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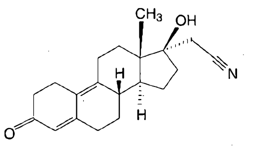
(54) Title: HIGH PURITY 17α-CYANOMETHYL-17β-HYDROXY-ESTRA-4,9-DIENE-3-ONE AND PROCESS FOR THE SYNTHESIS THEREOF

(57) Abstract: The invention relates to a process for the synthesis of high purity 17α-cyanomethyl-17β-hydroxy-estra-4,9-diene-3-one (further on dienogest) of formula (I)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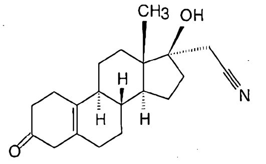
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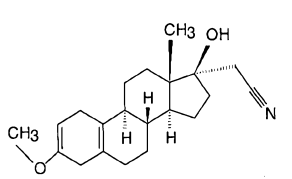
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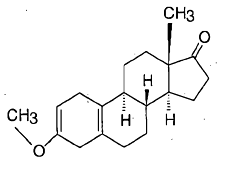
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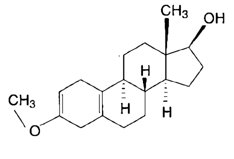
(V)

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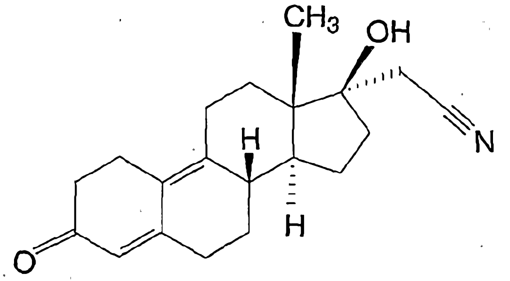
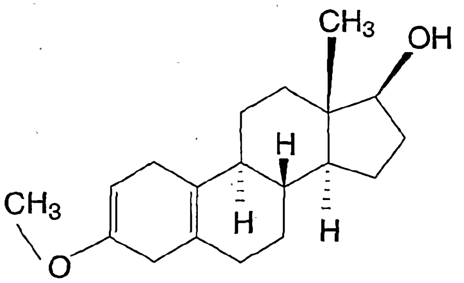
HIGH PURITY 17α-CYANOMETHYL-17β-HYDROXY-ESTRA-4,9-DIENE-3-ONE AND PROCESS FOR THE SYNTHESIS THEREOF

The invention relates to a new process for the synthesis of high purity 17α-cyanomethyl-17β-hydroxy-estra-4,9-diene-3-one (further on dienogest) of formula (I)



(I)

from 3-methoxy-17-hydroxy-estra-2,5(10)-diene of formula (V).



(V)

This compound is used as active ingredient in contraceptive pharmaceutical compositions as progestogene component, in the hormone replacement therapy as well as in compositions against endometriosis. The invention relates also to the high purity 17α-cyanomethyl-17β-hydroxy-estra-4,9-diene-3-one and pharmaceutical compositions containing that as active ingredient. The pharmaceutical compositions according to this invention contain high purity dienogest according to this invention as active ingredient or at least one of the active ingredients and auxiliary materials, which are commonly used in practice, such as carriers, excipients or diluents.

In this description high purity dienogest means, that the total amount of impurities is less than 0.1%, while the amount of 4-bromo-dienogest is under the detection limit (0.02%).

Known procedures for the synthesis of diogenest of formula (I) start from intermediates of the total synthesis of estrone. The main difference between the known procedures is that the two double bonds characteristic for the desired compound are already included in the starting material or not, and in the latter case they are formed in the last step of the synthesis.

According to the German patent application DD 132,497 3-methoxy-17β-spiro-1',2'-oxirane-estra-2,5(10)-diene is reacted with an alkali metal cyanide to yield a 17α-cyanomethyl-17β-hydroxy-3-enolether derivative. Then the so obtained compound is hydrolyzed, brominated and dehydrobrominated to furnish the dienogest of formula (I) in 32% yield. The purity of the obtained dienogest is characterized by the melting point (204-214 °C) and optical rotation ($[\alpha]_D^{25}$ = -290°, pyridine, c=0.5%). According to the method described in the patent application DD 80,023 3-methoxy-17β-spiro-1',2'-oxirane-estra-2,5(10)-diene used as starting material can be synthesized by reacting dimethylsulfonium methylide and the 17-oxo derivative obtained by Oppenauer oxidation of the 17-hydroxy group of 3-methoxy-17-hydroxy-estra-2,5(10)-diene of formula (V) – latter synthesized by known methods.

The process described in the German patent application DD 160,418 a modification of the above process, in which first the compound of formula (V) is transformed into 3,3-dimethoxy-17-hydroxy-estr-5(10)-ene, the 17 hydroxy group is oxidized with pyridinium chlorocromate – instead of Oppenauer oxidation – then 17β-spiro-1',2'-oxirane is formed with dimethylsulfonium methylide, and the latter is reacted with alkali metal cyanide to obtain 3,3-dimethoxy-17α-cyanomethyl-17β-hydroxy-estr-5(10)-ene. This compound is hydrolyzed with sulfuric acid to give 17α-cyanomethyl-17β-hydroxy-estr-5(10)-ene, from which after bromination and subsequent dehydrobromination the dienogest is obtained in 48% yield. The total yield of the process is 24%.

The German patent application DD 296,495 describes a one-pot synthesis, according to which first the starting keto-steroid – position 3 of which contains a hydroxy or an oxo group protected with one or more alkoxy group – is reacted with cyanomethyl lithium formed in situ in the reaction of lithium alkyls or lithium dialkylamides and acetonitrile in an organic solvent at low temperature. This way a 17-hydroxy and a 17-cyanomethyl group are formed from the 17 oxo group, the obtained reaction mixture is treated with water and the obtained

17-hydroxy-17-cyanomethyl derivative is isolated or transformed into dienogest by direct acidic hydrolysis. The yield of the final product is 82% starting from 3,3-dimethoxy-estra-5(10),9(11)-diene-17-one, while using the 3,3-(1,3-propylenedioxi)-estra-5(10),9(11)-diene derivative as starting material the yield is 80%. The purity of the product is characterized by the melting point: 208-211.5 °C. The synthesis consist of 6 steps included the preparation of the 17-oxo derivative used as starting material.

According to the patent application EP 0776904 3,3-(2,2-dimethylpropylene-1,3-dioxy)-4,5-seco-estr-9-ene-5,17-dione is transformed first to estra-4,9-diene-3,17-dione and the latter to 3,3-ethylenedioxy-estra-5(10),9(11)-diene-17-one. After reacting with dimethylsulfonium iodide a 17β-spiro-1',2'-oxirane derivative is obtained which is reacted with potassium cyanide to give 17α-cyanomethyl-17β-hydroxy-estra-5(10),9(11)-diene-3-ethyleneketal. The ketal group of this compound is hydrolyzed with hydrochloric acid to give the final product dienogest in > 98% purity.

According to the processes starting from the above mentioned 3-methoxy-17-hydroxy-estra-2,5(10)-diene of formula (V) first a 3,3-dialkoxy-ketal-5(10)-ene derivative is formed, then the latter is oxidized to a keto compound, which is reacted with dimethylsulfonium-methylide to give a 17β-spiro-1',2'-oxirane derivative, and this is transformed into 17α-cyanomethyl-17β-hydroxy derivative. The obtained compound is hydrolyzed with acid, then brominated and dehydrobrominated to yield the dienogest of formula (I) in 6 steps.

According to the other process starting also from compound of formula (V) after the oxidation of the hydroxyl group in position 17 by Oppenauer oxidation the 17β-spiro-1',2'-oxirane derivative is synthesized, which is reacted with alkali metal cyanide, the obtained 3-enolether is hydrolyzed, brominated and dehydrobrominated to yield dienogest in 5 steps.

According to the other method mentioned above 3,3-ethylenedioxy-estra-5(10),9(11)-diene-17-one is either reacted directly with cyanomethyl lithium or spiro-oxirane is formed first and the oxirane ring is opened with alkali cyanide to give the 17α-cyanomethyl-17β-hydroxy derivative, which is hydrolyzed to yield the final product of formula (I).

The syntheses of the 17β-spiro-1',2'-oxirane derivatives starting from 17-keto compounds and dimethylsulfonium derivatives according to the methods described in patent applications DD 132,497 and EP 0,776,904 are expensive and environmentally not friendly. The use of alkali cyanide for the opening of the oxirane ring requires keeping to strict safety instructions and after the work-up of the reaction mixture causes environmental problems.

According to the other method mentioned above 3,3-ethylenedioxy-estra-5(10),9(11)-diene-17-one is either reacted directly with cyanomethyl lithium or spiro-oxirane is formed first and the oxirane ring is opened with alkali cyanide to give the 17 β -cyanomethyl-17□-hydroxy derivative, which is hydrolyzed to yield the final product of formula (I).

The syntheses of the 17β -spiro-1',2'-oxirane derivatives starting from 17-keto compounds and dimethylsulfonium derivatives according to the methods described in patent applications DD 132,497 and EP 0,776,904 are expensive and environmentally not friendly. The use of alkali cyanide for the opening of the oxirane ring requires keeping to strict safety instructions and after the work-up of the reaction mixture causes environmental problems.

In the above mentioned patent applications the quality of the product is characterized only by melting point or at most substance content. The requirements of recent pharmacopoeia specify several other method of examination for the amount of substance and impurities, such as thin layer and liquid chromatography, as well as determine and limit the amount and the number of impurities.

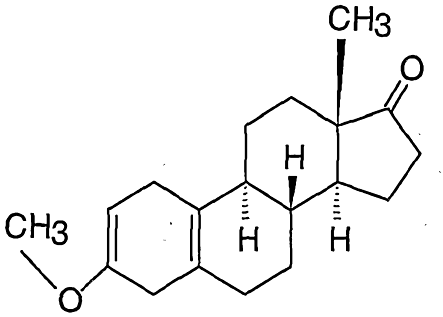
It is a desired feature to eliminate the above mentioned disadvantages of the known procedures and elaborate a shorter, more economical and environmentally friendly synthesis, which can be carried out on industrial scale preferably using an intermediate of the estrone total synthesis, the 3-methoxy-17-hydroxy-estra-2,5(10)-diene of formula (V) as starting material.

It is a further desired feature to synthesize a high purity product, in which the total amount of impurities is less than 0.1%, while the amount of 4-bromo-dienogest is under the detection limit (0.02%), therefore it is suitable for producing different formulations of drugs.

A reference herein to a patent document or other matter which is given as prior art is not to be taken as an admission that that document or matter was known or that the information it contains was part of the common general knowledge as at the priority date of any of the claims.

Throughout the description and the claims of this specification the word "comprise" and variations of the word, such as "comprising" and "comprises" is not intended to exclude other additives, components, integers or steps.

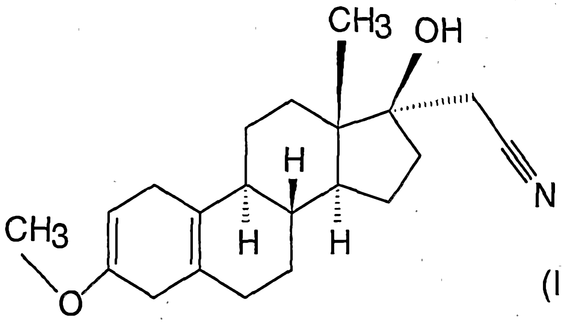
Surprisingly it was found, that using the compound of formula (V) as starting material in the synthesis of compound of formula (III) it is not necessary to form the 17β-oxirane derivative, followed by opening the epoxide ring with alkali cyanide, as well as it is not required to synthesize the 3,3-dialkoxy-ketal from the enolether group of compound of formula (V) and oxidize the hydroxyl group in position 17 with pyridinium chlorocromate. Using the reaction conditions according to our invention the



(IV)

is reacted with cyanomethyl lithium at a temperature between 0 and -30°C,

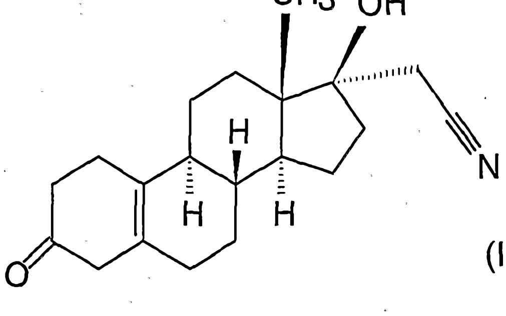
iii) the obtained 3-methoxy-17α-cyanomethyl-17β-hydroxy-estra-2,5(10)-diene of formula (III)



(III)

is reacted with a strong organic acid in tetrahydrofuran solution,

iv) the obtained 17α-cyanomethyl-17β-hydroxy-estr-5(10)-ene-3-one of formula (II)



(II)

is reacted with 1-1.5 equivalent of pyridinium tribromide in pyridine solution at a temperature between 0 and 60°C, then the obtained crude dienogest of formula (I) is purified by recrystallization and preparative HPLC.

Step ii) is preferably carried out at a temperature between -10 and -20°C, while step iv) between 25 and 50°C using 1.05 equivalent of pyridinium tribromide.

Recrystallization is preferably carried out using acetone, ethyl acetate, acetonitrile, methanol, ethanol, or aqueous mixtures of different ratio of these solvents, as well as mixtures of different ratio of dichloromethane and diisopropyl ether or isopropanol or tert-butyl methyl ether.

In order to obtain high purity the so obtained recrystallized product is further purified by preparative HPLC using silica gel as adsorbent and different solvent systems as eluents, such as dichloromethane/ethyl acetate, dichloromethane/tert-butyl methyl ether, or dichloromethane/acetone. Dichloromethane is evaporated from the eluate and the obtained high purity dienogest is isolated from the other component of the used solvent system, e.g. ethyl acetate, tert-butyl methyl ether, acetone, or diisopropyl ether, methanol, ethanol or aqueous mixtures of different ratio of these solvents.

Advantages of our process are as follows:

- the synthesis can be carried out on industrial scale, increasing the batch size compared to the size described in the Examples do not cause technical problems and do not influence the purity of the final product

- the starting material of the synthesis, the 3-methoxy-17-hydroxy-estra-2,5(10)-diene of formula (V), is an easily accessible industrial product,

- the synthesis consist of less reaction steps – only 4 – than the processes known from the literature – 5-6-8 steps,

- using the reaction conditions according to our invention the yields of the reaction steps of the synthesis are much higher, than yields given in the prior arts. The yield of every step is higher than 80%, therefore the total yield is over 50%.

- the quality of the synthesized high purity dienogest is better, than the quality requirements of the pharmacopoeia. The amount of impurities is determined by HPLC. According to these measurements in our product the total amount of impurities is less than 0.1% and the amount of 4-bromo-dienogest, which is an impurity detectable in the marketed pharmaceutical compositions in more than 0.1%, is under the detection limit (0.02%).

- In the cyanomethylation reaction alkali cyanides and dimethylsulfonium derivatives are not used in accordance with environmental regulations and economic considerations, as well as expensive and hazardous butyl lithium is not used either – a hexane solution of hexyllithium is used instead of them.

The process according to our invention is illustrated by the following not limiting examples.

Example 1

3-Methoxy-estra-2,5(10)-diene-17-one

To a stirred solution of 106.3 g (0.52 mmol) of aluminum isopropoxide in 2000 ml of dry toluene 720 ml of cyclohexanone, 0.35 g of 2,6-ditert-butyl-4-methyl-phenol and 100 g (0.307 mol) 3-methoxy-17-hydroxy-estra-2,5(10)-diene were added, then the reaction mixture was stirred at 108-110 °C for 1 h. The reaction was followed by TLC. After completion of the reaction the mixture was cooled to 20-25 °C, 200 ml of water was added and the so obtained mixture was stirred for 1 h. The precipitated aluminum hydroxide was filtered off and the filtrate was concentrated to a volume of 250 ml under reduced pressure. A mixture of 200 ml of methanol and 100 ml of water was added to this concentrated warm – about 60 °C – solution, the obtained suspension was cooled to 20-25 °C and stirred for 1 h. The precipitated crystalline product was filtered off and dried below 40 °C in vacuum to yield 76.4 g (87%) of the title compound.

Purity: min. 98% (HPLC)

Melting point: 106-110 °C.

Example 2

3-Methoxy-17α-cyanomethyl-17β-hydroxy-estra-2,5(10)-diene

410 ml (1.012 mol) of 2.5 M hexyllithium solution was diluted with 300 ml of dry tetrahydrofuran, the solution was cooled to -20 °C and 58 ml (1.112 mol) of acetonitrile was added. To the so obtained suspension of cyanomethyl lithium a solution of 144.8 g (0.506 mol) of 3-methoxy-estra-2,5(10)-diene-17-one in 1450 ml of tetrahydrofuran was added between -20 and -10 °C and the reaction mixture was stirred between -20 and -10 °C until completion of the reaction – followed by TLC. After completion of the reaction 640 ml of water was added, the organic phase was separated, washed twice with 60 ml of water, and concentrated to a volume of 720 ml under reduced pressure. The concentrated solution was cooled to 20-25 °C, 720 ml of water was added, the precipitated crystalline product was filtered off and dried below 40 °C in vacuum. The obtained crude product was recrystallized from ethanol to yield 143.4 g (86.5%) of the title compound.

Purity: min. 98% (HPLC)

Melting point: 145-150 °C.

Example 3

17α-Cyanomethyl-17β-hydroxy-estr-5(10)-ene-3-one

To a stirred solution of 100.8 g (0.8 mol) of oxalic acid dihydrate in 560 ml of water a solution of 131 g (0.4 mol) of 17α-cyanomethyl-17β-hydroxy-3-methoxy-estra-2,5(10)-diene in 1050 ml of tetrahydrofuran was added with cooling. After stirring at 20-25 °C for 1 h the precipitated product was filtered off and dried below 50 °C in vacuum. The obtained crude product was recrystallized from ethyl acetate to yield 107 g (85.6%) of the title compound.

Purity: min. 98% (HPLC)

Melting point: 170-175 °C.

Example 4

17α-Cyanomethyl-17β-hydroxy-estra-4,9-diene-3-one (crude dienogest)

A stirred solution of 142 g (0.45 mol) of 17α-cyanomethyl-17β-hydroxy-estr-5(10)-ene-3-one in 850 ml of pyridine was cooled to 20-25 °C and a solution of 150 g (0.47 mol) of pyridinium tribromide in 640 ml of pyridine was added while the temperature of the reaction mixture was allowed to rise to 50 °C. After stirring for 1 h the reaction mixture was added to a stirred mixture of 320 ml of concentrated sulfuric acid and 5600 ml of water. The precipitated crystals were filtered off and dried below 60 °C in vacuum. The obtained crude product was recrystallized from acetone to yield 116 g (83%) of the title compound.

Amount of active ingredient: min. 97% (HPLC).

4-Bromo-dienogest impurity: max. 1 % (HPLC).

Melting point: 210-213 °C.

$[\alpha]^{20}_{D}$ = - 318° (c=1%, dichloromethane).

Example 5

Purification of dienogest by preparative HPLC

A dynamic axial compression metal column (diameter: 5 cm; length: 60 cm) was filled with 510 g silica gel (Uetikon C-gel C-490, particle size: 15-35 μm) suspended in 1400 ml of dichloromethane and the column was conditioned with a 70:30 mixture of dichloromethane/ethyl acetate eluent (2500 ml). A solution of 8.5 g of crude dienogest in 210 ml of dichloromethane was injected to the column and the above mentioned solvent system was used as eluent with a flow rate of 85 ml/min. UV detector was used for detection. The

fractions containing the pure compound (3600 ml) were concentrated, ethyl acetate was distilled off from the residue and the obtained dienogest was recrystallized from ethyl acetate to yield after drying below 60 °C in vacuum 7.53 g (90.6%) of pure dienogest.
Total amount of impurities: maximum 0.1% (HPLC).
Individual impurities: maximum 0.02% (HPLC).
Melting point:211-214 °C.
$[\alpha]^{20}_{D} = -322°$ (c=1%, dichloromethane).

Example 6

Purification of dienogest by preparative HPLC

A glass column (diameter: 2.6 cm; length: 46 cm) was filled with 120 g silica gel (Uetikon C-gel C-490, particle size: 15-35 μm) and the column was conditioned with a 90:10 mixture of dichloromethane/acetone eluent. A solution of 2 g of crude dienogest in 50 ml of dichloromethane was injected to the column and the above mentioned solvent system was used as eluent with a flow rate of 10 ml/min. UV detector was used for detection. The fractions containing the pure compound (700 ml) were concentrated, acetone was distilled off from the residue and the obtained dienogest was recrystallized from acetone to yield after drying below 60 °C in vacuum 1.77 g (88.5%) of pure dienogest.
Total amount of impurities: maximum 0.1% (HPLC).
Individual impurities: maximum 0.02% (HPLC).
Melting point:211-214 °C.
$[\alpha]^{20}_{D} = -322°$ (c=1%, dichloromethane).

Example 7

Purification of dienogest by preparative HPLC

A glass column (diameter: 2.6 cm; length: 46 cm) was filled with 120 g silica gel (Uetikon C-gel C-490, particle size: 15-35 μm) and the column was conditioned with a 90:10 mixture of dichloromethane/acetone eluent. A solution of 2 g of crude dienogest in 50 ml of dichloromethane was injected to the column and the above mentioned solvent system was used as eluent with a flow rate of 10 ml/min. UV detector was used for detection. The fractions containing the pure compound (700 ml) were concentrated, acetone was distilled off from the residue and the obtained dienogest was recrystallized from acetone to yield after drying below 60 °C in vacuum 1.77 g (88.5%) of pure dienogest.

Total amount of impurities: maximum 0.1% (HPLC).

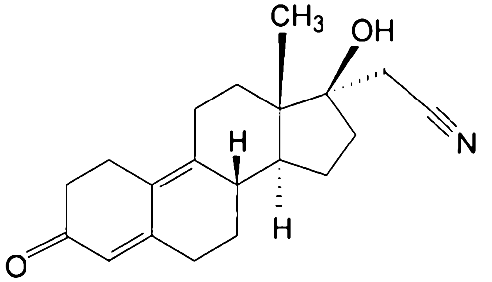
Individual impurities: maximum 0.02% (HPLC).

Melting point:211-214 °C.

$[\alpha]^{20}_{D}$ = -322° (c=1%, dichloromethane).

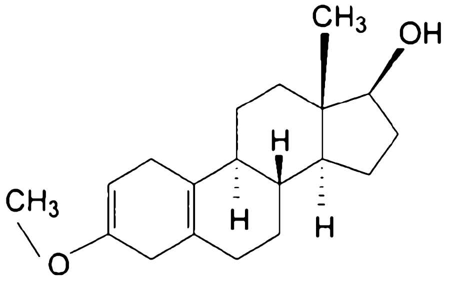
The claims defining the invention are as follows:

1. A new process for the synthesis of high purity 17α-cyanomethyl-17β-hydroxy-estra-4,9-diene-3-one (further on dienogest) of formula (I)



(I)

from 3-methoxy-17-hydroxy-estra-2,5(10)-diene of formula (V),

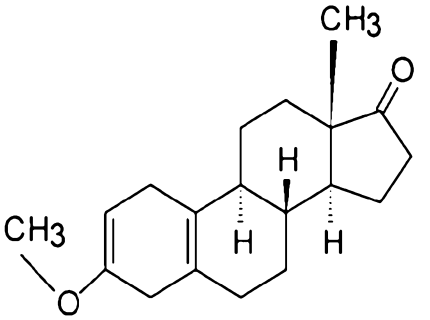


(V)

characterized by

i) reacting the 3-methoxy-17-hydroxy-estra-2,5(10)-diene of formula (V) with aluminum isopropylate in the presence of cyclohexanone in an inert organic solvent under heating

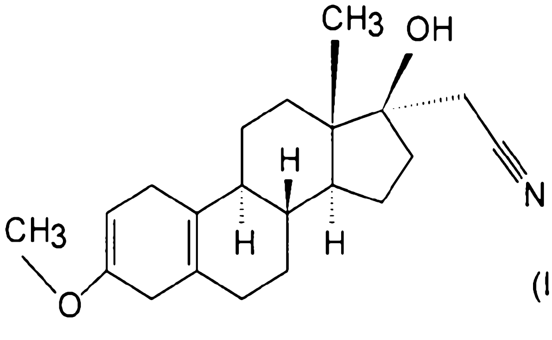
ii) then reacting the so obtained 3-methoxy-estra-2,5(10)-diene-17-one of formula (IV)



(IV)

with cyanomethyl lithium at a temperature between 0 and -30°C,

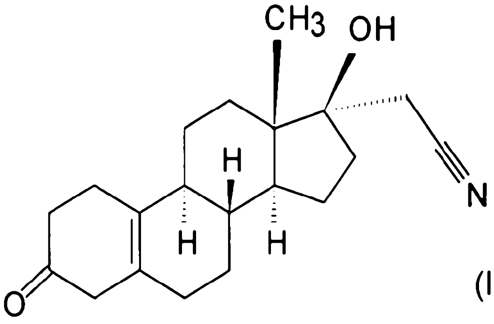
iii) then reacting the obtained 3-methoxy-17α-cyanomethyl-17β-hydroxy-estra-2,5(10)-diene of formula (III)



(III)

with a strong organic acid in tetrahydrofuran solution,

iv) reacting the obtained 17α-cyanomethyl-17β-hydroxy-estr-5(10)-ene-3-one of formula (II)



(II)

with 1-1.5 equivalent of pyridinium tribromide in pyridine solution at a temperature between 0 and 60°C,

then purifying the obtained crude dienogest of formula (I) by recrystallization and preparative HPLC.

2. The process according to claim 1 wherein the process includes the step of carrying out the oxidation of step i) in toluene in the presence of 20-25 equivalent of cyclohexanone between 100 and 120 °C.

3. The process according to claim 1 or 2 wherein the process includes the step of preparing the cyanomethyl lithium reagent of step ii) in situ from hexyllithium and acetonitrile.

4. The process according to any one of the preceding claims wherein the process includes the step of carrying out the cyanomethylation reaction of step ii) between 0 and -30 °C.

5. The process according to any one of the preceding claims wherein the process includes the step of carrying out the cyanomethylation reaction of step ii) between -10 and -20 °C.

6. The process according to any one of the preceding claims wherein the process includes the step of using 2 equivalent of cyanomethyl lithium reagent in step ii).

7. The process according to any one of the preceding claims wherein the process includes the step of carrying out the acidic treatment of step iii) with a di- or tribasic organic acid in tetrahydrofuran.

8. The process according to any one of the preceding claims wherein the process includes the step of carrying out the acidic treatment of step iii) with 2 equivalent of oxalic acid dihydrate.

9. The process according to any one of the preceding claims wherein the process includes the step of reacting the compound of formula (II) with 1.05 equivalent of pyridinium tribromide in step iv).

10. The process according to any one of the preceding claims wherein the process includes the step of reacting the compound of formula (II) with pyridinium tribromide between 0 and 60 °C in step iv).

11. The process according to any one of the preceding claims wherein the process includes the step of reacting the compound of formula (II) with pyridinium tribromide between 25 and 50 °C.

12. The process according to any one of the preceding claims wherein the process includes the step of purifying the dienogest of formula (I) by HPLC using silica gel as adsorbent.

13. The process according to any one of the preceding claims wherein the process includes the step of purifying the dienogest of formula (I) by HPLC using the following solvent mixtures as eluents: 70:30 dichloromethane/ethyl acetate or 80:20 dichloromethane/tert-butyl methyl ether or 90:10 dichloromethane/acetone.

14. The process according to any one of the preceding claims wherein the process includes the step of recrystallizing the dienogest of formula (I) obtained by preparative HPLC from ethyl acetate, acetone, tert-butyl methyl ether, diisopropyl ether, acetonitrile, methanol, ethanol or aqueous mixture of different ratio of these solvents.

15. A 17α-cyanomethyl-17β-hydroxy-estra-4,9-diene-3-one of formula (I) as defined in claim 1, produced by the process as claimed in claim 1.

16. A process as claimed in claim 1, substantially as hereinbefore described with reference to any one of the Examples.