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(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF 19-NORPREGN-4-EN-3,20-DION-17.ALPHA.-OL (GESTONORON) OG MELLEMPRODUKTER DERTIL**

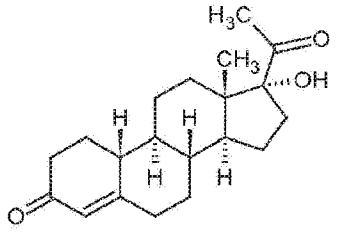
(56) Fremdragne publikationer:
DD-A5- 289 540
US-A- 3 423 435
RUI-REN TANG: "Stereoselective asymmertric synthesis and characterization of 17a-acetoxy- 19-nor-progesterone", J. CENT. SOUTH UNIV. TECHNOL. SEP, vol. 11, no. 3, 1 January 2004 (2004-01-01), pages 300-303, XP55175119, cited in the application
EMILIE CLAUDEL ET AL: "An Efficient Hemisynthesis of 20- and 21-[13C]-Labeled Cortexolone: A Model for the Study of Skin Sensitization to Corticosteroids", SYNTHESIS, no. 20, 3 September 2009 (2009-09-03), pages 3391-3398, XP055157974, ISSN: 0039-7881, DOI: 10.1055/s-0029-1216986
CÉCILE ARBEZ-GINDRE ET AL: "Methyl exchange on silicon during the addition of methylmagnesium iodide to a cyanohydrin O-silyl ether", CHEMICAL COMMUNICATIONS, no. 5, 1 January 1999 (1999-01-01), pages 431-432, XP55175439, ISSN: 1359-7345, DOI: 10.1039/a809782h
E. V. POPOVA ET AL: "Synthesis of pregnane derivatives", CHEMISTRY OF NATURAL COMPOUNDS, vol. 20,

Fortsættes ...

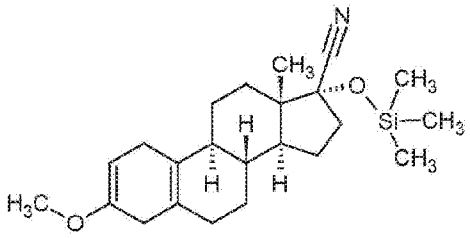
no. 3, 1 January 1984 (1984-01-01), pages 302-304, XP055157966, ISSN: 0009-3130, DOI: 10.1007/BF00575752

DESCRIPTION

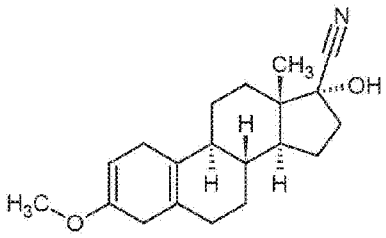
[0001] The present invention relates to a new stereoselective process for the synthesis of 17(α)-17-acetyl-17-hydroxy-estr-4-en-3-one of formula (I) using the compound of formula (IV) as starting material, as well as to the new intermediates of the process.



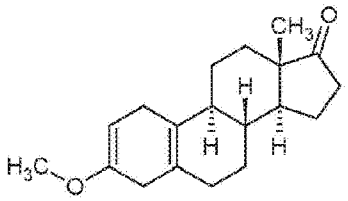
(I)



(II)



(III)



(IV)

[0002] The 17(α)-17-acetyl-17-hydroxy-estr-4-en-3-one (hereafter: gestonorone) is an important intermediate in the synthesis of the active ingredients having progestogen activity --- such as gestonorone capronate and nomegestrol acetate. There are various known processes in the literature for its synthesis. The first was described in 1953 (MXX762308, US 2,781,365; GB 762,308**).** In this process the gestonorone was synthesized starting from 17-acetyl-3-hydroxy-estra-1,3,5(10),16-tetraene via a derivative of 17β-acetyl-17α-hydroxy-3-methoxy-estra-1,3,5(10)-triene protected in position 20 with ethylene ketal.

[0003] In the US patent No. 3,381,003 the gestonorone is synthesized starting from estron-3-alkyl ether (Figure 1.). The pregnane side-chain in position 17 is synthesized in a complicated and time-consuming 7-step process. The oxo group in position 20 is protected as ethylene ketal, then the necessary transformations are carried out on the A-ring.

[0004] The estron-3-alkyl ether is ethynylated in position 17, the 17 hydroxyl group of the obtained compound is acylated and the ethynyl group is brominated with N-bromo-acetamide

in an organic solvent in the presence of terc-butanol and water. In the next debromination reaction the 17α-acetyl-3-alkoxy-17β-hydroxy-gona-1,3,5(10)-trien-17β-yl-acetate is formed in the presence of zinc and acetic acid, which is then reduced with calcium metal in liquid ammonia. The isopregnane side-chain of the obtained compound is isomerized in acetic acid in the presence of zinc at reflux temperature for 24 h. The hydroxyl group in position 17 is introduced the following way: the oxo group in position 20 is transformed into enol acetate with acetic anhydride in the presence of catalytic amount of p-toluenesulfonic acid and the formed $\Delta^{17(20)}$-double bond is oxidized with perbenzoic acid. Finally the oxo group in position 20 is transformed into ethylene ketal with ethylene glycol in the presence of catalytic amount of p-toluenesulfonic acid. The next two reaction steps are carried out as described in point 1, the derivative of 17β-acetyl-17α-hydroxy-3-methoxy-estra-1,3,5(10)-triene protected in position 20 with ethylene ketal is reduced with lithium metal in liquid ammonia and the obtained compound is transformed into gestonorone with acid hydrolysis.

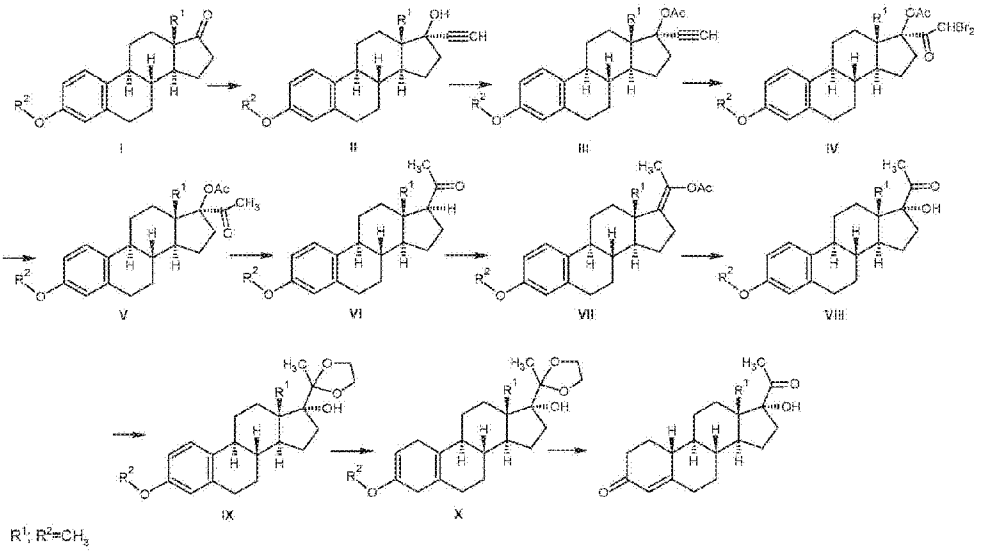


Figure 1.

[0005] According to the US patent No. 3,423,435 17-cyano-17-hydroxy-3-methoxy-estra-2,5(10)-diene (a mixture of isomers/diastereomers) is synthesized starting from 3-methoxy-estra-2,5(10)-dien-17-one with acetone cyanohydrin, which is acylated with acetic anhydride in pyridine (figure 2.). The synthesis of cyanohydrin is also described starting from 19-nor-androsten-dione.

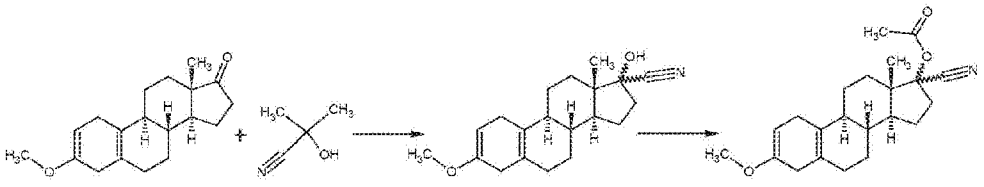


Figure 2.

[0006] During the two processes below the 17α-hydroxy-pregnane side-chain is synthesized

starting from estr-4-en-3-one or an estr-4-en-3-one derivatives.

[0007] In the US patent No. 3,764,615 the synthesis of the 17α-hydroxy-pregnane derivatives is described (Figure 3.). The pregnane side-chain is synthesized via the sulfite ester derivatives of 17α-ethynyl-17β-hydroxy steroids the following way: the ethynyl group is transformed into pregnane side-chain via hydration in the presence of mercury salt. The disadvantage of the process is the use of environmental pollutant mercury salt.

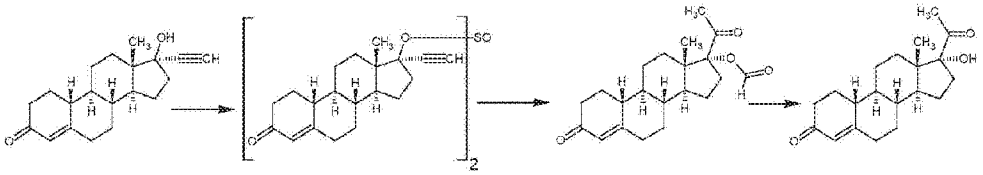


Figure 3.

[0008] In the Chinese article published in Journal of Central South University of Technology (English Edition) (2004), 1](3), 300-303 estr-4-en-3-on-17-cyanohydrine is synthesized from estr-4-en-3,17-dione with potassium cyanide in aqueous methanol, then the oxo group of the obtained product is protected as ketal using ethylene glycol and boron trifluoride as catalyst. The tertiary hydroxyl group is protected with butyl vinyl ether and the pregnane side-chain is formed with methyl lithium in diethyl ether as solvent. The protective groups are removed with hydrochloric acid hydrolysis. The overall yield of the six-step process is 63% (Figure 4.).

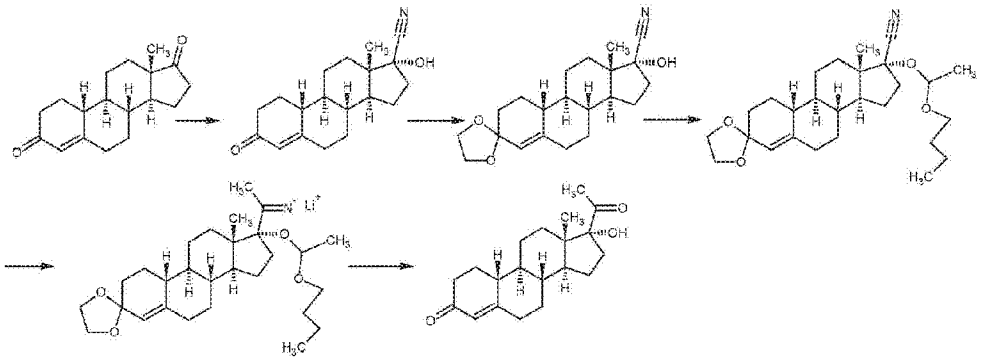


Figure 4.

[0009] During our experiments surprisingly it was found, that the pregnane side-chain can be synthesized in much fewer steps and under milder reaction conditions as compared to the above described processes. A cyanohydrine precursor compound with the proper steric arrangement is required for the formation of the pregnane side-chain. The β-cyanohydrine of formula (III) is obtained from the starting material in high epimeric purity, then the hydroxyl group in position 17 is protected as silyl ether. Although the starting material contains an acid labile enol ether moiety, but the silyl ether type protective group in position 17 can be synthesized under neutral reaction conditions used in our process.

[0010] The process can also be applied in those cases when the compounds contain acid labile moieties (for example enol ether), while the alkoxy ether type protective groups are not

suitable for this purpose.

[0011] The basis of our invention is the discovery, that the silyl ether protected cyanohydrines can be reacted with methyl lithium under proper reaction conditions and the pregnane side-chain can simply be synthesized.

[0012] The starting material, the 3-methoxy-estra-2,5(10)-dien-17-one of formula (IV), which can be synthesized for example according to the process described in the US patent No. 3,423,435 (from estron-3-methylether with Birch reduction) or from other aromatic intermediate with Birch reduction and oxidation, can easily be transformed into 3-oxo-4-ene derivative, on the other hand it has an appropriate protective group, therefor (17α)-17-acctyl-17-hydroxy-estr-4-en-3-one of formula (I) can be synthesized in fewer reaction steps. Because of the mild reaction conditions there is no need to use selective protective groups such as ketal or enol ether type protective groups in contrast to the synthesis starting from 3-oxo-4-ene intermediate.

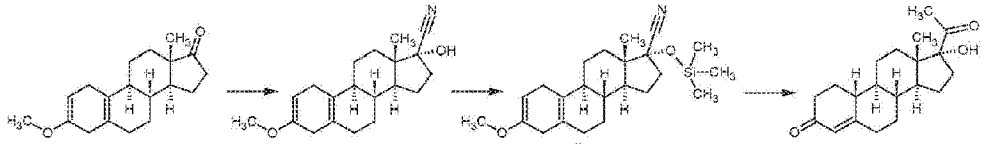
[0013] It is also advantageous that under appropriately selected reaction conditions the 17α-hydroxy-17β-nitril (β-cyanohydrine) of formula (III) is obtained from compound (IV) in excellent yield and in high epimeric purity. The explanation of this is that in the first phase of the reaction the amount of the starting material is reduced to less than 1% by choosing the right special reaction conditions, then in the second phase of the reaction the crystallization of the β-cyanohydrine is induced from the formed isomeric mixture of cyanohydrine by proper selection of the reaction conditions, this way the equilibrium of the isomerization reaction is shifted towards the β-cyanohydrine.

[0014] The methylation of cyanohydrine of formula (II) preferably protected in position 17 with silyl ether can not be carried out with methyl lithium, in fact only by-products are formed under harsh reaction conditions too. If a suitable complex-forming agent, for example tetraalkyl ethylenediamine, preferably N,N,N',N'-tetramethylethylendiamine, is used to transform the reagent containing methyl lithium oligomers into monomers, the methylation reaction of cyanohydrine protected in position 17 with silyl ether can be carried out in good yield and in good quality.

[0015] The invention also relates to the intermediates of formula (II) and (III) of the process.

[0016] According to the above mentioned facts the strategy of our synthesis was so elaborated that the requirements of the guidelines for planning a modern industrial synthesis of steroids were taken into consideration and best fulfilled.

[0017] The process of our invention is more simple and shorter and the obtained final product fulfills the high quality requirements owing to the properly chosen starting material.



IV III II I

Figure 5.

[0018] The process of our invention (Figure 5.) is described in detail hereunder.

[0019] The synthesis of compound (III) from compound (IV) is carried out the following way:

[0020] Short-chain aliphatic alcohols, preferably methanol or ethanol are used as solvent.

[0021] Alkali cyanides, preferably potassium or sodium cyanides are used as reagents, the molar ratio is selected between 1.5-10, preferably between 2-4 mol, and a mild organic acid, preferably acetic acid is used as further reagent for liberating hydrogen cyanide, the molar ratio is selected between 1.3-8, preferably between 1.5-3 mol.

[0022] The temperature of the reaction is kept between +20-+63°C., preferably the temperature program described in Example 1 is kept.

[0023] The synthesis of compound (II) from compound (III) is carried out the following way:

[0024] Ethers, for example diethyl ether, tetrahydrofuran, methyl tert-butyl ether, diisopropyl ether, preferably methyl tert-butyl ether or tetrahydrofuran are used as solvent.

[0025] Trimethyl chlorosilane is used as reagent in the presence of imidazole, the molar excess of the reagent is between 2-10 mol, preferably 2.5-4 mol.

[0026] The temperature of the reaction is kept between 0-+40°C, preferably between 0-+10°C.

[0027] The synthesis of compound (I) from compound (II) is carried out the following way:

[0028] Ethers or formaldehyde dialkylacetals, for example diethyl ether, tetrahydrofuran, methyltetrahydrofuran, methyl tert-butyl ether, diisopropyl ether, diethoxymethane, dimethoxymethane, preferably methyl tert-butyl ether, tetrahydrofuran or diethoxymethane, are used as solvent.

[0029] The excess of methyl lithium reagent can be 1.5-10 mol equivalent, preferably 2.5-5 mol equivalent.

[0030] The stability of methyl lithium oligomers can be reduced with substituted 1,2-diamino-ethanes, preferably with N,N,N',N'-tetramethylethylendiamine.

[0031] The temperature of the reaction is kept between -78 and -10°C, preferably between -40 and -20°C.

[0032] The protected imine obtained as intermediate is transformed into the final product of formula (I) with mineral acids or strong organic acids, for example with hydrochloric acid, sulfuric acid, potassium hydrogensulfate, sodium hydrogensulfate, p-toluenesulfonic acid, perchloric acid, preferably with hydrochloric acid.

[0033] During the hydrolysis alcohols or ethers, preferably methanol, ethanol or methyl tert-butyl ether, diethoxymethane, tetrahydrofuran, are used as solvent.

[0034] The hydrolysis is carried out at a temperature between 0°C and the boiling point of the applied solvent, preferably between +5 and +40°C.

[0035] The process of our invention is illustrated by the following not limiting examples.

Example 1

Synthesis of(17α)-17-hydroxy-3-methoxyestra-2,5(10)-dien-17-carbonitrile

[0036] Under inert atmosphere 50.0 g of 3-methoxyestra-2,5(10)-dien-17-one was suspended in 500 ml of ethanol and 34.25 g of potassium cyanide and 0.15 g of 2,6-ditert-butyl-4-methyl-phenol were added while stirring. After 10 minutes stirring 20.0 ml of acetic acid was added dropwise over a period of 10 minutes. The reaction mixture was warmed from 30-35°C. to 58-63°C., stirred at this temperature for 1 h, then cooled to 20-25°C and stirred for 16 h. 50 ml of water was added to the reaction mixture and the slurry was stirred for 1 h. The precipitated crystals were filtered off, suspended with 5x150 ml of water, and washed with 2x100 ml of water. The wet crystals were stirred under inert atmosphere with 300 ml of ion-exchanged water for 15 minutes, filtered off and washed with 2x100 ml of water. The wet crystals were washed with 75 ml of cold ethanol and 3x50 ml of methyl tert-butyl ether.
Yield: 53.0 g (96.9%)
Purity (HPLC): 97.49%

^{1}H NMR (DMSO-*d6*, 500 MHz) δ: 6.26 (s, 1H), 4.64 (t, J=3.3 Hz, 1H), 3.45 (s, 3H), 2.70-2.87 (m, 1H), 2.49-2.63 (m, 2H), 2.37-2.45 (m, 1H), 2.22-2.34 (m, 1H), 1.97-2.08 (m, 1H), 1.76-1.96 (m, 3H), 1.61-1.75 (m, 4H), 1.51-1.60 (m, 1H), 1.37-1.47 (m, 1H), 1.24-1.3cm (m, 2H), 1.11-1.25 (m, 2H), 0.83 (s, 3H)

^{13}C NMR (DMSO-*d6*, 125 MHz) δ: 151.8, 127.3, 124.3, 121.8, 90.4, 76.5, 53.4, 48.9, 46.6, 44.3, 38.7, 37.4, 33.6, 29.8, 27.8, 26.9, 24.6, 22.9, 16.2

Example 2

Synthesis of (17α)-3-methoxy-17-[(trimethylsilyl)-oxy]-estr-2,5(10)-dien-17-carbonitrile

[0037] Under inert atmosphere to a stirred mixture of 53.0 g of (17α)-17-hydroxy-3-methoxyestra-2,5(10)-dien-17-carbonitrile, 0.15 g of 2,6-ditert-butyl-4-methyl-phenol and 900 ml of methyl tert-butyl ether a solution of 36.0 g of imidazole in 100 ml of tetrahydrofuran was added. The reaction mixture was cooled to 0-5°C and 60.0 ml of trimethylchlorosilane was added dropwise at such a rate to keep the temperature below 5°C. After stirring for 2 h 50 ml of water was added to the reaction mixture and after 10 minutes stirring the organic phase was separated and washed with 3x50 ml of water. The organic phase was dried over 7.5 g of MgSO4, filtered and the filtered drying agent was washed with 2x25 ml of methyl tert-butyl ether. The filtrate was concentrated to half volume, and 3x300 ml of methyl tert-butyl ether was distilled off at 30-35°C. The solution was diluted to 600 ml and used in the next step.
Dry substance content: 58.9 g (90.4%)
Water content: 0.09 g/100 ml
Purity (HPLC): 96.53%

^{1}H NMR (CD_2Cl_2, 500 MHz) δ: 4.65 (t, J=3.3 Hz, 1H), 3.50-3.57 (m, 3H), 2.80-2.95 (m, 1H), 2.56-2.69 (m, 2H), 2.45-2.55 (m, 1H), 2.33-2.41 (m, 1H), 2.09 (br. s., 1H), 2.01 (ddd, J=14.8, 9.2, 5.6 Hz, 1H), 1.95 (dd, J=13.3, 2.8 Hz, 1H), 1.90 (dd, J=6.4, 0.7 Hz, 1H), 1.76-1.84 (m, 1H), 1.60-1.76 (m, 4H), 1.49-1.55 (m, 1H), 1.33-1.44 (m, 2H), 1.20-1.32 (m, 2H), 0.92 (s, 3H), 0.25 (s, 9H)

^{13}C NMR (CD_2Cl_2, 125 MHz) δ: 153.1, 128.1, 125.4, 121.6, 91.0, 79.4, 54.2, 51.0, 47.6, 45.3, 40.0, 39.5, 34.6, 31.0, 30.8, 28.8, 27.9, 25.8, 24.0, 16.7, 1.3

Example 3

Synthesis of (17α)-17-acetyl-17-hydoxy-estr-4-en-3one

[0038] The stirred solution of (17α)-3-methoxy-17-[(trimethylsilyl)-oxy]-estr-2,5(10)-dien-17-carbonitrile in 600 ml of methyl tert-butyl ether was cooled to -40°C, then 80 ml of N,N,N',N'-tetramethylethylendiamine and 180 ml of methyl lithium solution (3M in diethoxymethane) were added at such a rate to keep the temperature below -30°C. The reaction mixture was stirred at this temperature for 1 h, then poured into 1000 ml of 4N hydrochloric acid solution cooled to -15-(-10)°C with intensive cooling. The reaction mixture was stirred at 20-25°C for 16 h, then the pH of the solution was adjusted to 4-5 by the addition of about 800 ml of 3M sodium acetate. The volatile organic components were distilled off and the residue was stirred at 20-25°C. for 1 h. The precipitated crude product was filtered off, suspended with 5x500 ml of water, washed with 100 ml of cold methanol, and dried in vacuum oven.
Yield: 32.42 g (67.1%)
Purity (HPLC): 89.66%
Under inert atmosphere 32.42 g of crude product was added to 97 ml of methanol at 60°C, after a clear solution was obtained the mixture was cooled to 20-25°C. 16.2 ml of water was

added to the stirred slurry over a period of 2-3 minutes, then it was cooled to 0-5°C. After stirring for 1 h, the crystals were filtered off, suspended with a mixture of 11.2 ml of water and 67.1 ml of methanol, then dried in vacuum oven.
Yield: 25.67 g (79.2%)
Purity (HPLC): 98.47%

^{1}H NMR ($CDCl_3$, 800 MHz) δ: 5.82-5.85 (m, 1H), 2.85 (s, 1H), 2.69 (ddd, J=14.9, 11.5, 3.1 Hz, 1H), 2.47-2.51 (m, 1H), 2.39-2.43 (m, 1H), 2.28 (s, 3H), 2.23-2.31 (m, 3H), 2.06-2.11 (m, 1H), 1.89-1.93 (m, 1H), 1.81-1.88 (m, 2H), 1.72-1.80 (m, 2H), 1.61 (ddd, J=15.2, 9.2, 6.3 Hz, 1H), 1.52-1.58 (m, 1H), 1.35-1.44 (m, 3H), 1.22-1.29 (m, 1H), 1.12-1.18 (m, 1H), 0.90 (dtd, J=12.0, 10.6, 4.2 Hz, 1H), 0.78 (s, 3H)

^{13}C NMR ($CDCl_3$, 201 MHz) δ: 211.6, 199.9, 166.4, 124.6, 89.8, 49.2, 49.0, 48.4, 42.4, 40.2, 36.5, 35.5, 33.5, 31.1, 30.0, 27.9, 26.6, 25.9, 23.8, 15.5

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US2781365A [0002]
- GB762308A [0002]
- US3381003A [0003]
- US3423435A [0005] [0012]
- US3764615A [0007]

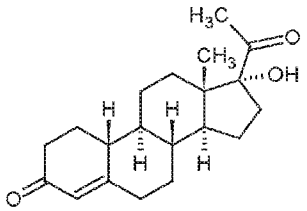
Non-patent literature cited in the description

- Journal of Central South University of Technology, 2004, vol. 1, 3300-303 [0008]

FREMGANGSMÅDE TIL FREMSTILLING AF 19-NORPREGN-4-EN-3,20-DION-17.ALPHA.-OL (GESTONORON) OG MELLEMPRODUKTER DERTIL

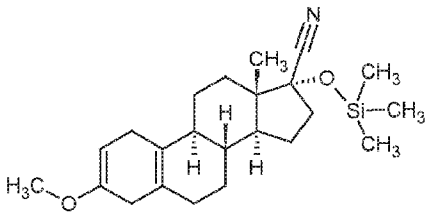
Patentkrav

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(I)

kendetegnet ved, at forbindelsen med formlen (II)

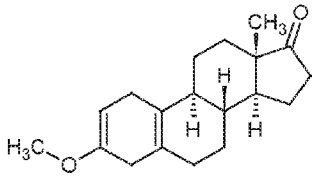


(II)

omsættes med 1,5-10 mol ækvivalent af methyllithium i nærværelse af substitueret 1,2-diamino-ethan i et opløsningsmiddel af ether- eller formaldehyddiacetaltypen eller en blanding deraf ved en temperatur på mellem -78 °C og -10 °C, og dernæst omsættes det beskyttede iminderivat, der blev opnået som mellemprodukt, med uorganiske syrer eller stærke organiske syrer ved en temperatur på mellem 0 °C og kogepunktet for det anvendte organiske opløsningsmiddel.

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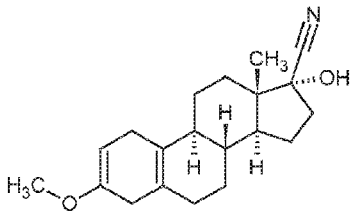
i) omsætning af forbindelsen med formlen (IV)



(IV)

med 1,5-10 mol ækvivalent af alkalicyanid i et opløsningsmiddel af kortkædet alifatisk alkohol-typen i nærværelse af en mild organisk syre, dernæst

ii) omsætning af den opnåede forbindelse med formlen (III)



(III)

med 2-10 mol ækvivalent af trimethylchlorosilan i nærværelse af imidazol i et opløsningsmiddel af ethertypen ved en temperatur på mellem 0 og +40 °C.

3. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** reaktionen i trin i) udføres i ethanol.

4. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** der anvendes kaliumcyanid eller natriumcyanid som reagens i trin i).

5. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** der fortrinsvis anvendes 2-4 mol overskud af cyanidreagens i trin i).

6. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** der fortrinsvis anvendes eddikesyre som mild organisk syre i trin i).

7. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** der fortrinsvis anvendes 1,5-3 mol overskud af eddikesyre i trin i).

8. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** reaktionen i trin ii) fortrinsvis udføres ved en temperatur på mellem 0 og +10 °C.

9. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** reaktionen i trin ii) udføres i methyl-tert-butyl-ether eller tetrahydrofuran.

10. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** der fortrinsvis anvendes 2,5-4 mol overskud af reagens i trin ii).

11. Fremgangsmåde ifølge krav 1, **kendetegnet ved, at** der anvendes 2,5-5 mol

overskud af methyllithium.

12. Fremgangsmåde ifølge krav 1, **kendetegnet ved, at** der anvendes N,N,N',N'-tetramethylethylendiamin som substitueret 1,2-diamino-ethan.

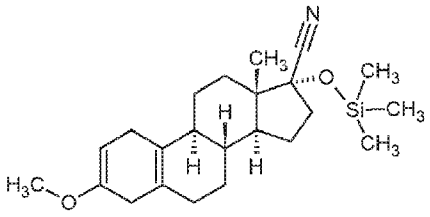
13. Fremgangsmåde ifølge krav 1, **kendetegnet ved, at** reaktionen udføres ved en temperatur på mellem -40 og -20 °C.

14. Fremgangsmåde ifølge krav 1, **kendetegnet ved, at** der anvendes saltsyre i transformationen af den beskyttede imin, der blev opnået som mellemprodukt, til forbindelsen med formlen (I).

15. Fremgangsmåde ifølge krav 1, **kendetegnet ved, at** transformationen af den beskyttede imin, der blev opnået som mellemprodukt, til forbindelsen med formlen (I) udføres i en blanding af vand og tert-butyl-methyl-ether eller diethoxymethan som opløsningsmiddel.

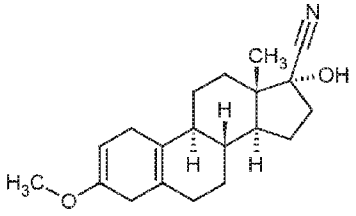
16. Fremgangsmåde ifølge krav 1, **kendetegnet ved, at** hydrolysen og syreomlejringen udføres ved en temperatur på mellem +5 og +40 °C.

17. (17α)-3-methoxy-17-[(trimethylsilyl)-oxy]-estr-2,5(10)-dien-17-carbonitril med formlen (II)



(II)

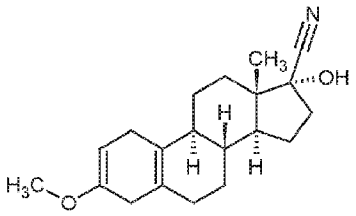
18. Fremgangsmåde til syntese af **(17α)-3-methoxy-17-[(trimethylsilyl)-oxy]-estr-2,5(10)-dien-17-carbonitril** med formlen (II), **kendetegnet ved, at** forbindelsen med formlen (III)



(III)

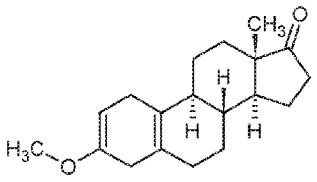
omsættes med 2-10 mol ækvivalent af trimethylchlorosilan i nærværelse af imidazol i et opløsningsmiddel af ethertypen ved en temperatur på mellem 0 og +40 °C.

19. (17α)-17-hydroxy-3-methoxyestra-2,5(10)-dien-17-carbonitril med formlen (III).



(III)

20. Fremgangsmåde til syntese af **(17α)-17-hydroxy-3-methoxyestra-2,5(10)-dien-17-carbonitril** med formlen (III), **kendetegnet ved, at** forbindelsen med formlen (IV)



(IV)

omsættes med 1,5-10 mol ækvivalent af alkalicyanid i et opløsningsmiddel af kortkædet alifatisk alkohol-typen i nærværelse af en mild organisk syre.