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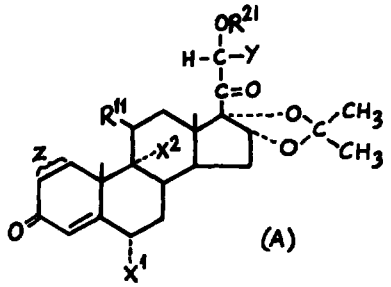
(19)

(54) 21-ACETALS AND MIXED ACETALS OF STEROIDAL 21-ALDEHYDES, INTERMEDIATES AND METHODS OF PREPARATION

(71) We, SYNTEX (U.S.A.) INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 3401 Hillview Avenue, Palo Alto, California 94304, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to cyclopentanophenanthrene derivatives and to certain novel compounds obtained as intermediates.

More particularly, the present invention relates to compounds represented by the formula:

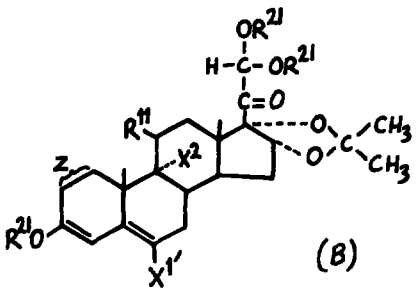


(A)

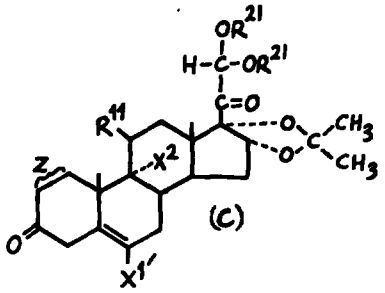
wherein R^{11} is chloro or hydroxy; R^{21} is lower alkyl having 1 to 8 carbon atoms; X^1 and X^2 are independently hydrogen, chloro or fluoro, with the proviso that when R^{11} is chloro, X^2 is chloro; Y is OR^{21}, SR^{21}, bromo, chloro, cyano, thiocyano or azido and R^{21} is lower alkyl having 1 to 8 carbon atoms or phenyl and R^{21} is defined as above, but independent thereof, and Z is a single or double bond.

Preferred compounds within the subclass defined in the previous paragraph are those wherein Y is OR^{21}. Even more particularly preferred compounds are the symmetrical 21,21-bis-alkyl ethers. Most particularly preferred compounds are the 21,21-bis-methyl ethers.

In addition, the present invention relates to certain compounds obtained as intermediates in the preparation of compounds of Formula (A) and exhibiting similar pharmacological activity. These novel intermediates are represented by the formulas:



(B)



(C)

wherein $X^{1'}$ is hydrogen, chloro or fluoro when Z is a single bond and chloro or fluoro

when Z is a double bond; R^{11}, R^{21} and X^2 are as previously defined and all R^{21}s are identical.

Preferred compounds embraced by Formulas (B) and (C) are those wherein R^{21} is methyl or ethyl.

The compounds of the instant invention are potent topical anti-inflammatory agents. Although the instant compounds exhibit low systemic activity in the rat as measured in standard assays, e.g. Rat Thymolytic Assay and the Anti-inflammatory Assay Utilizing Carrageenan induced Rat Paw Edema, they exhibit high topical activity in humans as measured in the Stoughton-McKenzie Assay (Human Vasoconstrictor Assay). In spite of the fact that systemic effects such as adrenal atrophy, mineralocorticoid effects and collagen disorders may be produced by large doses of the instant compounds if administrated for long periods of time, the favorable topical/systemic activity ratio of the instant compounds permits the use of such small doses that these systemic effects are minimized. This combination of high topical anti-inflammatory activity coupled with negligible systemic activity renders the instant compounds highly suitable for the alleviation of inflammatory disorders.

The present invention further relates to a method for treating symptoms associated with inflammatory disorders in non-humans which method comprises administering an effective amount of a compound selected from those represented by formulas (A), (B), and (C), or a pharmaceutical composition incorporating such a compound as an active ingredient.

The present invention still further relates to pharmaceutical compositions useful for treating inflammatory disorders. These compositions comprise an effective amount of a compound selected from those represented by formulas (A), (B), and (C) in admixture with a pharmaceutically acceptable non-toxic carrier.

Suitable carriers or medicament vehicles for topical application of the novel steroids of the instant invention include creams, ointments, lotions, emulsions, solutions. For example, a suitable ointment for topical application of compounds of the instant invention contains 15 to 45 percent by weight of a saturated fatty alcohol having 16 to 24 carbon atoms such as cetyl alcohol, stearyl alcohol and behenyl alcohol, and 45 to 85 wt. percent of a glycol solvent such as propylene glycol, polyethylene glycol, dipropylene glycol, and the mixtures thereof. The ointment can also contain 0 to 15 wt. percent of a plasticizer such as polyethylene glycol, 1,2,6-hexanetriol, sorbitol, glycerol; 0 to 15 wt. percent of a coupling agent such as a saturated fatty acid having from 16 to 24 carbon atoms, e.g., stearic acid, palmitic acid, behenic acid, a fatty acid amide e.g., oleamide, palmitamide, stearamide, behenamide and an ester of a fatty acid having from 16 to 24 carbon atoms such as sorbitol monostearate, polyethylene glycol monostearate, polypropylene glycol monostearate, or the corresponding mono-ester of other fatty acids such as oleic acid and palmitic acid; and 0 to 20 wt. percent of a penetrant such as dimethyl sulfoxide, dimethylacetamide and dimethylformamide.

The concentration of cortical steroid in pharmaceutical compositions suitable for topical application will vary depending upon the particular activity of the steroid used in conjunction with the condition and subject to be treated. In general, topical preparations containing .005 to 1% by weight of the active steroid are advantageously employed.

In the specification and claims the following definitions apply:

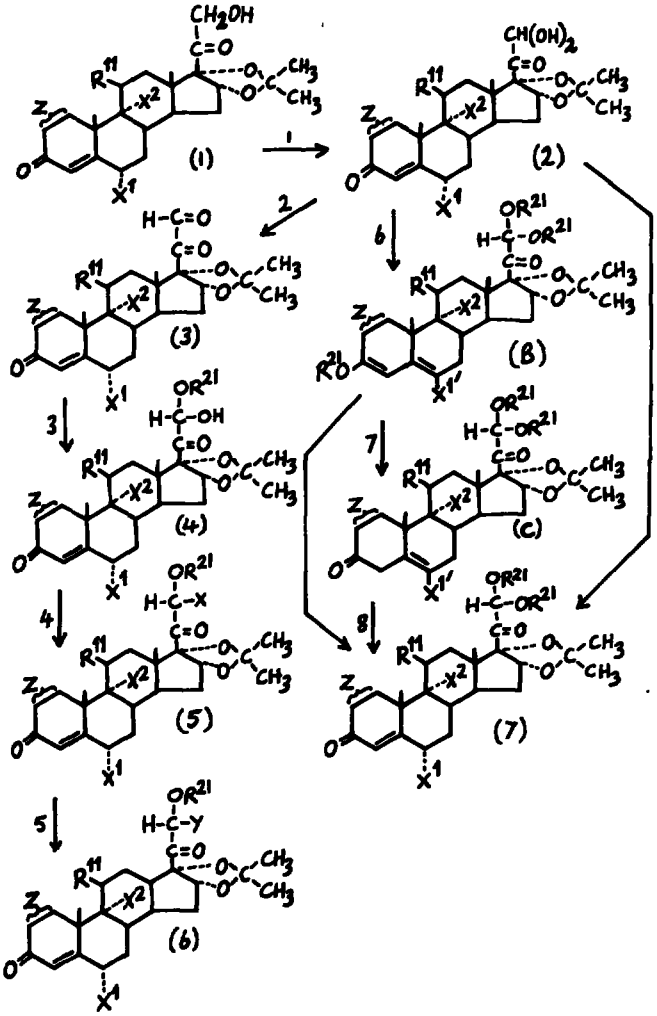
The broken line (- - -) used in the depicted formulas indicates that the substituent attached to those positions is in the α configuration.

The unbroken line (——) used in the depicted formulas indicates that the substituent attached to those positions is in the β configuration.

The term "lower alkyl" defines alkyl groups containing from 1 to 8 carbon atoms including all isomers thereof. Typical lower alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, n-amyl, n-hexyl, n-heptyl and n-octyl.

Compounds of Formula (A) wherein Y and OR^{21} are not identical exist in two epimeric forms, i.e., the 21(R) and 21(S) forms. Accordingly, all nomenclature, formulas and discussion herein is intended to refer to both forms and mixtures thereof unless otherwise specified.

The present invention, in a further aspect, is directed to methods for the preparation of compounds of Formulas (A), (B), and (C) according to the following reaction sequences:



In the above formulas R^{11}, R^{21}, X^1, X^2, and Z are as previously defined; Y is OR^{21}, $SR^{21'}$, cyano, thiocyano or azido and R^{21} and $R^{21'}$ are as previously defined; X is chloro or bromo; and $X^{1'}$ is hydrogen, chloro or fluoro when Z is a single bond and chloro and fluoro when Z is a double bond.

With reference to reaction steps 1—5, a 21-hydroxy steroid (1) is contacted with air in the presence of a copper (II) catalyst such as cupric acetate to yield the 21-aldehyde hydrate (2). The reaction is preferably conducted in methanol at a temperature of 5 to 30°C. for a period of 30 minutes to 6 hours.

The 21-aldehyde hydrate (2) is then heated under vacuum at a temperature of 100 to 130°C. for a period of 30 minutes to 3 hours to yield the 21-aldehyde (3) which is reacted with a lower alkanol containing 1 to 8 carbon atoms at a temperature of 20 to 60°C. for a period of 15 minutes to 1 hour to yield the 21-aldehyde hemiacetal (4).

Reaction of the 21-aldehyde hemiacetal (4) with a suitable halogenating agent such as methane sulfonyl chloride, thionyl chloride, or thionyl bromide suitably in the presence of an organic base such as triethylamine, pyridine and the like yields the 21-halo-21-alkyl ether (5). The reaction is preferably conducted in a chlorinated organic solvent such as methylene chloride, chloroform, 1,1-dichloroethane and the like for a period of 1 to 16 hours and a temperature of −20 to +10°C.

The thus obtained 21-halo-21-alkyl ether (5) is then used to prepare the 21-aldehyde acetal ((6), Y=OR^{21}), the 21-azido-21-alkyl ether ((6), Y=azido), the 21-thiocyano-21-alkyl ether ((6), Y=thiocyano), the 21-cyano-21-alkyl ether ((6), Y=cyano), the 21-phenylthio-21-alkyl ether ((6), Y=phenylthio), and the 21-alkylthio-21-alkyl ether ((6), Y=alkylthio).

Preparation of the 21-aldehyde acetal ((6), Y=OR^{21}) is accomplished by treating the 21-halo-21-alkyl ether (5) with an alkali metal alkoxide, preferably a sodium

alkoxide such as sodium methoxide, sodium ethoxide, etc. The reaction is conducted in a solvent medium usually containing the alkanol corresponding to the alkoxide utilized although a solvent inert to the other reactants may be employed. Reaction temperatures are preferably maintained at 20 to 60°C. for a period of 2 to 6 hours.

The 21-azido-21-alkyl ether ((6), Y=azido) is prepared by treating the 21-halo-21-alkyl ether (5) with an alkali metal azide, preferably sodium azide, in an aprotic inert organic solvent such as dimethylformamide, acetone, hexamethylphosphoramide, dimethyl sulfoxide and the like. The reaction is preferably conducted at a temperature of 20 to 60°C. for a period of 2 to 12 hours.

Preparation of the 21-thiocyano-21-alkyl ether ((6), Y=thiocyano), the 21-cyano-21-alkyl ether ((6), Y=cyano), the 21-phenylthio-21-alkyl ether ((6), Y=phenylthio), and the 21-alkylthio-21-alkyl ether ((6), Y=alkylthio) is accomplished according to the procedure outlined in the previous paragraph, i.e., the 21-halo-21-alkyl ether (5) is treated with a suitable alkali metal salt such as potassium thiocyanate, sodium cyanide, sodium thiophenylate or a sodium thioalkylate, suitably in an aprotic inert organic solvent such as dimethylformamide, acetone, hexamethyl phosphoramide, dimethyl sulfoxide and the like at a temperature of 20 to 80°C. for a period of 2 to 16 hours.

Compounds of Formula (A) having identical R^{21} groups are conveniently prepared via reaction steps 6—8 as follows:

A 21-aldehyde hydrate (2) is treated with a trialkyl orthoformate such as trimethyl orthoformate, triethyl orthoformate, tri-n-propyl orthoformate and the like in the presence of a strong acid such as perchloric acid, p-toluenesulfonic acid, sulfuric acid and the like to obtain the 3-alkoxy-3,5-dien-21-acetal (B). The reaction is suitably conducted in the presence of an alkanol corresponding to the trialkyl orthoformate employed at a temperature of 50 to 100°C. for a period of 2 to 12 hours.

Treatment of the thus obtained 3-alkoxy compound (B) with a dilute inorganic acid such as hydrochloric acid, sulfuric acid and the like yields the 3-oxo-5-en-21-acetal (C). This reaction is preferably conducted in aqueous acetone at a temperature of 50 to 80°C. for a period of 30 minutes to 4 hours.

Thereafter, the 3-oxo-5-en-21-acetal (C) is treated with a base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide and the like to yield the 3-oxo-4-en-21-acetal (7). This reaction is preferably conducted in a solvent such as methylene chloride/methanol, aqueous acetone or methanol at a temperature of 30 to 60°C. for a period of 30 minutes to 4 hours.

Alternatively, the 3-alkoxy-3,5-dien-21-acetal (B) can be treated with a higher concentration of a strong acid such as hydrochloric acid, perchloric acid, sulfuric acid and the like to yield directly the 3-oxo-4-en-21-acetal (7). This reaction is preferably conducted in aqueous acetone.

For those 21-aldehyde hydrates (2) wherein Z is a double bond and X^1 is hydrogen, the reaction conditions of step 6 lead directly to compounds of formula (7).

The 21-hydroxy steroid starting materials (1) used to prepare the 21-acetal and 21-difunctional compounds of the instant invention are available commercially or can be prepared according to known procedures. Information concerning the preparation of 21-hydroxy steroids suitable for use in the preparation of compounds of Formulas (A), (B), and (C) can be obtained, for example from U.S. Pat. Nos. 3,048,581 and 3,126,375; and from Fried et al., J. Am. Chem. Soc., 802, 338 (1958) and Mills et al., J. Am. Chem. Soc., 82, 3399 (1960). Additional information concerning the preparation of 21-hydroxy steroids suitable for use in the preparation of compounds of Formulas (A), (B), and (C) can be found for example, in U.S. Patents 2,894,963, 3,013,033 and 3,119,748; and Edwards et al., Proc. Chem. Soc. (London), p. 87 (1959), Edwards et al., J. Am. Chem. Soc., 82, 2318 (1960), and Taub et al., J. Am. Chem. Soc., 80, 4435 (1958).

Description of Specific Embodiments

The following specific description is given to enable those skilled in the art to more clearly understand and practice the present invention. It should not be considered as a limitation upon the scope of the invention but merely as being illustrative and representative thereof. Examples 1 to 3 relate to the preparation of starting materials.

Example 1

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide

To a slurry of 12.0 g of 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide in 130 ml. of dry methanol is added a solution of 0.68 g. of cupric acetate hydrate in 40 ml. methanol. Air is then sparged through the mixture for 2 hours. Thereafter, the mixture is evaporated to dryness and the residue is taken up in ethyl acetate and washed with water and then with a dilute aqueous solution of potassium bicarbonate and then again with water. The solution is evaporated to dryness and the resulting residue is then dissolved in acetone. The acetone solution is diluted with a substantial volume of water whereupon the resulting precipitate is filtered and dried under vacuum to yield 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide.

Example 2

6α,9α-difluoro-11β,16α,17α-trihydroxypregna-1,4-diene-3,20-dione-21-al 16,17-acetonide

6α,9α - difluoro - 11β,16α,17α,21,21 - pentahydroxypregna - 1,4 - diene - 3,20 - dione 16,17-acetonide (4.0 g.) is heated under high vacuum in an oil bath at 100°C. for 1 hour to yield 6α,9α-difluoro-11β,16α,17α-trihydroxypregna-1,4-diene-3,20-dione-21-al 16,17-acetonide.

Example 3

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether

6α,9α-difluoro-11β,16α,17α-trihydroxypregna-1,4-diene-3,20-dione-21-al 16,17-acetonide (obtained above in Example 2) is dissolved in 50 ml. of dry methanol. After stirring for approximately 15 minutes at room temperature the solution color changes from yellow to colorless. The solution is then evaporated and dried at 50°C. under vacuum to yield 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

Replacing methanol in the above procedure with other lower alkanols, e.g., ethanol, isopropanol, n-butanol, sec-butanol, amyl alcohol etc., is productive of the corresponding 21-aldehyde hemiacetals, for example,

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α,9α,-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α,9α,-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
6α,9α,-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether
6α,9α,-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
6α,9α,-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether.

Example 4

21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether

6α,9α - difluoro - 11β,16α,17α,21,21 - pentahydroxypregna - 1,4 - diene - 3,20 - dione 16,17--acetonide 21-methyl ether (2.5 g.) is dissolved in 100 ml. of dry methylene chloride and 1.2 ml. of triethylamine is added to the solution which is cooled to −15°C. under a nitrogen atmosphere. Methane sulfonyl chloride (1.2 ml.) is then added and the solution is allowed to warm to 0°C. with stirring. After 16 hours at 0°C. there is obtained 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, m.p. 207—213°C. The product can be recovered by evaporation of the solvent or used directly in solution in the next example.

Repeating the above procedure but substituting thionyl bromide for methane sulfonyl chloride is productive of the corresponding 21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

In like manner, other 21-halo-21-alkyl ether steroids are prepared, for example:

21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether,

and also the corresponding 21-bromo-21-alkyl ether steroids, e.g.,

21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether, and
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether.

Example 5

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether

To the methylene chloride solution of 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, obtained in Example 4, is added 200 ml. of dry methanol and the methylene chloride is then removed by distillation. The resulting solution is heated under nitrogen at 60°C. while a 0.5 normal solution of sodium methoxide in methanol is added dropwise at a rate sufficient to maintain a pH of 8. After approximately 4 hours the reaction is complete whereupon the reaction mixture is concentrated to approximately 50 ml. by evaporation. The resultant precipitate is filtered, washed with water and vacuum dried. The precipitate is recrystallized from a mixture of methanol and methylene chloride to yield 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 291—292°C.

Repeating the above procedure, but substituting other alkoxides for sodium methoxide and using an alkanol corresponding to the alkoxide used is productive of the corresponding 21-methyl-21-alkyl ether steroids, for example,

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-isopropyl diether,

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-butyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl-21-sec-butyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-amyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-hexyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-heptyl diether, and
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-octyl diether, epimer A m.p. 189—193°C.; epimer B m.p. 113—116°C.

In like manner, other 21,21-bis-alkyl ether steroids and 21-mixed alkyl ether steroids are prepared, for example

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether, m.p. 269—275°C.,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether, m.p. 244—248°C.,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-isopropyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-sec-butyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-amyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-hexyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-heptyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-octyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-butyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl,21-n-butyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-hexyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-heptyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-octyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl,21-n-amyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl,21-n-hexyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl,21-n-heptyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl,21-n-octyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl,21-n-hexyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl,21-n-heptyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16.17-acetonide 21-n-amyl,21-n-octyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16.17-acetonide 21-n-heptyl,21-n-hexyl diether, and
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl,21-n-octyl diether.

Example 6

21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether

To a solution of 100 mg. of 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether in 50 ml. of methylene chloride (obtained in Example 4) is added 10 ml. of dry dimethylformamide and the methylene chloride is then removed from the solution by distillation. Sodium azide (40 mg.) is added to the resulting solution and the mixture is stirred at room temperature for 16 hours. The reaction mixture is then poured into water and the resulting mixture extracted with chloroform. The chloroform extracts are washed with water and dried over sodium sulfate, and evaporated to dryness. The resulting impure product is chromatographed on a silica GF plate (1 m.×20 cm.×0.5 mm.) which is developed twice with 12% acetone in hexane. The product is removed from the plate to yield 21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, m.p. 220—222°C.

In like manner, other 21-azido-21-alkyl ether steroids are prepared, for example

21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether, and
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether.

Example 7

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether

To a solution of 160 mg. of 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether in 80 ml. of methylene chloride (obtained in Example 4) is added 30 ml. of dry dimethylformamide and the methylene chloride is removed by distillation. Thereafter, 265 mg. of potassium thiocyanate is added and the mixture is heated under nitrogen at 70°C. After 4 hours the mixture is poured into water and the resulting aqueous mixture extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulfate and evaporated to dryness. The product is then chromatographed on a silica GF plate (1 m.×20 cm.×0.5 mm.) which is developed with 15% acetone and hexane. The product is removed from the plate to yield 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, m.p. 233—237°C.

In like manner, other 21-thiocyano-21-alkyl ether steroids are prepared, for example

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether, and
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyanopregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether.

Example 8

21-Cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether

To a solution of 160 mg. of 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether in 80 ml. of methylene chloride (obtained in Example 4) is added 30 ml. of dry dimethylformamide and the methylenechloride is removed by distillation. Thereafter, 200 mg. of sodium cyanide is added and the mixture is heated under nitrogen at 70°C. After 4 hours the reaction mixture is poured into water and the product extracted with ethyl acetate. The organic phase is then washed with water, dried over sodium sulfate and evaporated to dryness. The residue is purified by preparative thin layer chromatography to yield 21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, epimer A m.p. 272—275°C.; epimer B m.p. 219—222°C.

In like manner, other 21-cyano-21-alkyl ether steroids are prepared, for example

21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether, and
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether.

Example 9

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthiopregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether

To a solution of 140 mg. of 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether in 70 ml. of methylene chloride (obtained in Example 4) is added 30 ml. of acetone and the methylene chloride is removed by distillation. Approximately 0.5 g. of sodium thiophenylate is added and the mixture is stirred at room temperature for 16 hours. The reaction mixture is then poured into water and the product extracted with ethyl acetate. The combined extracts are washed with water, dried over sodium sulfate and evaporated to dryness. The resulting impure product is chromatographed on a silica GF plate (1 m.×20 cm.×0.5 mm.) which is developed with 20% ethyl acetate in benzene to yield 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, epimer A m.p. 247—250°C., epimer B m.p. 219—222°C.

In like manner, other 21-phenylthio-21-alkyl ether steroids are prepared, for example

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether, and
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether.

Example 10

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether

To a solution of 140 mg. of 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether in 70 ml. of methylene chloride (obtained in Example 4) is added 30 ml. of acetone and the methylene chloride is removed by distillation. Approximately 0.5 g. of sodium thioethylate is added and the mixture is stirred at room temperature for a period of 16 hours. The reaction mixture is then poured into water and the product extracted with ethyl acetate. The combined extracts are washed with water, dried over sodium sulfate and evaporated to dryness. The resulting impure product is chromatographed on a silica GF plate (1 m.×20 cm.×0.5 mm.) which is developed twice with 12% acetone in benzene to yield 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, epimer A m.p. 280—282°C., epimer B m.p. 254—256°C.

In like manner, other 21-alkylthio-21-alkyl ether steroids are prepared, for example

6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-n-butylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-n-hexylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-n-octylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

Example 11

6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether

a) 6α,9α - difluoro - 11β,16α,17α,21,21 - pentahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide (300 mg.) is dissolved in a mixture of 8 ml. of trimethyl orthoformate and 2 ml. of methanol. Two drops of concentrated perchloric acid is then added to the mixture which is stirred and heated at 50°C. under nitrogen. After 2 hours, the reaction mixture is diluted with ethyl acetate, washed with water until neutral, dried over sodium sulfate and evaporated to dryness to yield 6,9α - difluoro - 3,11β,16α,17α,21,21 - hexahydroxypregna - 1,3,5 - trien - 20 - one 16,17 - acetonide 3,21,21-tris-methyl ether, m.p. 168—176°C.

b) 30 mg. of the crude triene obtained above is dissolved in 5 ml. of acetone and 2 ml. of water and 1 drop of concentrated HCl is added. After refluxing for 30 minutes under nitrogen, water is added to the reaction mixture and the acetone is removed by distillation. The resulting precipitate is filtered off and dried under

vacuum to yield 6,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 267—270°C.

c) 100 mg. of the crude 1,5-diene obtained above is dissolved in 15 ml. of a 2:1 mixture of methylene chloride and methanol and 1 drop of aqueous 3N sodium hydroxide is added. After 15 minutes at room temperature, the reaction mixture is diluted with ethyl acetate. The organic phase is then separated, washed with water and dried over sodium sulfate. The product is recrystallized from a mixture of methanol and methylene chloride to yield 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

Repeating the above procedures but substituting other alkyl orthoformates in paragraph a) for trimethyl orthoformate, e.g. triethyl orthoformate, tri-n-propyl orthoformate, tri-n-butyl orthoformate, and so forth is productive of the corresponding 1,4-diene-3,20-dione-21,21-bis-alkyl ether steroids and also the 1,3,5-trien-20-one-3,21,21-trialkyl ether steroids, for example

6,9α-difluoro-3,11β,16α,17α,21,21-hexyhydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-ethyl ether,
6,9α-difluoro-3,11β,16α,17α,21,21-hexyhydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-n-propyl ether,
6,9α-difluoro-3,11β,16α,17α,21,21-hexyhydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-n-butyl ether, and so forth.

and also the 1,5-diene-3,20-dione-21,21-bis-alkyl ether steroids for example

6,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether, and
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether.

Example 12

In similar manner to the procedures of Examples 1—10, using reactants as dictated by the particular 21-acetal or 21-mixed acetal desired, the following compounds are prepared:

21-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
9α,11β,21-trichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether, decomp. 180—190°C.
9α,21-dichloro-6α-fluoro-11β,16α,17α,21tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-chloro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,21-dichloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α,11β,21-trichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α,21-dichloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,

21-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-chloro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α,21-dichloro-11β,16α,17α,21-tetrahydroxypreg-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
21-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-octyl ether,
9α,11β,21-trichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
9α,21-dichloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
21-chloro-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl-ether,
21-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-octyl ether,
21-chloro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether,
21-bromo-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-bromo-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-bromo-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-bromo-9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-bromo-9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-bromo-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-bromo-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-bromo-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-bromo-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-bromo-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
21-bromo-9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether,
21-bromo-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-bromo-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-octyl ether,
6α-fluoro-11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 297—299°C.,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 246—250°C.,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 270—273°C.,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 179—181°C.,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 280—282°C.,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 250—253°C.,
11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether, m.p. 154—158°C.,

6α-chloro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether, m.p. 224—227°C.,
11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6α-chloro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
6α-chloro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-amyl ether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-n-hexyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-octyl ether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-n-octyl ether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl-21-ethyl diether,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
11β,16α,17α,21-,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,

6α-chloro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-ethyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
6α-chloro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-n-propyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene,3,20-dione 16,17-acetonide 21-ethyl-21-n-propyl ether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
6α-chloro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl,21-n-propyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-n-butyl diether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl,21-n-butyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl,21-n-propyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-n-octyl diether,
6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl,21-n-hexyl diether,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl,21-n-heptyl diether,
9α-chloro-6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl,21-n-hexyl diether,
9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl,21-n-octyl diether,
11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl,21-n-octyl diether,
11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl,21-n-octyl diether,
6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-amyl,21-n-hexyl diether,
9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl,21-n-hexyl diether,
21-azido-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,

21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-6α-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-azido-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-azido-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-azido-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-azido-9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-thiocyano-pregn-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide-21-ethyl ether,

9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-chloro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-n-octyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregn-4-ene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
21-cyano-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-6α-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
21-cyano-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-6α-chloro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-octyl ether,
21-cyano-6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-propyl ether,
21-cyano-9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-butyl ether,
21-cyano-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether,
21-cyano-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-n-amyl ether,

6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-chloro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-chloro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-n-amyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-n-octyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-isopropyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-methylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-methylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,

6α-chloro-11β,16α,17α,21-tetrahydroxy-21-methylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-chloro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-n-propyl ether,
11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-propyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-octylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-octyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-sec-butylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-sec-butyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-heptylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-heptyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-hexylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-hexyl ether,
11β,16α,17α,21-tetrahydroxy-21-n-amylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-n-amyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methylether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-chloro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
9α,11β-dichloro-6α-fluoro-16α,17α,21-trihydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,

9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether,
6α-chloro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether,
6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-ethyl ether,
6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-heptylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-n-propyl ether,
9α-chloro-6α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
9α-fluoro-11β,16α,17α,21-tetrahydroxy-21-n-propylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-ethyl ether,
11β,16α,17α,21-tetrahydroxy-21-n-octylthio-pregn-4-ene-3,20-dione 16,17-acetonide 21-methyl ether.

Example 13

In similar manner to procedures a) and b) of Example 11, using reactants as dictated by the particular 3-alkoxy-3,5-dien-21-acetal or 3-oxo-5-en-21-acetal desired, the following compounds are prepared:

6-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-methyl ether,
6,9α-difluoro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-methyl ether,
6-fluoro-3-11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-methyl ether,
9α,11β-dichloro-6-fluoro-3,16α,17α,21,21-pentahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-methyl ether,
9α-chloro-6-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-methyl ether,
3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-methyl ether,
6α-chloro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-methyl ether,
6α-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21,tris-ethyl ether,
6α,9α-difluoro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-ethyl ether,
6α-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-ethyl ether,
9α,11β-dichloro-6α-fluoro-3,16α,17α,21,21-pentahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-ethyl ether,
9α-chloro-6α-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-ethyl ether,
3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-ethyl ether,
6-chloro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-ethyl ether,
6-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-isopropyl ether,
6,9α-difluoro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-n-propyl ether,
6-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-n-propyl ether,
9α,11β-dichloro-6-fluoro-3,16α,17α,21,21-pentahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-n-propyl ether,
9α-chloro-6-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-n-propyl ether,
3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-n-propyl ether,

6-chloro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-n-propyl ether,
6-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-n-butyl ether,
6,9α-difluoro-3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-n-butyl ether,
6-fluoro-3,β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-n-butyl ether,
9α,11β-dichloro-6-fluoro-3,16α,17α,21,21-pentahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-n-butyl ether,
9α-chloro-6-fluoro-3,11β,16α,17α,21,21-hexahydroxypregna-1,3,5-trien-20-one 16,17-acetonide 3,21,21-tris-n-butyl ether,
3,11β,16α,17α,21,21-hexahydroxypregna-3,5-dien-20-one 16,17-acetonide 3,21,21-tris-n-butyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.
6,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
9α,11β-dichloro-6-fluoro-16α,17α,21,21-tetrahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
9α-chloro-6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
6-chloro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
9α,11β-dichloro-6-fluoro-16α,17α,21,21-tetrahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
9α-chloro-6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6-chloro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
6,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-isopropyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
9α,11β-dichloro-6-fluoro-16α,17α,21,21-tetrahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
9α-chloro-6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
6-chloro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,
6,9-difluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,
6-fluoro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,
9α,11β-dichloro-6-fluoro-16α,17α,21,21-tetrahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,

9α-chloro-6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,
11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether, and
6-chloro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether.

Example 14

The topical antiinflammatory activity of certain compounds of the present invention was determined by the Stoughton McKenzie Assay (Human Vasoconstrictor Assay) on adult volunteers not receiving any steroids and who had not participated in a study using steriods for at least four weeks prior to testing.

Two solutions of each test compound were prepared immediately prior to application by adding 5 ml. of ethanol to each of 2 vials containing 0.05 mg. and 0.005 mg. of test compound per vial. The subjects forearms were then outlined by a rubber grid coated with silicon grease. Ten lambda of each solution was then applied to designated squares according to a standard randomization sheet. The subject's forearms were then allowed to dry and then covered with Saran (Trade Mark) and the margins sealed with tape.

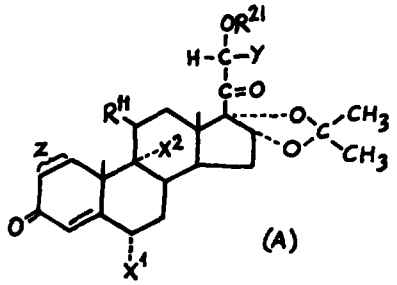
Occlusion time was 18 hours. Readings for vasoconstriction were taken 24 hours after application.

The ability of the test compound to cause vasoconstriction relative to the standard (Fluocinolone acetonide) is illustrated in the following results:

Compound	Potency
Fluocinolone acetonide (i.e., 6α,9α-difluoro-16α-hydroxy-prednisolone 16,17-acetonide)	1.0
6α,9α-Difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-diethyl ether	1.2
6α,9α-Difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-dimethyl ether	1.5

WHAT WE CLAIM IS:—

1. A compound having the formula:



(A)

wherein:

R^{11} is chloro or hydroxy;

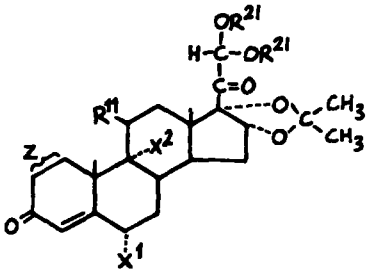
R^{21} is lower alkyl having 1 to 8 carbon atoms;

X^1 and X^2 are independently hydrogen, chloro or fluoro, with the proviso that when R^{11} is chloro, X^2 is chloro;

Y is OR^{21}, $SR^{21'}$, bromo, chloro, cyano, thiocyano or azido and $R^{21'}$ is lower alkyl having 1 to 8 carbon atoms or phenyl and R^{21} is as defined above but independent thereof; and

Z is a single or double bond.

2. A compound of Claim 1 having the formula:



wherein R^{11}, R^{21}, X^1, X^2 and Z are as defined in Claim 1.

9α-chloro-6-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,5-diene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether,
11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether, and
6-chloro-11β,16α,17α,21,21-pentahydroxypregn-5-ene-3,20-dione 16,17-acetonide 21,21-bis-n-butyl ether.

Example 14

The topical antiinflammatory activity of certain compounds of the present invention was determined by the Stoughton McKenzie Assay (Human Vasoconstrictor Assay) on adult volunteers not receiving any steroids and who had not participated in a study using steriods for at least four weeks prior to testing.

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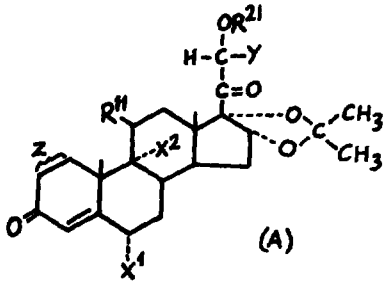
Occlusion time was 18 hours. Readings for vasoconstriction were taken 24 hours after application.

The ability of the test compound to cause vasoconstriction relative to the standard (Fluocinolone acetonide) is illustrated in the following results:

Compound	Potency
Fluocinolone acetonide (i.e., 6α,9α-difluoro-16α-hydroxy-prednisolone 16,17-acetonide)	1.0
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6α,9α-Difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-dimethyl ether	1.5

WHAT WE CLAIM IS:—

1. A compound having the formula:

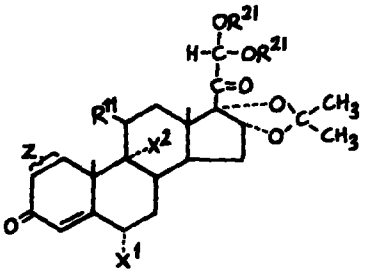


(A)

wherein:

R^{11} is chloro or hydroxy;
R^{21} is lower alkyl having 1 to 8 carbon atoms;
X^1 and X^2 are independently hydrogen, chloro or fluoro, with the proviso that when R^{11} is chloro, X^2 is chloro;
Y is OR^{21}, $SR^{21'}$, bromo, chloro, cyano, thiocyano or azido and $R^{21'}$ is lower alkyl having 1 to 8 carbon atoms or phenyl and R^{21} is as defined above but independent thereof; and
Z is a single or double bond.

2. A compound of Claim 1 having the formula:



wherein R^{11}, R^{21}, X^1, X^2 and Z are as defined in Claim 1.

* C L M S *

3. A compound of Claim 2 wherein both R^{21} groups are identical.

4. The compound of Claim 3 which is 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

5. The compound of Claim 3 which is 6α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

6. The compound of Claim 3 which is 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

7. The compound of Claim 3 which is 6α-fluoro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

8. The compound of Claim 3 which is 9α,11β-dichloro-6α-fluoro-16α,17α,21,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

9. The compound of Claim 3 which is 9α-fluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

10. The compound of Claim 3 which is 11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

11. The compound of Claim 3 which is 11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

12. The compound of Claim 3 which is 6α-chloro-11β,16α,17α,21,21-pentahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21,21-bis-methyl ether.

13. The compound of Claim 3 which is 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-ethyl ether.

14. The compound of Claim 3 which is 6α,9α-difluoro-11β,16α,17α,21,21-pentahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21,21-bis-n-propyl ether.

15. The compound of Claim 1 which is 21-azido-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

16. The compound of Claim 1 which is 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-thiocyano-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

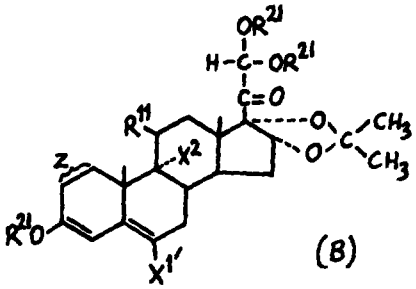
17. The compound of Claim 1 which is 21-cyano-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

18. The compound of Claim 1 which is 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-phenylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

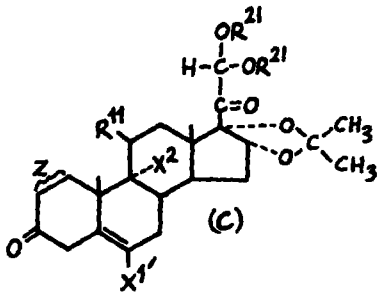
19. The compound of Claim 1 which is 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxy-21-ethylthio-pregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

20. The compound of Claim 1 which is 21-chloro-6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-methyl ether.

21. A compound selected from the group represented by the following formulas:



(B)



(C)

wherein:

R^{11} is chloro or hydroxy;

all R^{21}'s are the same lower alkyl having 1 to 8 carbon atoms;

Z is a single or double bond;

$X^{1'}$ is hydrogen, chloro or fluoro when Z is a single bond and chloro or fluoro when Z is a double bond, and

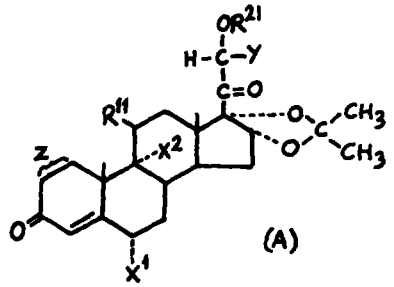
* C L M S *

X^2 is hydrogen, fluoro or chloro, with the proviso that when R^{11} is chloro, X^2 is chloro.

22. A compound of Claim 21 having Formula (B).

23. A compound of Claim 21 having Formula (C).

24. A pharmaceutical composition useful for treating inflammatory disorders comprising a pharmaceutically acceptable non-toxic carrier in admixture with an effective amount of a compound having the formula:



(A)

wherein:

R^{11} is chloro or hydroxy;

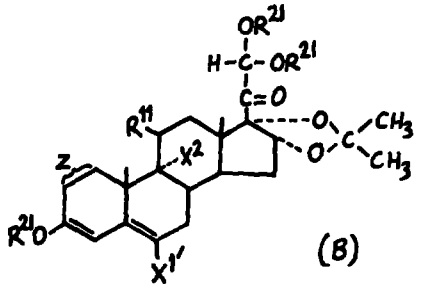
R^{21} is lower alkyl having 1 to 8 carbon atoms;

X^1 and X^2 are independently hydrogen, chloro or fluoro, with the proviso that when R^{11} is chloro, X^2 is chloro;

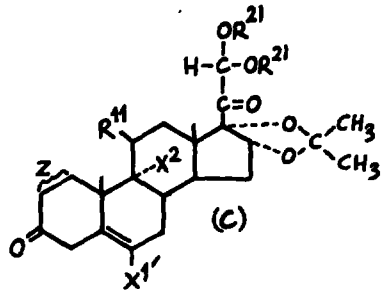
Y is OR^{21}, $SR^{21'}$, bromo, chloro, cyano, thiocyano or azido and $R^{21'}$ is lower alkyl having 1 to 8 carbon atoms or phenyl and R^{21} is as defined above but independent thereof; and

Z is a single or double bond.

25. A pharmaceutical composition useful for treating inflammatory disorders comprising a pharmaceutically acceptable non-toxic carrier in admixture with an effective amount of a compound selected from the group represented by the formulas:



(B)



(C)

wherein:

R^{11} is chloro or hydroxy;

all R^{21}'s are the same lower alkyl having 1 to 8 carbon atoms;

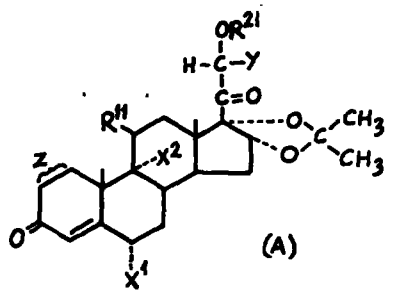
Z is a single or double bond;

$X^{1'}$ is hydrogen, chloro or fluoro when Z is a single bond and chloro or fluoro when Z is a double bond; and

X^2 is hydrogen, fluoro or chloro, with the proviso that when R^{11} is chloro, X^2 is chloro.

* C L M S *

26. A method for relieving symptoms associated with inflammatory disorders in non-humans, comprising administering an effective amount of a compound having the formula:



(A)

wherein:

R^{11} is chloro or hydroxy;

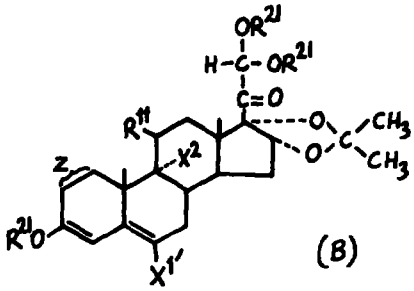
R^{21} is lower alkyl having 1 to 8 carbon atoms;

X^1 and X^2 are independently hydrogen, chloro or fluoro, with the proviso that when R^{11} is chloro, X^2 is chloro;

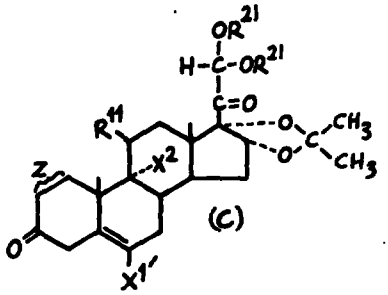
Y is OR^{21}, $SR^{21'}$, bromo, chloro, cyano, thiocyano, or azido and $R^{21'}$ is lower alkyl having 1 to 8 carbon atoms or phenyl and R^{21} is as defined above but independent thereof; and

Z is a single or double bond; or a pharmaceutical composition containing same.

27. A method for relieving symptoms associated with inflammatory disorders in non-humans, comprising administering an effective amount of a compound selected from the group represented by the formulas:



(B)



(C)

wherein:

R^{11} is chloro or hydroxy;

all R^{21}'s are the same lower alkyl having 1 to 8 carbon atoms;

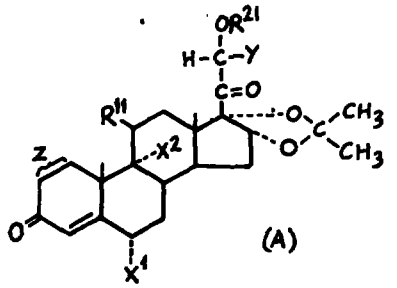
Z is a single or double bond;

$X^{1'}$ is hydrogen, chloro or fluoro when Z is a single bond and chloro or fluoro when Z is a double bond;

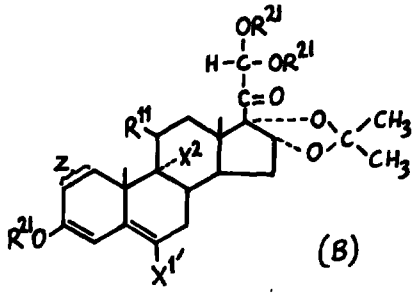
X^2 is hydrogen, chloro or fluoro, with the proviso that when R^{11} is chloro, X^2 is chloro; or a pharmaceutical composition containing same.

28. A process for preparing a compound selected from the group represented by the formulas:

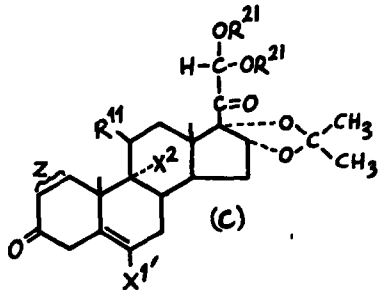
* C L M S *



(A)



(B)



(C)

wherein:

R^{11} is chloro or hydroxy;

R^{21} is lower alkyl having 1 to 8 carbon atoms and all R^{21}'s are the same lower alkyl in compounds of Formulas (B) and (C);

Z is a single or double bond;

Y is OR^{21}, $SR^{21'}$, bromo, chloro, cyano, thiocyano or azido and $R^{21'}$ is lower alkyl having 1 to 8 carbon atoms or phenyl and R^{21} is as defined above, but independent thereof;

X^1 and X^2 are independently hydrogen, chloro or fluoro, with the proviso that when R^{11} is chloro, X^2 is chloro, and

$X^{1'}$ is hydrogen, chloro or fluoro when Z is a single bond and chloro or fluoro when Z is a double bond;

which process comprises:

1) for the preparation of compounds of Formula (A) wherein Y is halo, treating a corresponding 21-aldehyde hemiacetal with a halogenating agent to obtain a 21-halo-21-alkyl ether;

2) for the preparation of compounds of Formula (A) wherein Y is OR^{21}, $SR^{21'}$, cyano, thiocyano or azido, treating a corresponding 21-halo-21-alkyl ether with a compound of the formula

MY

wherein halo is Cl or Br, M is an alkali metal and Y is OR^{21}, $SR^{21'}$, cyano, thiocyano or azido to obtain the corresponding compound of Formula (A);

3) for the preparation of compounds of Formula (A) wherein Z is a double bond, X^1 is hydrogen and Y is OR^{21}, treating a corresponding 21-aldehyde hydrate wherein Z is a double bond and X^1 is hydrogen with a trialkyl orthoformate in the presence of a strong acid to obtain a 21,21-bis alkyl ether of Formula (A);

* C L M S *

4) for the preparation of compounds of Formula (B), treating a corresponding 21-aldehyde hydrate wherein X^1 is chloro or fluoro when Z is a double bond and hydrogen, chloro or fluoro when Z is a single bond, with a trialkyl orthoformate in the presence of a strong acid to obtain a 3-alkoxy-3,5-dien-21-acetal of Formula (B);

5) for the preparation of compounds of Formula (C), treating a 3-alkoxy-3,5-dien-21-acetal of Formula (B) with a dilute inorganic acid to obtain a 3-oxo-5-en-21-acetal of Formula (C);

6) for the preparation of compounds of Formula (A) wherein X^1 is hydrogen, chloro or fluoro when Z is a single bond and chloro or fluoro when Z is a double bond and Y is OR^{21}, treating a 3-oxo-5-en-21-acetal of Formula (C) with a base to obtain the 21,21-bis alkyl ether of Formula (A); and/or

7) for the preparation of compounds of Formula (A) wherein X^1 is hydrogen, chloro or fluoro when Z is a single bond and chloro or fluoro when Z is a double bond and Y is OR^{21}, treating a compound of Formula (B) with a suitably high concentration of a strong acid to obtain a 21,21-bis alkyl ether of Formula (A).

29. A compound according to claim 1, as exemplified herein.

30. A compound according to claim 21, as exemplified herein.

31. A pharmaceutical composition according to claim 24 as exemplified herein.

32. A pharmaceutical composition according to claim 25 as exemplified herein.

33. A method of preparing a compound according to claim 1 or claim 21, according to the invention as described herein.

34. A compound according to claim 1 or claim 21 whenever prepared by a method according to claim 28 or claim 33.

35. A pharmaceutical composition comprising a pharmaceutically acceptable non-toxic carrier in admixture with a compound of any one of claims 2, 3, 22, 23, 29, 30 and 34.

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* C L M S *

ERRATA

SPECIFICATION No. 1,529,249

Page 2, line 12, *for* administrated *read* administered
Page 9, line 12, *for* tetahydroxy- *read* tetrahydroxy-
Page 10, line 44, *for* methylthio *read* ethylthio
Page 11, lines 17 and 19, *for* hexyhydroxypregna *read* hexahydroxypregna
Page 11, line 40, *after* 21 (second occurrence) *insert* -
Page 12, line 49, *after* 17α, *insert* 21,
Page 18, line 44, *for* methylether *read* methyl ether
Page 20, line 7, *after* 3, (first occurrence) *insert* 11
Page 20, line 59, *for* 6,9- *read* 6,9α-
Page 21, line 17, *for* were *read* are

THE PATENT OFFICE
12th March, 1979