le groupe constitué d'hypohalogénures de métaux alcalins et de métaux alcalino-terreux, d'iode, d'oxygène en présence de CuCl, de peroxymonosulfate de potassium et de 1, 3, 5-trichloro-2,4,6-triazinétrione.

4. Procédé selon la revendication 3, dans lequel ledit agent oxydant est choisi parmi l'hypochlorite de sodium et l'hypochlorite de calcium.

5. Procédé selon la revendication 1, dans lequel ledit dérivé du radical 2,2,6,6-tétraméthylpipéridine-1-oxyle est choisi parmi le groupe constitué du radical 4-hydroxy-2,2,6,6-tétraméthylpipéridine-1-oxyle, du radical 4-méthoxy-2,2,6,6-tétraméthylpipéridine-1-oxyle et du radical 4-(benzoyloxy)-2,2,6,6-tétraméthylpipéridine-1-oxyle.

6. Procédé selon la revendication 1, dans lequel ledit solvant organique est choisi parmi le groupe constitué d'éthers, d'esters, d'hydrocarbures, d'hydrocarbures halogénés et de mélanges de ceux-ci.

7. Procédé selon la revendication 1, dans lequel ledit solvant organique est choisi parmi le groupe constitué d'acétone, de toluène, d'éther méthyl t-butylique, d'acétate d'éthyle, de chlorure de méthylène, de tétrahydrofurane et de mélanges de ceux-ci.

8. Procédé selon la revendication 1, dans lequel ladite oxydation est exécutée à une température comprise entre 0 et 40 °C.

9. Procédé selon la revendication 1, dans lequel ladite oxydation est exécutée avec de l'hypochlorite de calcium en utilisant comme solvant organique un mélange de chlorure de méthylène/tétrahydrofurane à une température comprise entre 20 et 25 °C en présence d'une quantité catalytique du radical 2,2,6,6-tétraméthylpipéridine-1-oxyle et en présence d'une solution aqueuse de bicarbonate de sodium.

10. Procédé selon la revendication 9, dans lequel ledit mélange de chlorure de méthylène/tétrahydrofurane est utilisé dans un rapport de 8,5/1.

11. Procédé selon la revendication 1, dans lequel ledit acide protique est choisi parmi le groupe constitué d'acide chlorhydrique concentré, d'acide chlorhydrique dilué et d'acide p-toluènesulfonique.

12. Procédé selon la revendication 11, dans lequel ledit acide protique est le monohydrate d'acide p-toluènesulfonique.

13. Procédé selon la revendication 1, dans lequel ledit ajout d'acide protique est effectué à une température comprise entre 0 et 40 °C.

14. Procédé selon la revendication 13, dans lequel ledit ajout d'acide protique est effectué à une température comprise entre 20 et 25 °C.

15. Procédé selon la revendication 1, dans lequel ledit acide protique est ajouté directement à la solution organique dans laquelle la réaction d'oxydation a eu lieu.

16. Procédé selon la revendication 1, dans lequel ledit acide protique est ajouté à la solution obtenue en dissolvant dans un solvant organique adapté le résidu semi-solide issu de la distillation de la solution organique dans laquelle la réaction d'oxydation a eu lieu.

17. Procédé selon la revendication 2, dans lequel ladite réaction de bromuration à l'étape a) est exécutée en ajoutant du chlorure de mésyle et de la pyridine au composé de départ à température ambiante avec la formation du mésylate correspondant, puis en ajoutant du bromure de lithium dissous dans de l'eau et en amenant la température à des valeurs comprises entre 70 et 75 °C.

18. Procédé selon la revendication 1, comportant en outre la purification de la drospirénone brute par un processus comportant une filtration sur gel et une cristallisation du filtrat à partir de solvant organique, ledit processus étant éventuellement répété une ou plusieurs fois.

19. Procédé selon la revendication 18, dans lequel ladite purification comporte les étapes suivantes consistant à :

i) dissoudre de la drospirénone brute dans un solvant organique adapté, contenant en outre du gel de silice et du carbone décolorant, et filtrer la solution ainsi obtenue,
ii) distiller la solution issue de l'étape i) et redissoudre le distillat dans un second solvant organique,
iii) distiller la solution issue de l'étape ii) et redissoudre le distillat dans ledit second solvant organique,
iv) cristalliser de la drospirénone pure à partir de la solution issue de l'étape iii),
v) récupérer la drospirénone pure par filtration, lavage au-dessus du filtre au moins une fois avec un solvant organique adapté, et séchage à une pression inférieure à la pression atmosphérique,
vi) répéter facultativement les étapes i) à v), en débutant par la drospirénone issue de l'étape v).

20. Procédé selon la revendication 19, dans lequel la quantité de gel de silice et de carbone décolorant utilisés est inférieure à 5 % en poids par rapport au poids de la drospirénone brute à purifier.

21. Procédé selon la revendication 19, dans lequel la température de distillation aux étapes ii) et iii) est comprise entre 35 et 45 °C.

22. Procédé selon la revendication 19, dans lequel ladite distillation aux étapes ii) et iii) est exécutée à une pression inférieure à la pression atmosphérique.

23. Procédé selon la revendication 19, dans lequel ladite cristallisation à l'étape iv) est exécutée à une température comprise entre 0 et 5 °C pendant une période de temps comprise entre 60 et 180 minutes.

24. Procédé selon la revendication 19, dans lequel ledit solvant organique aux étapes i), ii), iii) et v) est choisi parmi le groupe constitué d'éther éthylique, d'éther isopropylique, d'acétate d'éthyle, d'éther méthyl tert-butylique, d'acétate d'isopropyle, d'acétate de méthyle, de diméthoxyéthane, de méthanol, d'éthanol, d'isopropanol, de chlorure de méthylène, d'acétone, de diméthylacétamide, de diméthylformamide et de mélanges de ceux-ci.

25. Procédé selon la revendication 19, dans lequel ledit solvant organique à l'étape i) est le chlorure de méthylène, ledit solvant organique à l'étape ii) est l'acétate d'isopropyle, et à l'étape v), deux lavages sont réalisés, le premier à l'acétate d'isopropyle et le second à l'éther éthylique.

REFERENCES CITED IN THE DESCRIPTION

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