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(54) **16 alpha-methyl steroids and their preparation.**

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Description

This invention relates to 16α-methyl steroids and their preparation.

16α-Methyl cortocoids, including dexamethasone, flumethasone and paramethasone, are known anti-inflammatory agents.

The transformation of 16-unsaturated pregnanes to 16α-methyl pregnanes, using a Grignard reagent, is known. Conjugate addition to a 16-unsaturated-2-keto steroid, to form a 16α-methyl-$\Delta^{17(20)}$-20-enolate, using a methyl Grignard reagent in the presence of a copper salt catalyst, is described in "Organic Reactions in Steroid Chemistry", Vol. II, J. Fried and J. A. Edwards, Van Nostrand Reinhold Co., NY (1972) 75. The product may be trapped as the 20-acetate (see p.76). While the addition can give equal amounts of 1,2 and 1,4 products, the use of cuprous chloride gives exclusively 1,4-addition, in yields of greater than 90%.

US—A—3231568 discloses the transformation of a 16-unsaturated progesterone to the corresponding 17α-hydroxy-16α-methylprogesterone. The progesterone had no C_{21} functionality and no C-ring substitution. Acetate is used for trapping.

US—A—4031080 discloses using copper for the conjugate addition reaction, to produce an enol acetate, in the preparation of a 17α-bromo-16α-methyl corticoid.

US—A—4277409 discloses transforming a 16-unsaturated-21-acetate to a 16α-methyl-21-acetate, without introducing a 17α-hydroxyl group.

GB—A—2001990 discloses transforming a 16-unsaturated corticoid to the corresponding 16α-methyl corticoid, by methylation with a methyl Grignard reagent in the presence of a copper catalyst, to produce a 6α-methyl-$\Delta^{17(20)}$-20-(magnesium bromide)enolate, oxygenation to a 17α-hydroperoxide, and reduction to the corresponding 16α-methyl-17α,21-dihydroxy-20-one 21-acetate.

US—A—3072686 discloses the transformation of a 16-unsaturated progesterone to a 17α-hydroxy-16α-methyl-progesterone by reaction with a Grignard reagent and cuprous chloride, via a $\Delta^{17(20)}$-20-enol acetate.

J.A.C.S. *80* (1958) 3160 and 4428 report the transformation of a 16-unsaturated progesterone to a 16α-methylprogesterone, by reaction with a Grignard reagent followed by peracid oxidation, to produce a 17α-hydroxy-16α-methylprogesterone which is brominated and acylated to form a 21-acetoxy-17α-hydroxy-16α-methyl steroid.

US—A—3700660 discloses converting a 20-acyloxy-17,20-epoxy steroid to a 17αα-acyloxy-20-keto steroid, using a strong acid and a 20-acetate.

US—A—3513163 and US—A—4036831 respectively disclose C_{21} and C_{11} trimethylsiloxy ethers.

$\Delta^{17(20)}$-20-0-Substituted steroids in which the substituent is an acyl group or a Grignard substituent (—Mg—X) are disclosed in US—A—3072686, US—A—3231568 and US—A—4031080. The Mg—X substituted compounds are not isolatable.

US—A—3876633 discloses 17α,20-epoxy-16α-methyl-20-0-acyl steroids, selective epoxidation of the $\Delta^{9(11)}$ double bond in a $\Delta^{9(11),16}$-diene, and 9β,11β-epoxy-Δ^{16}-steroids in which the A-ring is reduced.

US—A—3210341 (Example 9b) discloses 9β,11β-epoxy-6α-fluoro-21-hydroxypregna-1,4,16-triene-3,20-dione 21-acetate.

US—A—4036831 discloses protecting the 11β-hydroxyl group of a steroid with the trimethylsilyl group, and the removal of the trimethylsilyl group by hydroylsis with 40 to 60% aqueous hydrogen fluoride.

Helv. Chim. Acta 61 (1978) 3069—3070 describes the preparation of a 20-silyl ether steroid, as an intermediate for preparing a 17α-substituted steroid.

Novel compounds according to the present invention are the $\Delta^{17(20)}$-steroids of formulae IIA, IIB and IIC, the 17α,20-epoxides of formulae IIIA, IIIB and IIIC, and the 17α-silyl ethers of formulae IVA, IVB and IVC.

A first process according to the invention, for the preparation of the $\Delta^{17(20)}$-steroids comprises (1) reacting a 16-unsaturated corticoid (IA—C) with a methylating agent in the presence of a copper catalyst, and (2) contacting the product of step 1 with a silylating agent.

A second process according to the invention, for the preparation of the 17α,20-epoxides, comprises reacting a $\Delta^{17(20)}$-steroid with a peracid.

The use of a peracid represents mild conditions. Such conditions would be unsatisfactory for reaction of the enol acetate described in US—A—3231568, US—A—4031080 or US—A—3072686, or for the 20-acetate of US—A—3700660. The known 20-acylate is non-functionalised, since otherwise it cannot be subjected to epoxidation, but the $\Delta^{17(20)}$-20-enol silanes (II) of the present invention are much more reactive.

The products and processes of the invention will now be described with reference to the accompanying Charts. The 16-unsaturated corticoids (I) are known or can be readily prepared from known steroids by methods well known to those skilled in the art. See, for example, US Patents, 2,773,080, 2,864,834, 3,210,341, 3,441,559, 3,461,144, 3,493,563, 3,839,369, 4,031,080, and 4,277,409.

The C_3 functionality of the Δ^4-3-keto (A), $\Delta^{1,4}$-3-keto (B) and 3β-hydroxy-Δ^5- (C) steroid does not have to be protected for the processes of the present invention. The 3β-hydroxy-Δ^5- (C) steroid can have its C_3-hydroxyl group (Ca) protected as the silyl ether (Cb), ether (Cc) or ester (Cd), see Chart C. The free hydroxyl group (Ca) can be protected as the ether (Cc) or ester (Cd) as is well known to those skiled in the art. See Protective Groups in Organic Synthesis, Theodora W. Greene, Wiley & Sons, New York 1981. The ethers

(Cc) are prepared by methods well known to those skilled in the art, see Steroid Reactions, Edited by Carl Djerassi, Holden-Day, San Francisco 1967, p 76—82. If the free 3β-hydroxy group (Ca) is not protected as the ether (Cc) or ester (Cd) during the silation reaction, the free hydroxy group will be silated to form the silyl ether (Cb). During the silylation reaction, if the 3β-hydroxyl group is free and will be silylated, one additional equivalent of Grignard and silylating agent will be consumed. The C_3 protected forms of the 3β-hydroxy steroids (C) are considered equivalent to the non-protected or free form (C) respectively since the C_3 protecting groups are readily removable to convert the C_3 protected forms (Cb, Cc and Cd) to (A and C) The protecting group remains on until the hydrolysis (acid or base) of the 17α,20-epoxide. If acid-hydrolysis is utilized and the C_3 protecting group is acid labile (Cb and Cc) it will be removed. Likewise if base hydrolysis is utilized and the C_3 protecting group is base-sensitive (Cd) it will be removed. If the C_3 protecting group is not sensitive to the hydrolysis agent, the C_3 protected steroid wil have to be treated with the appropriate agent to remove the C_3 protecting group.

It is preferred that the 16-unsaturated corticoid (I A—C) be a Δ^4-3-keto (A) or a $\Delta^{1,4}$-3-keto (B) corticoid, more preferably a $\Delta^{1,4}$-3-keto (B) corticoid. It is preferred that the 16-unsaturated corticoid have the C-ring $\Delta^{9(11)}$ or 9β,11β-epoxy. It is more preferred that the C-ring be 9β,11β-epoxy. It is preferred that R_6 be a hydrogen or fluorine atom, more preferred that R_6 be a hydrogen atom.

While it is preferred that the C-ring is $\Delta^{9(11)}$) or 9β,11β-epoxy, the C-ring can be converted to the desired 9α-fluoro-11β-hydroxy functionality prior to the Grignard addition of the methyl group to the Δ^{16} double bond. If this is done, the 11β-hydroxy group should be protected as is well known to those skilled in the art, see for example, US Patent 4,036,831 where the protecting group is trimethylsilyl. Following the formation of the desired 16α-methyl cordicoid, the (trimethylsilyl) protecting group is removed as is well known to those skilled in the art, see for example, US Patent 4,036,831.

The conjugate addition of a methylating agent, such as methyl Grignard, to a 16-unsaturated steroid to give the corresponding 16α-methyl steroid is well known, see Organic Reactions in Steroid Chemistry, Vol. II, J. Fried and J. A. Edwards, p 75 and US Patent 3,072,686.

The 16-unsaturated corticoid (I) is reacted with a methylating agent followed by a silating agnt to give the enol silane $\Delta^{17(20)}$-steroid (II). The methylating agent is selected from the group consisting of CH_3Cu, $(CH_3)_2CuM$ or CH_3MgQ and a catalytic amount of a copper (cupric) salt. The preferred methylating agent is methyl Grignard, preferably methyl magnesium chloride. The copper salt can be a cuprous salt such as cuprous chloride, bromide, iodide or cyanide or a cupric salt such as cupric chloride, cupric acetate, cupric propionate or complexes thereof. Examples of copper complexes include, cuprous bromide dimethylsulfide, cuprous chloride tris-n-butylphosphine and cuprous acetylacetonate. The nature of the copper complex is not critical. Hundreds (or thousands) of copper complexes are known which are considered equivalent to those set forth above. Preferred is cupric acetate or propionate. Additional catalysts which are considered equivalent to those disclosed above are well known to those skilled in the art, see, for example, Alfa Catalog, 1983—1984, Morton Thiokol, Inc., Alpha Products, PO Box 299, 152 Andover Street, Danvers, Mass. 01923. Solvents suitable for the methylation reaction include those selected from the group consisting of THF, t-butylmethyl ether or dimethoxyethane. The reaction is performed in a range of from about −50° to about 20°, preferably at about −20°. When TLC indicates that no starting material is left (indicating the probable formation of an enolate intermediate), the silating agent is added and the resulting product is the $\Delta^{17(20)}$ steroid (II). After the silylating agent is added the reaction temperature is kept in the range of about −25° to about 25°, preferably about 0°.

In the present invention the enolate intermediate is trapped with the silylating agent which gives the $\Delta^{17(20)}$-20-(substituted silyl) product. Operable silylating agents include $(R_{20})_3$—Si—E, bistrimethylsilylacetamide. It is preferred that the silylating agent be of the formula $(R_{20})_3$—Si—E, more preferably trimethylsily chloride. Additional silylating agents considered equivalent to those disclosed above are well known to those skilled in the art, see, for example Silicon Compounds, Petrarch Systems, Inc., Bartram Rd. Bristol, PA 19007. The trapping of the enolate intermediate to produce the $\Delta^{17(20)}$-20-(acetate) is known, see US Patent 4,031,080 and Organic Reactions in Steroid Chemistry, Vol. II, supra, p 76. These enol acylates are too unreactive to react selectively over A, B, C-ring functionality such as $\Delta^{9(11)}$). However, surprisingly and unexpectedly the $\Delta^{17(20)}$-20-(substituted silyl) derivative (II) is sufficiently reactive to react with electrophiles without affecting most of the other functionality in the A, B, C-rings.

The $\Delta^{17(20)}$-steroid (II) can be isolated if desired by means well known to those skilled in the art, see for example, Example 1 and 8. However, since the desired product is the 16α-methyl corticoid (V), it is not necessary and preferable not to isolate the $\Delta^{17(20)}$-steroid (II) but rather to continue the reaction, see Examples 3—5, 11 and 12.

The $\Delta^{17(20)}$-steroid (II) is reacted with a peracid to produce the 17α,20-epoxide (III). While most peracids are operable, preferred peracids include m-chloroperbenzoic, perbenzoic, peracetic. The peracid-reaction conditions are well known to those skilled in the art. The peracid reaction does not significantly affect the Δ^1, Δ^4, or $\Delta^{9(11)}$) functionalities in the remainder of the molecule, see Example 2. The solvent used during the methylation reaction producing the $\Delta^{17(20)}$-steroid (II) is removed and replaced by a non-polar solvent such as toluene, methylene chloride, ethyl acetate or t-butyl methyl ether. The inorganic salts remaining after the methylation reaction are removed by extraction. The peracid oxidation is performed in the temperature range of about −10° to 25°. When the reaction is complete, the excess peracid is destroyed by addition of an agent such as powdered sodium thiosulfate or sodium bisulfite. The 17α,20-epoxide (III) can

be isolated if desired by means well known to those skilled in the art. However, since the desired product is the 16α-methyl corticoid (V), it is not necessary and preferable not to isolate the 17α,20-epoxide (III) but rather to continue the reaction in situ.

The 17α,20-epoxide (III) is transformed to the corresponding 16α-methyl corticoid (V) by acid or base hydrolysis. If base is used the 16α-methyl corticoid will be obtained as the 21-hydroxy compound (R_{21} is a hydrogen atom). If acid is used the 16α-methyl corticoid will be the 21-ester (R_{21} is —COR—R_{21}'). Suitable base hydrolyzing agents include hydroxide, carbonate, bicarbonate, alkoxide in alcohol at low temperature etc. It is preferred that the hydrolyzing agent be an acid. Suitable acids include mineral acids and other sufficiently strong acids such as p-TSA, sulfuric, hydrochloric, citric or acetic. The acid hydrolysis is sufficiently fast that reaction is complete in about ½ hour at 20—25°.

The α-methyl corticoids (V) are adrenocorticoid agents with glucocorticoid activity and are useful primarily for their anti-inflammatory effects as is well known to those skilled in the art. These include dexamethasone, flumethasone and paramethsone. One of the best known 16α-methyl corticoids is dexamethasone, see US Patent 3,375,261 and Reissue 28,369 as well as the Physicians Desk Reference 1983, 37th edition, p 1270—1283.

If the C-ring of the 16α-methyl corticoid (V) is $\Delta^{9(11)}$ or 9β,11β-epoxy, it is readily convertible to the pharmacologically active 9α-fluoro-11β-hydroxy C-ring by means well known to those skilled in the art.

Definitions

The definitions and explanations below are for the terms as used throughout the entire patent application including both the specification and the claims.

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

THF refers to tetrahydrofuran.

TMS refers to trimethylsilyl.

THP refers to tetrahydropyranyl.

EEE refers to (1-ethoxy) ethyl ether [—O—$CH(CH_3)OCH_2CH_3$].

p-TSA refers to p-toluenesulfonic acid monohydrate.

When solvent pairs are used, the ratio of solvents used are volume/volume (v/v).

DMSO refers to dimethylsulfoxide.

UV refers to ultraviolet spectroscopy.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from tetramethylsilane.

$[\alpha]_D^{25}$ refers to the angle of rotation of plane polarized light (specific optical rotation) at 25° with the sodium D line (5893A).

Dexamethasone refers to 9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Paramethasone refers to 6$_\alpha$-fluoro-11β,17α-,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Flumethasone refers to 6$_\alpha$,9-α-difluoro-11β-,17α-,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

R_3 is alkyl of 1 thru 3 carbon atoms, a TMS, THP, or EEE group.

R_3' is alkyl of 1 thru 5 carbon atoms or phenyl.

R_6 is a hydrogen or fluorine atom or methyl group.

R_9 is nothing, a hydrogen, fluorine or oxygen atom which makes the C ring

a) $\Delta^{9(11)}$ when R_9 is nothing and

b) 9β,11β-epoxide when R_9 and R_{11} taken together are an oxygen atom.

R_{11} is a hydrogen or oxygen atom, two hydrogen atoms, or α- or β-hydroxy group or trimethysilyl ether thereof which makes the C-ring

a) $\Delta^{9(11)}$ when R_{11} is a hydrogen atom,

b) 9β,11β-epoxide when R_9 and R_{11} taken together are an oxygen atom and ⎯ between C_{11} and R_{11} is a single bond, and

c) a ketone when R_{11} is an oxygen atom and ⎯ between C_{11} and R_{11} is a double bond.

R_{20} is alkyl of 1 thru 4 carbon atoms or phenyl, the R_{20}'s can be the same or different.

R_{21} is a hydrogen atom, —CO—R_{21}' or —$Si(R_{121})_3$.

R_{21}' is alkyl of 1 thru 4 carbon atoms or phenyl.

R_{121} is alkyl of 1 thru 4 carbon atoms or phenyl, the R_{121}'s can be the same or different.

~ indicates that the attached group can be in either the α or β configuration.

⎯ is a single or double bond.

When the term "alkyl of ___ through ___ carbon atoms" is used, it means and includes isomers thereof where such exist.

X is a hydrogen atom or nothing; when X is nothing the ⎯ at C_3 is a double bond and when X is a hydrogen atom the ⎯ at C_3 is a single bond.

M is a lithium or magnesium ion.

Q is a chlorine, bromine or iodine atom.

E is a chlorine, bromine or iodine atom or —NRαRβ.

Rα is alkyl of 1 thru 5 carbon atoms or phenyl and may be connected or cyclized with Rβ in a ring with or without an oxygen or additional nitrogen atom.

Rβ is alkyl of 1 thru 5 carbon atoms or phenyl and may be connected or cyclized with Rα in a ring with or without an oxygen or additional nitrogen atom.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed example describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

Example 1

20,21-Dihydroxy-16α-methylpregna-1,4,9(11),17(20)-tetraen-3-one 20-trimethyl silyl ether 21-acetate (IIb)

Methyl magnesium chloride in THF (2 M, 4.5 ml) is added over a period of 2.5 hr to a mixture of 21-hydroxypregna-1,4,9(11),16-tetraene-3,20-dione 21-acetate (IB, US Patent 4,031,080, 2.0 g), THF (27 ml) and cupric acetate monohydrate (60 mg) previously cooled to −52°. The reaction temperature is kept at less than −40° during the Grignard addition. Following the Grignard addition, TLC indicated no starting amterial is left and the reaction temperature is quenched with trimethylsilyl chloride (1.1 ml). The reaction temperature is then slowly permitted to rise to 4° over a period of 3 hr at which time TLC indicated the reaction is complete. Toluene (15 ml) is added and the THF removed under reduced pressure maintaining the reaction medium at 10—15°. The reaction mixture is first extracted with a pH 7 buffer, then 4 times with buffer (1 ml) and water (9 ml) and lastly with water. The layers are separated and the organic layer is dried over sodium sulfate at less than 0° for 48 hr. The toluene solution is divided into 35 two-ml portions, one of which is concentrated under reduced pressure to give the title compound.

Example 2

17α,21-Dihydroxy-16α-methylpregna-1,4,9(11-triene-3,20-dione 21-acetate (V)

m-Chlorperbenzoic acid (0.556 g) is added dropwise to 20,21-dihydroxy-16α-methylpregna-1,4,9(11),17(20)-tetraen-3-one 20-trimethylsilyl ether 21-acetate (IIB, Example 1, one 35 ml aliquot) over about a 3 hr period keeping the bath temperature in the range of about −9° to about 0°. The reaction is quenched with sodium bisulfite (1 M, 2.8 ml). Water is added and the phases are separated. The organic phase is washed with water, buffer and water, dried over sodium sulfate and concentrated to a solid. The solid is dissolved in ethyl acetate/hexane (5 ml) and crystals formed overnight. The filtrate is concentrated to a solid which is dissolved in methanol and cooled to 0°. The mixture is filtered, and the crystals washed with cold methanol.

TLC shows some 21-hydroxy compound (V) is present. Acetic anhydride (0.1 ml) and pyridine (0.4 ml) is added and the mixture stirred overnight. The mixture is worked up as is well known to those skilled in the art to give a solid which is crystallized from 40% aqueous methanol to give the title compound.

Example 3

9β,11β-Epoxy-17α,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate (VB)

A mixture of 9β,11β-epoxy-21-hydroxypregna-1,4,16-triene-3,20-dione 21-acetate (IB), Example 7, 3.824 g) and cupric acetate monohydrate (200 mg) and anhydrous THF (70 ml) at −15° is treated with methyl magnesium chloride (2.2 M, 8.2 ml) added dropwise over 1 hour. After 10 minutes of stirring at −15° trimethylchlorosilane (1.64 ml) is added. The mixture is immediately warmed to 20°, stirred for 1 hour at which time TLC shows enol ether (II) formation to be complete. The mixture is added to toluene (100 ml) and this is washed with monobasic phosphate buffer (pH 4.25, 50 ml). The organic layer is separated and washed with water (2 × 50 ml) and each aqueous layers is back-extracted with toluene (15 ml). The oganic phases are combined and concentrated at 55° under reduced pressure to a residue.

Toluene (30 ml) at 0° is added and the mixture treated with peroxyacetic acid (34.5%, 2.91 ml) containing sodium acetate (164 mg). The stirred mixture is warmed to 20° and after 10 minutes TLC indicates the peroxidation is complete. The excess peracid is destroyed by addition of powdered sodium thiosulfate (2.5 g) slurried in methanol (10 ml). Hydrochloric acid (6 N, 3.0 ml) is added and the hydrolysis is complete in about 10 minutes. The mixture is added to toluene (75 ml) and the organic phase washed with water (2 × 50 ml), sodium carbonate solution (5%, 40 ml) and finally with water (50 ml). Each aqueous phase is back-extracted sequentially with toluene (20 ml). The organic phases are combined and concentrated under reduced pressure to a crystalline residue which is dissolved in hot ethyl acetate and filtered to remove traces of inorganics. Ethyl acetate (about 5 ml) is used for rinse. The combined volumes of the filtrate and rinse are reduced to about 10 ml. The solids formed and after about 1 hour hexane (40 ml) is added. After standing at 30—40° for 2 hours the slurry is cooled to 20°, and the solids collected by vacuum filtration. The solids are washed with cold ethyl acetate:hexane, 1:1 (3 ml), and dried under reduced pressure at 50—60° for 3 hours to give the title compound, mp 180—186° with softening at about 135°; NMR ($CDCl_3$) 0.89, 0.92, 1.43, 3.18 and 4.83 δ.

Example 4

9β,11β-Epoxy-6α-fluoro-17α,21-dihydroxy-16α-methyl pregna-1,4-diene-3,20-dione (VB)

A mixture of 9β,11β-epoxy-6α-fluoro-21-hydroxy-1,4,16-triene-3,20-dione 21-acetate (IB, US Pate 3,210,341, 8.009 g) cupric acetate monohydrate (400 mg) and tri-n-butyl phosphine (1 ml) in anhydrous TH (120 ml) at +11° is treated with methyl magnesium chloride (1.95 M, 26.5 ml) added dropwise over 1 hou Trimethylchlorosilane (4 ml) at −8° is then added. The mixture is immediately allowed to warm to 14° ar after 20 minutes TLC indicates the reaction is complete. The mixture is added to ethyl acetate (300 ml) ar washed with ammonium hydroxide:saturated ammonium chloride, 1:1 (2 × 75 ml). Each aqueous extra is sequentially ··· ed with the same portion of ethyl acetate (210 ml). The combined organic phases a then concentrated at 45° under reduced pressure to an oil. The oil is taken up in methylene chloride (120 m at −10° and treated with m-chloroperoxybenzoic acid (85%, 6.092 g) and after 1.5 hours TLC indicates th epoxidation is complete. The mixture is vacuum distilled to replace the solvent with methanol (100 ml) an then the mixture is treated with saturated sodium carbonate (20 ml). After stirring 16 hours at 20—25° an 5.25 hours at 55° TLC showed the hydrolysis is complete. After cooling to 20—25° water (100 ml) is adde and the pH adjusted to 7.5 using acetic acid (0.2 ml). Water (160 ml) is then added portion-wise at 5°. Th solids that formed are collected by filtration, washed with 0° methanol in water (25:75, 50 ml) and drie under reduced pressure at about 84° over 16 hours to give the title compound, mp 241—241.5 $[\alpha]_D^{25}$ = +45.7° (DMSO); Uv λ_{max} = 245 nm (ε = 15,300); NMR ($CDCl_3$/DMSO-d_6) 0.82, 0.82, 1.40, 3.30, 4.3 and 5.52 δ.

Example 5

17α,21-Dihydroxy-16α-methylpregna-4,9(11)-diene-3,20-dione 21-acetate (VA)

Methyl magnesium chloride in THF (2 M, 6.2 ml) is added to a mixture of 21-hydroxypregna-4,9(11),16 triene-3,20-dione 21-acetate (IA, US Patent 4,216,159, 3.68 g) and cupric acetate monohydrate (200 mg) i dry THF (100 ml) at −50° over a period of 17 minutes. The mixture is stirred at −45 to −50° for 20 minute and then treated with trimethylchlorsilane (1.9 ml) and allowed to warm to 20—25°. After 1.5 hours a 20—25° TLC indicates the enol silyl ether formation is complete. The reaction mixture is added to ethy acetate (150 ml) and this mixture is washed with cold sulfuric acid (5%, 200 ml), the layers are separated the aqueous layer is back-extracted with ethyl acetate (25 ml). The original organic layer is washed wit cold water (2 × 150 ml) which in turn was back-extracted with additional ethyl acetate. The organic layer phases are combined and concentrated under reduced pressure to about 100 ml.

m-Chloroperoxybenzoic acid (85%, 1.72 g) is added and the mixture stirred 1 hour at −15° following which another 300 mg of peracid is added and the mixture stirred at 20° overnight. The excess peracid i destroyed by treatment with sodium bisulfite solution (10%, 20 ml). The mixture is stirred for 20 minute and then diluted with toluene (200 ml). The mixture is then washed with sulfuric acid (5%, 100 ml) an water (2 × 100 ml). After concentration to dryness under reduced pressure the residue is dissolved i methanol (100 ml) and treated again with hydrochloric acid (3 N, 0.5 ml). The mixture is again concentrate to a higher boiling residue which is taken up in toluene (200 ml). This mixture is washed with saturate sodium carbonate (100 ml) to remove the m-chlorobenzoic acid. Finally the organic layers are washed wit water (2 × 100 ml) and concentrated as above. The residue dissolved in hot methanol (20 ml) fo crystallization. After cooling to 0° for several hours a solid is obtained which is collected by vacuum filtration. The product is washed with cold methanol and dried at 20° to give the title compound; NMR 0.73 0.93, 1.33 and 4.98 δ.

Example 6

9β,11β-Epoxy-21-hydroxypregna-4,16-diene-3,20-dione 21-acetate (IA)

Following the general procedure of US Patent 3,876,633 and making non-critical variations, but starting with 21-hydroxypregna-4,9(11),16-triene-3,20-dione 21-acetate (US Patent 2,773,080), the title compound is obtained, mp 129—130.5°.

Example 7

9β,11β-Epoxy-21-hydroxypregna-1,4,16-diene-3,20-dione 21-acetate (IB)

Following the general procedure of US Patent 3,876,633 and making non-critical variations, but starting with 21-hydroxypregna-1,4,9(11),16-tetraene-3,20-dione 21-acetate (US Patent 2,864,834) the title compound is obtained, mp 163.5—165°.

Example 8

9β,11β-Epoxy-17α,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione (VB)

A mixture of 9β,11β-epoxy-21-hydrocypregna-1,4,16-triene-3,20-dione 21-acetate (IB, Example 7, 7.650 g) and cupric acetate (monohydrate (400 mg) in dry THF (130 ml) is stirred under nitrogen. The temperature is adjusted to −20° and 1,1,3,3-tetramethylurea (5.0 ml) is added. Methyl magnesium chloride (2M, 16.6 ml) is added dropwise over 50 min at −17 to −19°. TLC indicates the Grignard reaction is complete. The mixture is stirred for 40 min at −19°, following which the magnesium enolate is quenched with trimethylchlorosilane (3.28 ml). The temperature rises to 25° during the 1hr stir period. TLC shows this reaction is complete. The mixture is added to toluene (150 ml) and monobasic potassium phosphate buffer

(pH 4.3, 10%, 50 ml). The aqueous layer is extracted with toluene (25 ml) and then is discarded. The two organic layers are washed sequentially with water (2 × 50 ml), the combined and concentrated to a high boiling residue.

The residue containing the $\Delta^{17(20)}$-20-enol silane is dissolved in toluene (60 ml). After cooling to −5, 5.9 ml of 4.4 *M* peroxyacetic acid containing sodium acetate (91 mg) is added and the mixture stirred for 80 min. TLC shows the epoxidation is complete. The excess peracid is destroyed with aqueous sodium bisulfite (1.5 M, 10ml) at about 0°. After stirring 5 min the mixture is added to toluene (40 ml) and water (55 ml). The layers are separated and the aqueous phase is extracted with toluene (20 ml) and then discarded. The two organic layers are washed sequentially with saturated sodium bicarbonate (20 ml) and water (35 ml). The combined organic layers are filtered thru cotton and concentrated to a high boiling residue of the 17α,20-epoxide.

The epoxide is taken up in methanol (60 ml) and treated with p-TSA (5 mg) at 21°. After 6 min TLC indicates the epoxide is opened and the 16α-methyl corticoid has formed (as the 21-acetate). A saturated sodium carbonate solution (1.9 ml) is added and the slurry stirred at 55° for 45 min. TLC indicates the hydrolysis is complete. Water (30 ml) is added and the slurry is stored at 0° overnight. The solids are collected by filtration, washed with methanol/water (1/1) and dried under reduced pressure at 70° for 4.5 hr to give the title compound, mp 238—239.5°.

Example 9

9β,11β-Epoxy-20,21-dihydroxy-16α-methylpregna-1,4,17(20)-trien-3-one-20-trimethylsilyl ether 21-acetate (IIB)

Following the general procedure of Example 1 and making non-critical variations but starting with 9β,11β-epoxy-21-hydroxy-1,4,16-triene-3,20-dione 21-acetate (IB, Example 7) the title compound is obtained.

Example 10

9α-Fluoro-11β,21-dihydroxypregna-1,4,16-triene-3,20-dione 21-acetate (IB)

9β,11β-Epoxy-21-hydroxypregna-1,4,16-triene-3,20-dione 21-acetate (IB, Example 7, 15.3 g) is added to a stirred mixture of aqueous hydrogen fluoride (72%, 55 ml) and methylene chloride (15 ml) at −25° in a 200 ml monel reactor fitted with a mechanical agitator. About 30 ml of methylene chloride is used as a rinse. The mixture is stirred at −22° for 2.5 hr and then at −4° to −11° for 4.0 hr. The mixture is treated with THF (35 ml) at −10° and then quenched carefully by slow addition of a mixture of THF (60 ml), aqueous potassium carbonate (47%, 202 ml) and water (100 ml). After stirring 20 min the mixture is added to toluene (400 ml) and water (400 ml). The phases are separated and the organic layer is washed with water (3 × 150 ml), dried by filtration thru cotton and concentrated to about 150 ml. Methylene chloride (about 150 ml) and magnesol (0.90 g) is added to the mixture. After 15 min the magnesol is removed by filtration. The filtrate is again concentrated to 150 ml and then cooled to 0°. Solids form after stirring at 0° for 3 hr and the product is collected by filtration. The solids are washed with toluene (2 × 25 ml) and dried at 60° for 3 hr under vacuum to give the title compound, mp = 223—225°; NMR ($CDCl_3$) 1.27, 1.59, 4.29, 4.93 and 6.77 δ.

Example 11

9α-Fluoro-11β,20,21-trihydroxy-16α-methylpregna-1,4,17(20)-trien-3-one 11,20-bis(trimethylsilyl)ether 21-acetate (IIB)

A solution of copper (II) propionate (151 mg) in dry THF (60 ml) is cooled to −30° and then treated with methyl magnesium chloride (2 M, about 1ml) in order to reduce the copper to copper (I). 9α-Fluoro-11β,21-dihydroxypregna-1,4,16-triene-3,20-dione 21-acetate (IB, Example 10, 2.025 g) is added to the copper mixture. The temperature is adjusted to −33° and the above Grignard reagent (3.0 ml) is added. A slurry forms which is dissolved when treated with trimethylsilyl chloride (1.50 ml). After stirring 1 hr at −40° another 7.4 ml of the Grignard reagent is added portionwise over 50 min. The mixture is stirred another 2 hr and the temperature is allowed to rise to −26°. Then trimethylsilyl chloride (2.0 ml) is added over 1.25 hr at −15°. TLC indicates formation of the $\Delta^{17(20)}$-enol ether is not complete after another 0.5 hr at −15°. Grignard reagent (3.0 ml) is added at −35°. After 20 min the mixture is added to toluene (150 ml). This mixture is washed with 150 ml of water containing 20 ml of 5% phosphate buffer (pH 6.5). The phases are separated and the organic layer is washed with water (2 × 75 ml) and then dried by filtration thru cotton to give the title compound in solution.

Example 12

17α,20-Epoxy-9α-fluoro-11β,20,21-trihydroxy-16α-methylpregna-1,4-dien-3-one 11,20-bis(trimethylsilyl)ether 21-acetate (IIIB)

The above filtrate (Example 11) is concentrated to about 50 ml and after cooling this mixture to −17°, peroxyacetic acid (4.44 M, 3.37 ml) containing sodium acetate (67 mg) is added. The mixture is stirred for 4 hr while the temperature is allowed to rise to 7°. The mixture is diluted with toluene and then washed with water (75 ml), dilute sodium sulfite and finally with water (75 ml). Each aqueous wash is back-extracted

with toluene (50 ml). The organic phases are combined, and concentrated under vacuum distillation to give a higher boiling residue of crude 17(20)-epoxide-20-trimethylsilyl ether (III).

Example 13

9α-Fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate (VB)

The residue (Example 12) is dissolved in methanol (30 ml) and allowed to stand at room temperature. After 0.75 hr the mixture is concentrated to 15 ml and water (10 ml) is added. The mixture is filtered to remove traces of insoluble material. The filtrate is diluted with more water and a waxy solid is collected by decantation. The solid is dried and then recrystallized from acetone/hexane (1/2, 35 ml). The solids are collected by filtration, washed with acetone/hexane (1/2, 5 ml) and dried at room temperature to give the title compound. A pure sample of the title compound is obtained by column chromatography followed by crystallization from acetone/hexane (1/1), mp = 227 - 229°; NMR ($CDCl_3$) 0.89, 1.03, 1.57, 4.29 and 4.93 δ.

Example 14

17α,20-Epoxy-20,21-dihydroxy-16α-methylpregna-1,4,3(11)-trien-3-one 20-trimethylsilyl ether 21-acetate (IIIB)

Following the general procedure of Example 12 and making non-critical variations, but starting with 20,21-dihydroxy-16α-methylpregna-1,4,9(11),17(20)-tetraen-3-one 20-trimethylsilyl ether 21-acetate (IIB, Example 1) the title compound is obtained.

Example 15

9β,11β,17α,20-Diepoxy 20,21-dihydroxy-16α-methylpregna-1,4-dien-3-one 20 trimethylsilyl ether 21-acetate (IIIB)

Following the general procedure of Example 12 and making non-critical variations, but starting with 9β,11β-epoxy-20,21-dihydroxy-16α-methylpregna-1,4,17(20)-trien-3-one 20-trimethylsilyl ether (21-acetate (IIB, Example 9) the title compound is obtained

CHART A

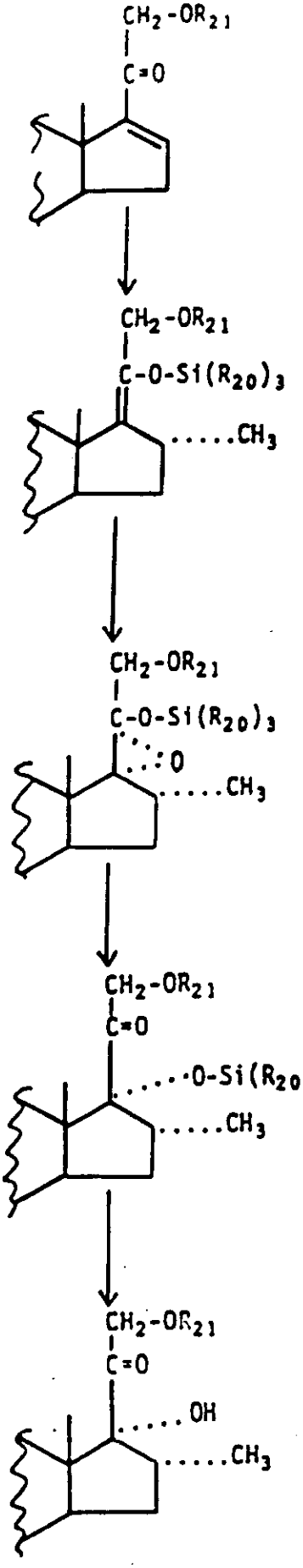
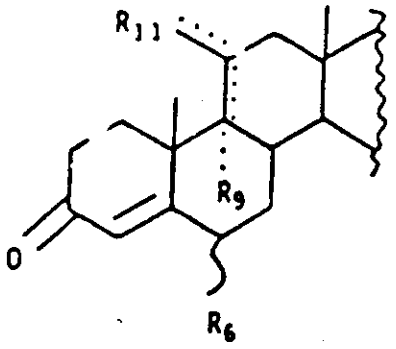
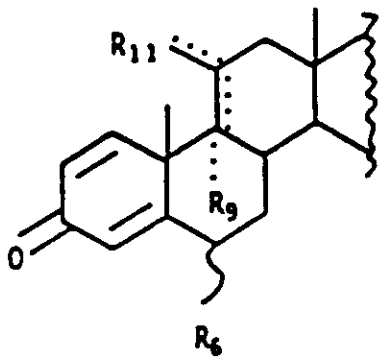

CH2-OR21
C=O
(I)
CH2-OR21
C-O-Si(R20)3
.....CH3
(II)
CH2-OR21
C-O-Si(R20)3
O
.....CH3
(III)
CH2-OR21
C=O
.....O-Si(R20)3
.....CH3
(IV)
CH2-OR21
C=O
.....OH
.....CH3
(V)

CHART B



(A)



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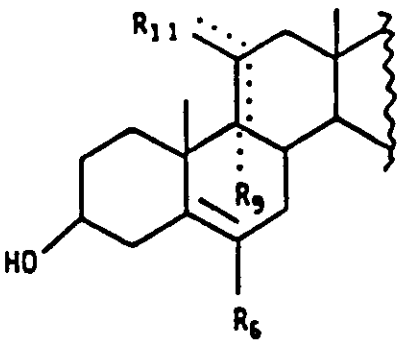
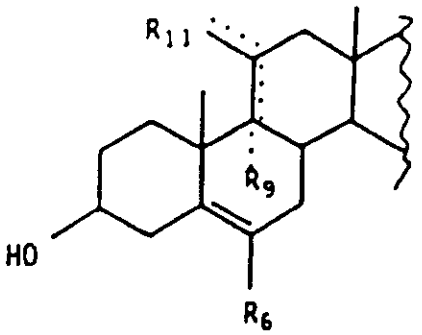


(C)

CHART C



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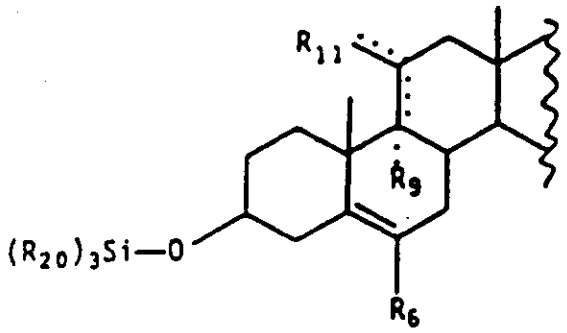

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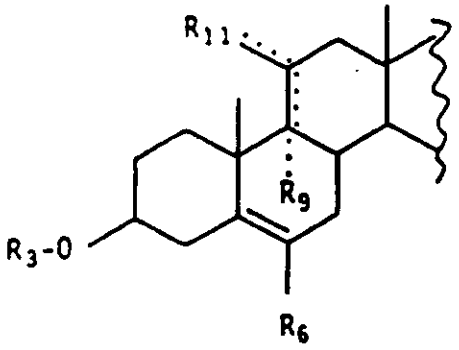

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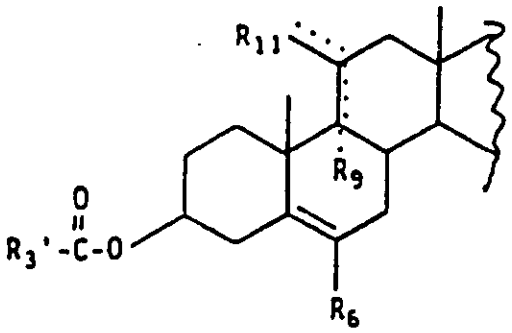
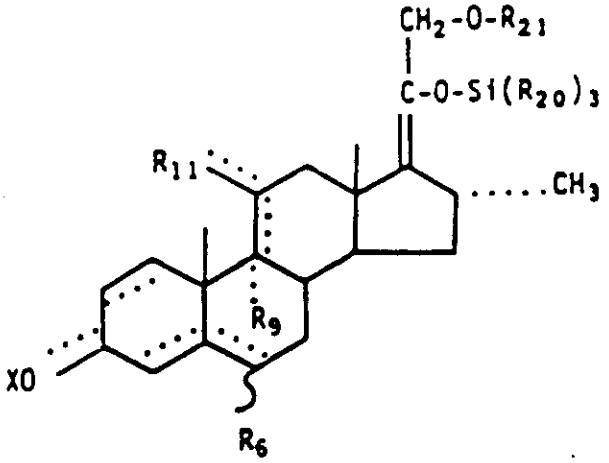


(Cd)

Claims

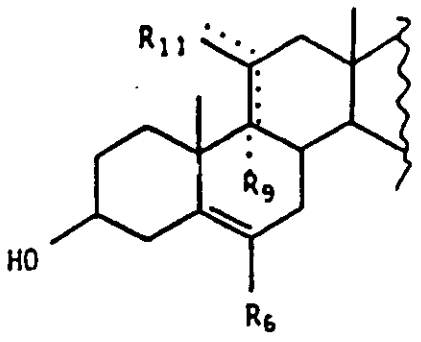
1. A $\Delta^{17(20)}$-corticoid of the formula



(II A-C)

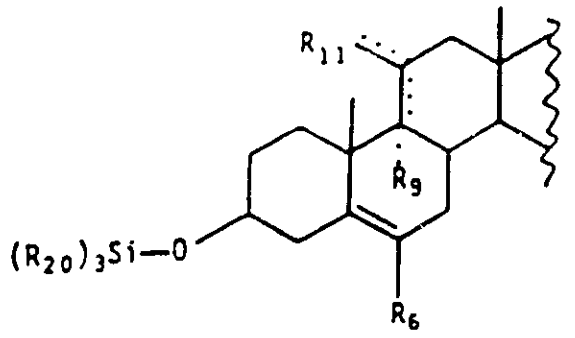
or a C_3-protected form of the 3β-hydroxy-Δ^5-compound thereof, where
R_6 is a hydrogen or fluorine atom or methyl group;
R_9 is nothing, a hydrogen, fluorine or oxygen atom which makes the C ring
a) $\Delta^{9(11)}$ when R_9 is nothing and
b) 9β,11β-epoxide when R_9 and R_{11} taken together are an oxygen atom;
R_{11} is a hydrogen or oxygen atom, two hydrogen atoms, or α- or β-hydroxyl group or trimethylsilyl ether thereof which makes the C-ring
a) $\Delta^{9(11)}$ when R_1 is a hydrogen atom,
b) 9β,11β-epoxide when R_9 and R_{11} taken together are an oxygen atom and ⎯ between C_{11} and R_{11} is a single bond, and
c) a ketone when R_{11} is an oxygen atom and ⎯ between C_{11} and R_{11} is a double bond;
R_{20} is alkyl of 1 thru 4 carbon atoms or phenyl, the R_{20}'s can be the same or different;
R_{21} is a hydrogen atom, —CO—R_{21}' or —Si(R_{121})$_3$;
R_{21}' is alkyl of 1 thru 4 carbon atoms or phenyl;
R_{121} is alkyl of 1 thru 4 carbon atoms or phenyl, the R_{121}'s can be the same or different;
~ indicates that the attached group can be in either the α or β configuration;
⎯ is a single or double bond, and
X is a hydrogen atom or nothing; when X is nothing the ⎯ at C_3 is a double bond and when X is a hydrogen atom the ⎯ at C_3 is a single bond.

2. A $\Delta^{17(20)}$-corticoid according to Claim 1, which is a 3β-hydroxy-Δ^5 steroid in the free form

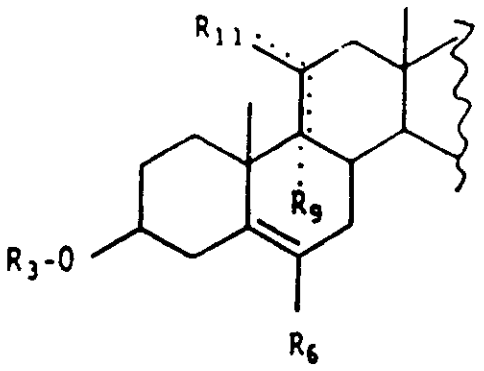


(Ca)

or C_3 protected form selected from the group consisting of



(Cb)



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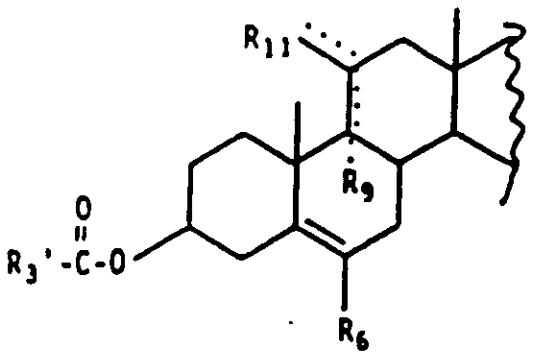
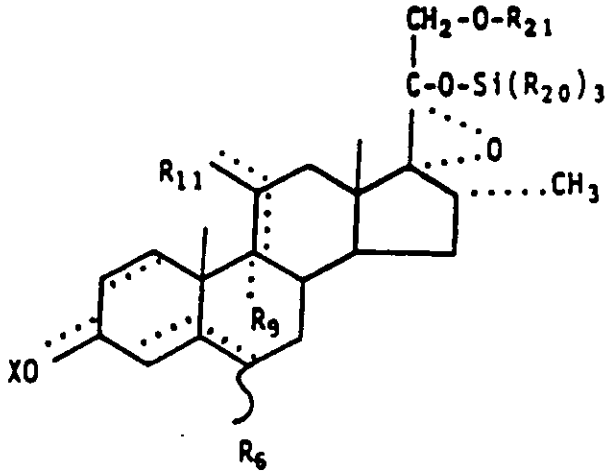


(Cd)

wherein R_3 is C_1—C_3 alkyl, trimethylsilyl, tetrahydropyranyl or 1-(ethoxy)ethoxy;
R_3' is C_{1-6} alkyl or phenyl; and
R_6, R_9, R_{11}, R_{20} and ⌒ are defined in claim 1.

3. A $\Delta^{17(20)}$-corticoid according to claim 1, wherein R_9 is nothing or an oxygen atom and R_{11} is a hydrogen atom or an oxygen atom, making the C-ring $\Delta^{9(11)}$ or a 9β,11β-epoxide.

4. A 17α,20-epoxy steroid of the formula

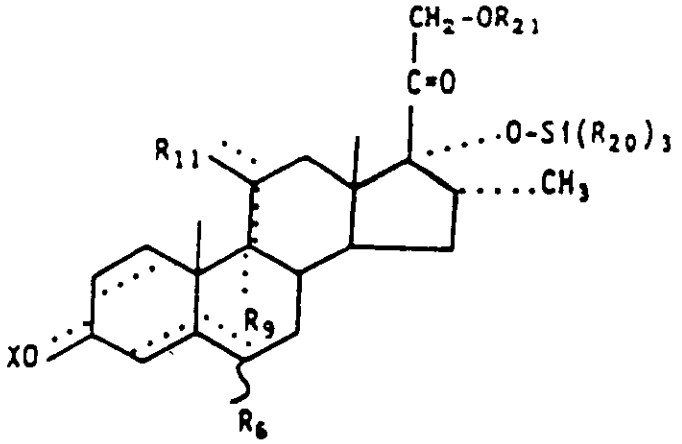


(III A-C)

or a C_3-protected form of the 3β-hydroxy-Δ^5 compound thereof, wherein R_6, R_9, R_{11}, R_{20}, R_{21}, ~, ⌒ and X are as defined in claim 1.

5. A 17α,20-epoxy steroid according to claim 4, which is
17α,20-epoxy-20,21-dihydroxy-16α-methylpregna-1,4,9(11)-trien-3-one 20 trimethylsilyl ether 21-acetate;
9β,11β,17α,20-diepoxy-20,21-dihydroxy-16α-methylpregna-1,4-dien-3-one 20 trimethylsilyl ether 21 acetate; or
17α,20-epoxy-9α-fluoro-11β,20,21-trihydroxy-16α-methylpregna-1,4-dien-3-one 11,20-bis(trimethylsilyl) ether 21-acetate.

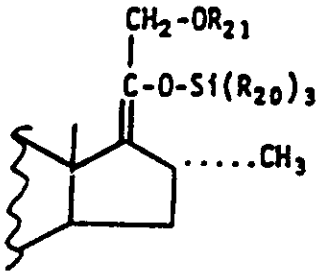
6. A 17α-silyl ether of the formula



(IV A-C)

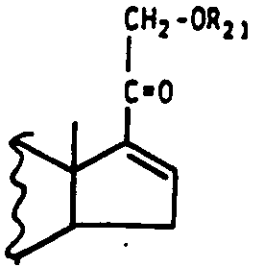
or a C_3 protected form of the 3α-hydroxy-Δ^5 compound thereof, wherein R_8, R_9, R_{11}, R_{20}, R_{21}, ~, ⌒ and X are as defined in claim 1.

7. A process for the preparation of a $\Delta^{17(20)}$-steroid of the formula



(II)

which comprises (1) contacting a 16-unsaturated corticoid of the formula

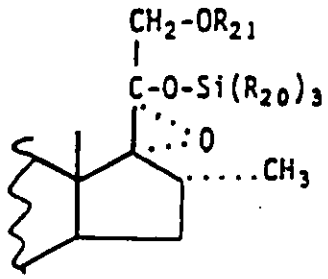


(I)

with a methylating agent in the presence of a copper catalyst; and (2) contacting the product of step (1) with a silylating agent; wherein R_{20} and R_{21} are as defined in claim 1.

8. A process according to claim 7, wherein the methylating agent is selected from CH_3Cu, $(CH_3)CuM$ and CH_3MgQ where M is a lithium or magnesium ion and Q is a chlorine, bromine or iodine atom.

9. A process for the preparation of a 17α,20-epoxide of the formula

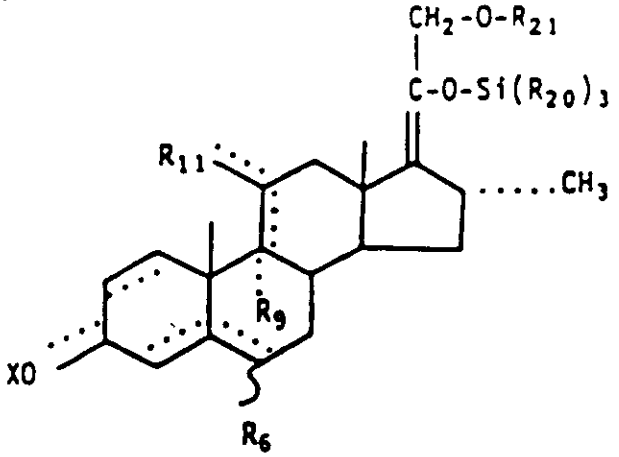


(III)

wherein R_{20} and R_{21} are as defined in claim 1, which comprises contacting a $\Delta^{17(20)}$-steroid of formula (II) as defined in claim 7, with a peracid.

Patentansprüche

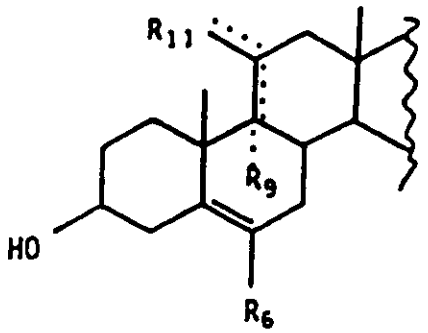
1. Ein $\Delta^{17(20)}$-Cortocoid der Formel



(II A-C)

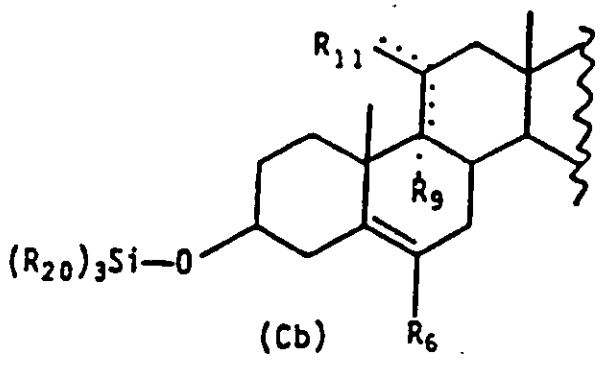
oder eine C_3-geschützte Form der 3β-Hydroxy-Δ^5-Komponente davon, in welcher,
R_6 ein Wasserstoff- oder Fluoratom oder Methylgruppe ist;
R_9 nichts, ein Wasserstoff-, Fluor- oder Sauerstoffatom, ist, welches den folgenden C Ring darstellt
a) $\Delta^{9(11)}$, wenn R_9 nichts ist und
b) 9β, 11β-Epoxid, wenn R_9 und R_{11} zusammengenommen ein Sauerstoffatom sind;
R_{11} ein Wasserstoff- oder Sauerstoffatom, zwei Wasserstoffatome, oder α- oder β-Hydroxylgruppe oder Trimethylsilyläther davon ist, welches den folgenden C-Ring darstellt
a) $\Delta^{9(,11)}$, wenn R_{11} ein Wasserstoffatom ist,
b) 9β, 11β-Epoxid, wenn R_9 und R_{11} zusammengenommen ein Sauerstoffatom sind und ⎯ zwischen C_{11} und R_{11} eine Enfachbindung ist, und
c) ein Keton, wenn R_{11} ein Sauerstoffatom ist und ⎯ zwischen C_{11} und R_{11} eine Doppelbindung ist;
R_{20} Alkyl von 1 bis 4 Kohlenstoffatomen oder Phenyl ist, die R_{20} können gleich oder verschieden sein;
R_{21} ein Wasserstoffatom, —CO—R_{21}' oder —Si$(R_{121})_3$ ist;
R_{21}' Alkyl von 1 bis 4 Kohlenstoffatomen oder Phenyl ist;
R_{121} Alkyl von 1 bis 4 Kohlenstoffatomen oder Phenyl ist, die R_{121} können gleich oder verschieden sein;
~ zeigt an, dass die angegliederte Gruppe entweder in der α oder β Konfiguration sein kann;
⎯ eine Einfach- oder Doppelbindung ist; und
X ein Wasserstoffatom oder nichts ist; wenn X nichts ist, ist die ⎯ bei C_3 eine Doppelbindung, und wenn X ein Wasserstoffatom ist, ist die ⎯ bei C_3 eine Einfachbindung.

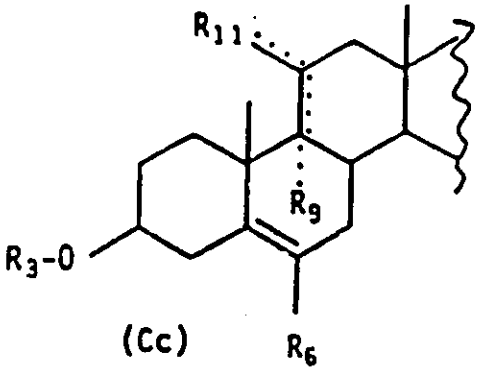
2. Ein $\Delta^{17(20)}$-Corticoid nach Anspruch 1, welches ein 3β-Hydroxy-Δ^5Steroid in der freien Form

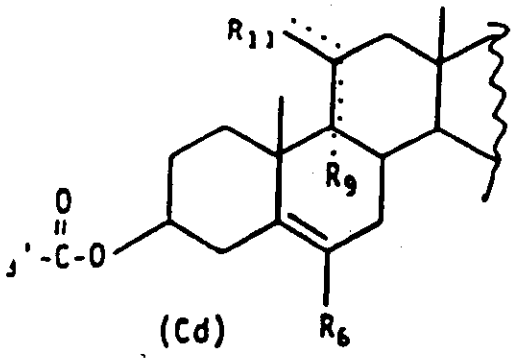


(Ca)

ist, oder der C_3 geschützten Form, ausgewählt von der Gruppe bestehend aus





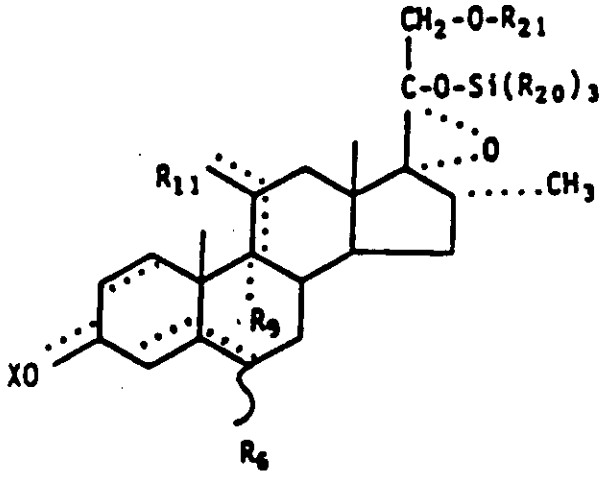


(Cd)

worin R_3 C_{1-3}Alkyl, Trimethylsilyl, Tetrahydropyranyl oder 1-(Äthoxy)äthoxy ist;
R_3' C_{1-5}Alkyl oder Phenyl ist; und
R_6, R_9, R_{11}, R_{20} und ⌒ in Anspruch 1 definiert sind.

3. Ein $\Delta^{17(20)}$-Corticoid nach Anspruch 1, worin R_9 nichts oder ein Sauerstoffatom ist und R_{11} ein Wasserstoffatom oder ein Sauerstoffatom ist, das den C-Ring $\Delta^{9(11)}$ oder ein 9β,11β-Epoxid darstellt.

4. Ein 17α,20-Epoxysteroid der Formel

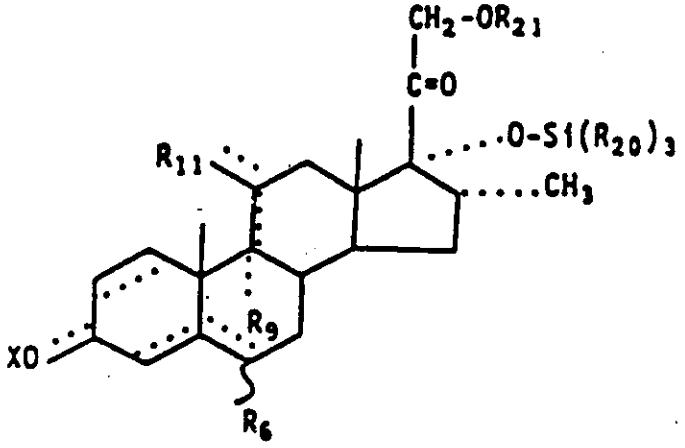


(III A-C)

oder eine C_3— geschützte Form der 3β-Hydroxy-Δ^5 Verbindung davon, worin R_6, R_9, R_{11}, R_{20}, R_{21}, ~, ⌒ und X wie in Anspruch 1 definiert sind.

5. Ein 17α,20-Epoxysteroid nach Anspruch 4, welches 17α,20-Epoxy-20,21-dihydroxy-16α-methylpregna-1,4,9(11)-trien-3-on 20-Trimethylsilyläther 21-Acetat; 9β,11β,17α, 20-Diepoxy-20,21-dihydroxy-16α-methyl-pregna-1,4-dien-3-on 11,20- Bis(trimethylsilyl)äther 21-Acetat; oder
17α,20-Epoxy-9α-fluor-11β,20,21-trihydroxy-16α-methylpregna-1,4-dien-3-on 11,20-Bis(trimethylsilyl)äther 21-Acetat ist.

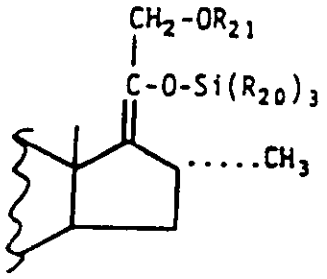
6. Ein 17α-Silyläther der Formel



(IV A-C)

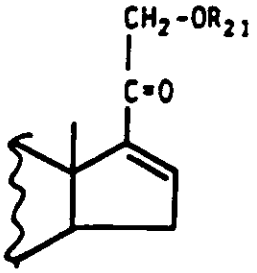
oder eine C_3 geschützte Form der 3α-Hydroxy-Δ^5 Verbindung davon, worin R_6, R_9, R_{11}, R_{20} R_{21}, ~, ⌒ und X wie in Anspruch 1 definiert sind.

7. Ein Verfahren zur Herstellung eines $\Delta^{17(20)}$-Steroids der Formel



(II)

welches umfasst (1) Kontaktieren eines 16-ungesättigten Corticoids der Formel

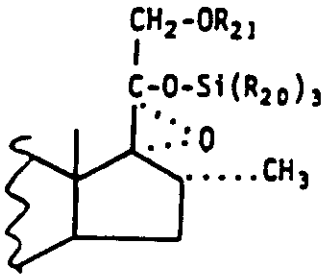


(I)

mit einem methylierenden Reaktonsmittel in der Gegenwart eines Kupferkatalysators; und (2) Kontaktieren des Produktes von Schritt (1) mit einem silylierenden Reaktionsmittel; worin R_{20} und R_{21} wie in Anspruch 1 definiert sind.

8. Ein Verfahren nach Anspruch 7, worin das methyleirende Reaktionsmittel von CH_3Cu, $(CH_3)CuM$ und CH_3MgQ gewählt wird, wobei M ein Lithium- oder Magnesiumion und Q ein Chlor-, Brom- oder Jodatom ist.

9. Ein Verfahren zur Herstellung eines 17α,20-Epoxids der Formel

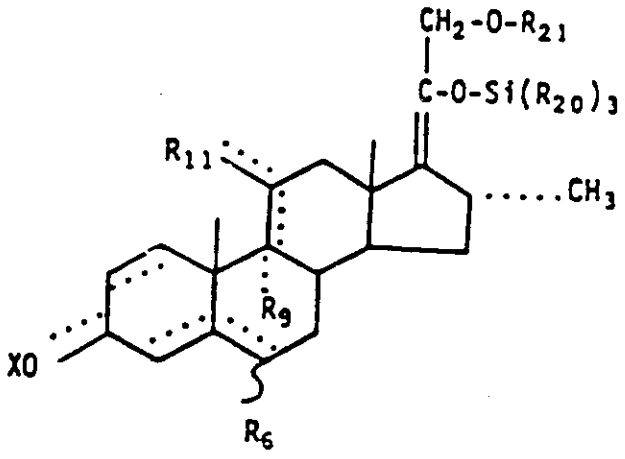


(III)

worin R_{20} und R_{21} wie in Anspruch 1 definiert sind, welches Kontaktieren eines $\Delta^{17(20)}$-Steroids der Formel (II), wie definiert in Anspruch 7, mit einem Peracid umfasst.

Revendications

1. $\Delta^{17(20)}$-corticoïde de formule



(II A-C)

ou une forme protégée au niveau de l'atome C_3 du dérivé à fonctionnalité 3β-hydroxy-Δ^5 de ce composé, formule dans laquelle

R_6 représente un atome d'hydrogène ou de fluor ou un groupe méthyle;

R_9 ne représente rien ou représente un atome d'hydrogène, de fluor ou d'oxygène, ce qui confère au noyau C

a) une fonctionnalite $\Delta^{9(11)}$ lorsque R_9 ne représente rien, et

b) une fonctionnalité 9β,11β-époxyde lorsque R_9 et R_{11}, pris conjointement, représentent un atome d'oxygène;

R_{11} représente un atome d'hydrogène ou d'oxygène, deux atomes d'hydrogène ou un groupe α- ou β-hydroxyle, ou bien un éther de triméthylsilyle de ce groupe, ce qui confère au noyau C

a) une fonctionnalité $\Delta^{9(11)}$ lorsque R_{11} représente un atome d'hydrogène,

b) une fonctionnalité 9β,11β-époxyde lorsque R_9 et R_{11}, pris conjointement, représentent un atome d'oxygène et la liaison ⋯ entre C_{11} et R_{11} est une liaison simple, et

c) une cétone lorsque R_{11} représente un atome d'oxygène et la liaison ⋯ entre C_{11} et R_{11} représente une double liaison;

R_{20} représente un groupe alkyle ayant 1 à 4 atomes de carbone ou un groupe phényle, les groupes R_{20} pouvant être identiques ou différents;

R_{21} représente un atome d'hydrogène, un groupe —CO—R_{21}' ou —Si(R_{121})$_3$;

R_{21}' représente un groupe alkyle ayant 1 à 4 atomes de carbone ou un groupe phényle;

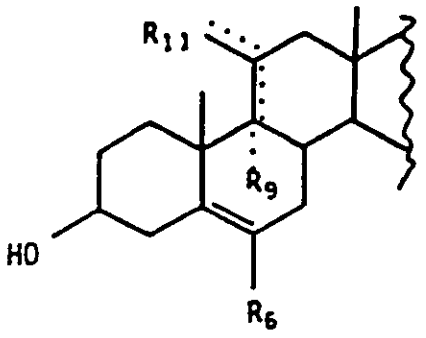
R_{121} représente un groupe alkyle ayant 1 à 4 atomes de carbone ou un groupe phényle, les groupes R_{121} pouvant être identiques ou différents;

le signe ~ indique que le groupe fixé peut présenter la configuration α ou β;

la liaison ⋯ est une liaison simple ou une double liaison; et

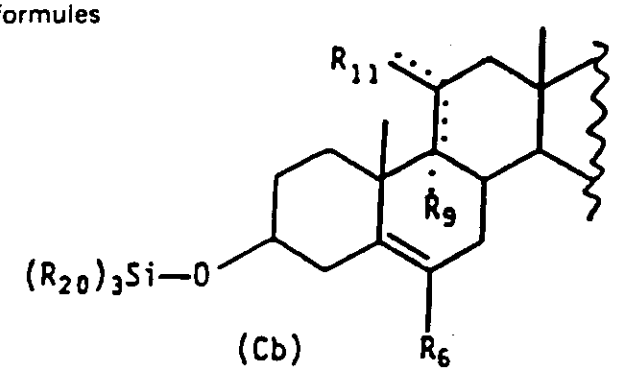
X représente un atome d'hydrogène ou ne représente rien; lorsque X ne représente rien, la liaison ⋯ au niveau de l'atome C_3 est une double liaison et, lorsque X représente un atome d'hydrogène, la liaison ⋯ au niveau de l'atome C_3 est une liaison simple.

2. $\Delta^{17(20)}$-corticoïde suivant la revendication 1, qui est un 3β-hydroxy-Δ^5-stéroïde sous forme libre, de formule

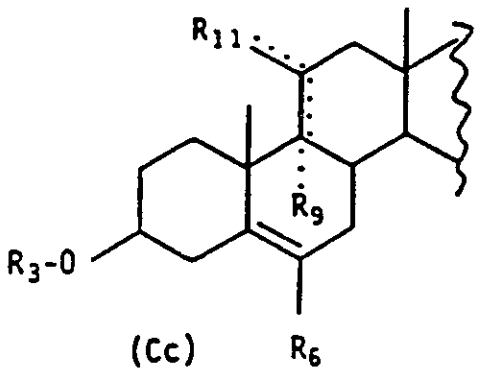


(Ca)

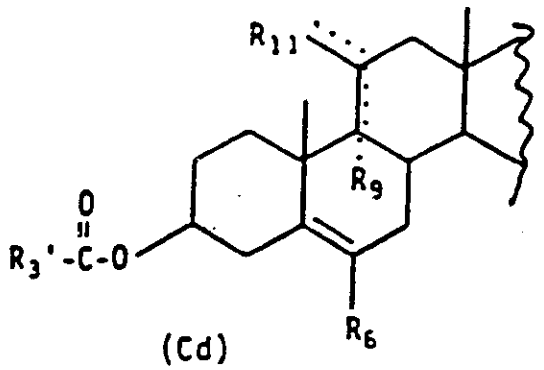
ou sous une forme protégée au niveau de l'atome C_3, choisie dans le groupe comprenant les composés de formules



(Cb)



(Cc)



(Cd)

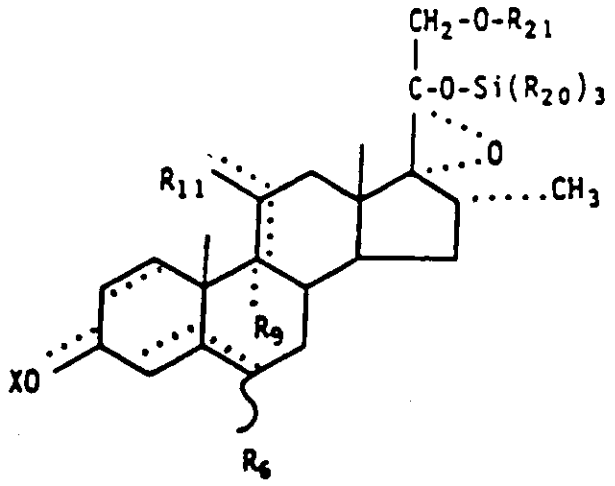
dans lesquelles R_3 représente un groupe alkyle en C_1 à C_3, triméthylsilyle, tétrahydropyrannyle ou 1-(éthoxy)éthoxy;

R_3' représente un groupe alkyle en C_1 à C_5 ou phényle; et

R_6, R_9, R_{11}, R_{20} et la liaison .... sont définis dans la revendication 1.

3. $\Delta^{17(20)}$-corticoïde suivant la revendication 1, dans lequel R_9 ne représente rien ou représente un atome d'oxygène et R_{11} représente un atome d'hydrogène ou un atome d'oxygène, ce qui confère au noyau C une fonctionnalité $\Delta^{9(11)}$ ou 9β,11β-époxyde.

4. 17α,20-époxy-stéroïde de formule



(III A-C)

ou une forme protégée au niveau de l'atome C_3 du dérivé à fonctionnalité 3β-hydroxy-Δ^5 de ce composé, formule dans laquelle R_6, R_9, R_{11}, R_{20}, R_{21}, le signe ~, la liaison .... et X répondent aux définitions suivant la revendication 1.

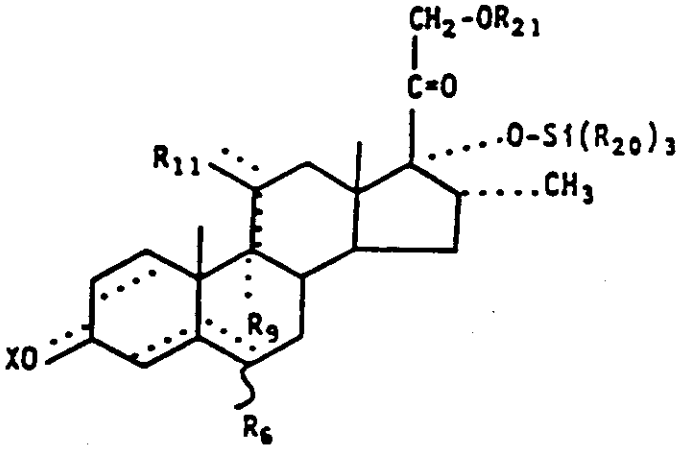
5. 17α,20-époxy-stéroïde suivant la revendication 4, qui est

le 21-acétate d'éther 20-triméthylsilylique de 17α,20-époxy-20,21-dihydroxy-16α-méthylprégna-1,4,9(11)-triène-3-one;

le 21-acétate d'éther 20-triméthylsilylique de 9β,11β,17α,20-diépoxy-20,21-dihydroxy-16α-méthylprégna-1,4-diène-3-one; ou

le 21-acétate d'éther 11,20-bis(triméthylsilylique) de 17α,20-époxy-9α-fluoro-11β,20,21-trihydroxy-16α-méthylprégna-1,4-diène-3-one.

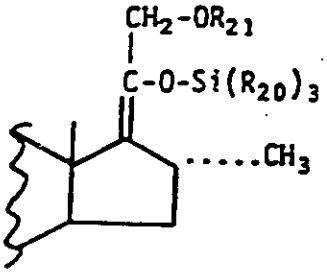
6. Ether 17α-silylique de formule



(IV A-C)

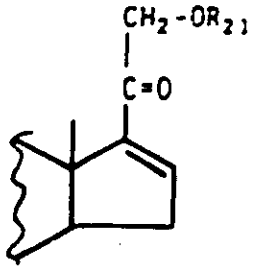
ou une forme progégée au niveau de l'atome C_3 du dérivé à fonctionnalité 3α-hydroxy-Δ^5 de ce composé, formule dans laquelle R_6, R_9, R_{11}, R_{20}, R_{21}, le signe ~, la liaison .... et X répondent aux définitions suivant la revendication 1.

7. Procédé de préparation d'un $\Delta^{17(20)}$-stéroïde de formule



(II)

qui consiste (1) à mettre en contact un corticoïde insaturé en position 16, de formule

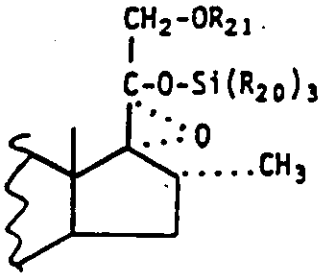


(I)

avec un agent de méthylation en présence d'un catalyseur au cuivre; et (2) à mettre en contact le produit de l'étape (1) avec un agent de silylation; formules dans lesquelles R_{20} et R_{21} répondent aux définitions suivant la revendication 1.

8. Procédé suivant la revendication 7, dans lequel l'agent de méthylation est choisi entre CH_3Cu, $(CH_3)CuM$ et CH_3MgQ dans lesquels M représente un ion lithium ou magnésium et Q représente un atome de chlore, de brome ou d'iode.

9. Procédé de préparation d'un 17α,20-époxyde de formule



(III)

dans laquelle R_{20} et R_{21} répondent aux définitions suivant la revendication 1, qui consiste à mettre en contact un $\Delta^{17(20)}$-steroïde de formule (II) répondant à la définition suivant la revendication 7, avec un peracide.

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Title 16 ALPHA-METHYL STEROIDS AND THEIR PREPARATION

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