

Description

The invention involves the chemical transformation of a steroidal 17-cyanohydrin to a 17 α -hydroxy-21-halo-20-keto steroid intermediate which can readily be converted to pharmaceutically useful corticoids.

17 α -Hydroxy-17 β -cyanosteroids (I) are known to those skilled in the art. The transformation of the 17 α -hydroxy-17 β -cyanosteroids (I) to 17 α -hydroxyprotected-17 β -cyanosteroids (II) is also known to those skilled in the art.

The reduction of nitriles to imines followed by hydrolysis to give aldehydes is well known in organic chemistry. US Patent 4,424,159 discloses the transformation of a C₁₇-cyano steroid to the corresponding steroidal C₁₇-carboxaldehyde using diisobutylaluminum hydride. However, because the other substituent at C₁₇ was -H, that reaction was much simpler and did not in any way indicate that the reduction of a compound of the formula STERIOD-17 α -[O-protected]-17 β -[CN] would be operable. The transformation of ketone-derived, protected cyanohydrins to the corresponding protected aldehydes with sodium bis(2-methoxyethoxy)aluminum hydride in 57-70% yields is reported in *Helv. Chim. Acta* 61, 1903 (1978), see p 1905. *J.A.C.S.* 102, 1742 (1980) reports the reduction of a trimethylsilyl protected cyanohydrin to the corresponding aldehyde in only 75% yield using 4 equivalents of diisobutylaluminum hydride in toluene at 0°. The transformation of protected steroidal cyanohydrins (II) to the corresponding protected steroidal aldehydes (III) has not been reported. The reduction of the 17 α -hydroxy protected-17 β -cyano-steroids (II) of the present invention surprisingly gives the protected aldehyde (III) in > 90% yield.

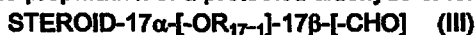
Protected steroid aldehydes (III) are not known. Unprotected steroidal 17 α -hydroxy-17 β -carboxaldehydes are known, see French patents 1,369,325 ($\Delta^9(11)$) and 1,369,314 (11-keto), Dutch patent 89,348 (11-keto) and *Endocrinol. Japan* 4, 214 (1957) (11 β -hydroxy).

The conversion of aldehydes to α -chloroketones via the addition of Cl₂CHLi followed by treatment with butyllithium was reported in *J. Organometal. Chem.*, 40, C1 (1972). The yield was only about 60% and the product was contaminated with 8-15% of α -chloroaldehydes formed in a competing rearrangement. The same reaction was reported, *Tetrahedron Letters* 4117 (1972), using lithium piperidide in place of butyllithium giving yields of 56, 70 and 87% using simple monofunctional ketones, not aldehydes. The authors did not take into account the yield for the formation of their substrate from aldehydes and ketones. The conversion of a simple monofunctional aldehyde to an α -bromoketone in 62% yield using Br₂CHLi was reported in *Bull. Soc. Chim. France* 1797 (1975). The same authors then reported, *J. Organometal. Chem.*, 97, 325 (1975), the conversion of a few more simple carbonyls to α -haloketones using CH₂X₂ and lithium piperidide. Yields of the reaction of the carbonyl with X₂CHLi ranged from 50-87% (typically 60-65%) for production of the halohydrin and conversion of these adducts to α -haloketones in 60-90% yield (typically 70-80%) which gives a typical overall yield of about 40-60%. Many of these products contained 8-65% α -haloaldehyde, although some reactions provided the α -haloketone selectively. All of these references disclose reactions which involved the generation of X₂CHLi where X is a bromine or chlorine atom by treating X₂CH₂ with either a lithium amide base or butyllithium at < -70°. Solutions of these reagents are unstable at temperatures above -70°. The process of the present invention avoids the need to work with such unstable solutions at such low temperatures.

J. Am. Chem. Soc., 96, 3010 (1974) and *Bull. Chem. Soc. Japan* 50, 1588 (1977) report a simple procedure for the reaction of methylene bromide with aldehydes and ketones to give the same halohydrin intermediates as described in the above references. Their procedure required the use of a large excess (2-24 equivalents) of CX₂H₂ and the yield with the aldehyde substrates was only 73-79%. The process of the present invention uses < 3 equivalents of base, preferably about 2.8 equivalents, to transform the protected steroidal aldehyde (III) all the way to the desired protected 21-halo-17 α -hydroxy-20-keto steroid (IV), not just to the halohydrin intermediate as with the above references.

The conversion of protected 21-halo-17 α -hydroxy-20-keto steroids to the corresponding protected 21-acyloxy-17 α -hydroxy-20-keto steroids and then to corticoids is well known to those skilled in the art.

Disclosed is a process for the preparation of a protected aldehyde of formula (III)



where R₁₇₋₁ is -Si-(R₁₇₋₂)₂(R₁₇₋₃) where R₁₇₋₂ and R₁₇₋₃ are C₁-C₄ alkyl or ϕ , which comprises

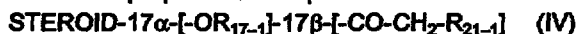
(1) contacting a protected cyanohydrin of formula (II)



where R₁₇₋₁ is as defined above with at least one hydride equivalent of a reducing agent in the presence of an ether and

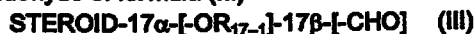
(2) hydrolyzing the reaction mixture of step (1).

Also disclosed is a process for the preparation of a protected 21-halo steroid of formula (IV)



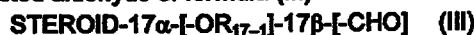
where R_{17-1} is $-\text{Si}-(R_{17-2})_2(R_{17-3})$ where R_{17-2} and R_{17-3} are $\text{C}_1\text{-C}_4$ alkyl or ϕ and R_{21-1} is $-\text{Cl}$ or $-\text{Br}$, which comprises

(1) contacting a protected aldehyde of formula (III)



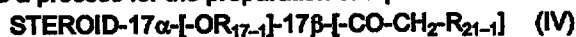
where R_{17-1} is as defined above, with a strong base in the presence of a compound of the formula $\text{CH}_2(R_{21-1})_2$ where R_{21-1} is as defined above.

Further disclosed is a protected aldehyde of formula (III)



where R_{17-1} is $-\text{Si}-(R_{17-2})_2(R_{17-3})$ where R_{17-2} and R_{17-3} are $\text{C}_1\text{-C}_4$ alkyl or ϕ .

Additionally disclosed is a process for the preparation of a protected 21-halo steroid of formula (IV)

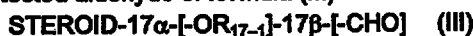


where R_{17-1} is $-\text{Si}-(R_{17-2})_2(R_{17-3})$ where R_{17-2} and R_{17-3} are $\text{C}_1\text{-C}_4$ alkyl or ϕ and R_{21-1} is $-\text{Cl}$ or $-\text{Br}$, which comprises

(1) contacting a protected cyanohydrin of formula (II)



where R_{17-1} is as defined above with at least one hydride equivalent of a reducing agent in the presence of an ether to produce a protected aldehyde of formula (III)



where R_{17-1} is as defined above and

(2) contacting the protected aldehyde of formula (III) with a strong base in the presence of a compound of the formula $\text{CH}_2(R_{21-1})_2$ where R_{21-1} is as defined above.

The steroidal cyanohydrins (I) are known to those skilled in the art or can be readily be prepared by methods known to those skilled in the art from known steroid starting materials. The steroid A-, B- and C- rings are known to those skilled in the art include the usual steroidal nucleus. More particularly, they include the A-, B- and C-rings set forth in CHART B.

First, the A-ring C_3 ketone of the cyanohydrins (I) is protected as is known to those skilled in the art, for example, as the alkyl $\Delta^{3,5}$ -dienoether, $\Delta^{5,3}$ -ketal or enamine. Next, the 17α -hydroxy group of the cyanohydrin is protected as is known to those skilled in the art. Suitable protecting groups include silyl ethers, acetals, or readily removed ethers. The silyl ether is the preferred protecting group but any group which remains on and protects the 17α -hydroxyl group during the reaction and is readily removable at the end of the process is acceptable. Preferred is the trimethylsilyl ether.

The protected cyanohydrin (II) is transformed to the corresponding protected aldehyde (III) by reaction with at least one hydride equivalent of a reducing agent. Suitable reducing agents are aluminum hydrides. These include diisobutylaluminum hydride, lithium aluminum hydride, sodium bis-(2-methoxyethoxy)aluminum hydride and lithium tri-tert-butoxyaluminum hydride. Preferred is diisobutylaluminum hydride. At least 1 hydride equivalent of reducing agent is necessary. Preferred is 1.2 - 2.0 equivalents, more preferred is 1.4 - 1.5 equivalents. The term "hydride equivalent" is used since one molar equivalent of some of the above reducing agents contain more than one hydride equivalent. The reaction is performed in any organic solvent compatible with the reducing agent, however some ether must be present. The quantity of ether may range from about 0.1% to 100%. Ethers include THF, ether and methyl t-butyl ether and mixtures thereof. Suitable co-solvents include the above ethers and toluene, methylene chloride and mixtures thereof. It is preferred that at least 0.1 % ether be present, more preferably at least 0.5 %, still more preferably at least 5 % ether. The amount of ether depends on the particular ether, the particular reducing agent, the particular protected cyanohydrin (II) etc. Preferred is methyl t-butyl ether containing about 10% THF (v/v). Temperature is not critical and the process can be performed from about -80° to about 80° , preferably about -30° to about 0° . Any order of addition is operable, the reducing agent can be added to the steroid or the steroid to the reducing agent. Following contacting the protected cyanohydrin (II) with at least one hydride equivalent of the reducing agent in the presence of an ether, the reaction mixture is hydrolyzed. It is preferred to perform the hydrolysis with aqueous acid. It is preferred that the acid be a carboxylic acid, it is preferred that the carboxylic acid be acetic acid.

The protected aldehyde (III) can be isolated by means known to those skilled in the art or can be carried on through to the next step without isolation; it is preferred that the protected aldehyde (III) be carried on without isolation. For the protected aldehyde (III) it is preferred that R_{17-1} is trimethylsilyl. It is preferred that the protected aldehyde (III) A-ring have

(A-I) R_5 is $R_{5-1};R_{5-2}$, R_6 is $R_{6-1};R_{6-2}$, R_{10} is $\alpha\text{-}R_{10-1};\beta\text{-}R_{10-2}$ where one of R_{6-1} and R_{6-2} is $-\text{H}$ and the other taken together with one of R_{5-1} and R_{5-2} forms a second bond between C_5 and C_6 , R_{10-2} is $-\text{CH}_3$, R_{10-1} and the other of R_{6-1} and R_{6-2} taken together are $-\text{CH}_2\text{-CH}_2\text{-C}(\text{R}_{3-1})=\text{CH-}$ where R_{3-1} is $\text{C}_1\text{-C}_8$ alkyloxy, $-\text{O-}\phi$ where ϕ

is optionally substituted with 1 C₁-C₄ alkyl;

(A-II) R₅ is R₅₋₃:R₅₋₄, R₆ is R₆₋₃:R₆₋₄ and R₁₀ is α-R₁₀₋₃:β-R₁₀₋₄, where one of R₅₋₃ and R₆₋₄ is -H and the other taken together with one of R₅₋₃ and R₅₋₄ forms a second bond between C₅ and C₆, R₁₀₋₄ is -CH₃, R₁₀₋₃ and the other of R₅₋₃ and R₅₋₄ taken together are -CH₂-CH₂-C(α-R₃₋₃)(β-R₃₋₄)-CH₂-, where R₃₋₃ and R₃₋₄ taken together are -O-CH₂-C(CH₃)₂-CH₂-O- or -O-(CH₂)_{n1}-O- where n₁ is 2 or 3. It is preferred that the protected aldehyde (III) C-ring have R₁₁ is R₁₁₋₁:R₁₁₋₂ or α-R₁₁₋₃:β-R₁₁₋₃ where R₁₁₋₃ and R₁₁₋₄ are both -H. It is preferred that the protected aldehyde (III) D-ring have R₁₆₋₁ and R₁₆₋₂ are both -H. The preferred protected aldehydes (III) are selected from the group consisting of

3,17α-dihydroxyandrost-3,5,9(11)-triene-17β-carboxaldehyde 3-methyl 17-trimethylsilyloxy diether,
3,3,17α-trihydroxyandrost-5-ene-17β-carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether,
3,3,17α-trihydroxyandrost-5,9(11)-diene-17β-carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether.

The protected aldehyde (III) is transformed to the corresponding protected 21-halo steroid (IV) by contacting with a strong base in the presence of CH₂(R₂₁₋₁)₂ where R₂₁₋₁ is -Br or -Cl. Strong bases are amide bases of the formula Metal-N-(R₁)₂ where Metal is lithium, sodium, potassium and magnesium and R₁ is -H, C₁-C₆ alkyl, -Si(R₂)₃ where R₂ is C₁-C₆ alkyl. It is preferred that the amide is selected from the group consisting of lithium diisopropylamide, lithium diethylamide, lithium piperidide and lithium dicyclohexylamide. The preferred base is lithium diisopropylamide. It is preferred that the halogenated agent be methylene bromide. About 2.5 to 3, preferably 2.8, equivalents of strong base are utilized. One equivalent per equivalent of CH₂R₂₁ is needed plus 1.8 equivalents for the transformation of the halohydrin intermediate to the 21-halo ketone. Slightly greater than 1 equivalent of halogenated agent is required, preferably 1.05 equivalents. The reaction is performed in an etheral solvent with or without a hydrocarbon co-solvent. Preferred is about 50 % hydrocarbon with about 50 % ether; preferably hexane/THF (1/1). Temperature is not critical, about -100 to about 0° is operable, preferred is about -40 to about -30°. The order of addition of reactants is not critical so long as the base is added last.

The protected 21-halo steroid (IV) is then transformed to the corresponding protected 21-ester (V) by means known to those skilled in the art, see Organic Reactions in Steroid Chemistry, Vol II, Fried and Edwards, Van Nostrand editor, Reinhold Co, N.Y., 1972, p 217-227.

The protected 21-ester (V) is transformed to the corresponding corticoid (VI) by means known to those skilled in the art.

The protection of the steroid A-ring is necessary during the transformation of the protected cyanohydrin (II) to the protected aldehyde (III) and then for the protected aldehyde (III) to the 21-halo steroid (IV). While it is not necessary, in a number of cases it is desirable to leave the C₃ protecting group on after the protected 21-halo steroid (IV) is obtained. When desired the protecting groups are removed by means known to those skilled in the art. Hence, the nature of the steroid nucleus does not change during the reaction. In the present invention all process chemistry changes take place in the side chain attached to C₁₇. Therefore, for simplicity the traditional 4 ring steroid nucleus in the present process has been defined in CHART B and identified as "STEROID".

DEFINITIONS AND CONVENTIONS

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

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "Z_i" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z_i would represent a bivalent variable if attached to the formula CH₃-C(=Z_i)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH₃-CH₂-C(R_i)(R_j)H₂. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are

bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as steroids, these carbon atoms are designated as C_i , where "i" is the integer corresponding to the carbon atom number. For example, C_6 represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry. Likewise the term " R_6 " represents a variable substituent (either monovalent or bivalent) at the C_6 position.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus $\text{CH}_3\text{-O-CH}_2\text{-CH(R)}_i\text{-CH}_3$ represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., $\text{CH}_2=\text{C(R)}_i\text{-O-CH}_3$, and the symbol "≡" represents a triple bond, e.g., $\text{HC}\equiv\text{C-CH(R)}_i\text{-CH}_2\text{-CH}_3$. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)- , with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by $\text{N}^+=\text{C(CH}_3\text{)-CH=CCl-CH=C}^*\text{H}$ with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by $\text{-N}^*(\text{CH}_2)_2\text{-N(C}_2\text{H}_5\text{)-CH}_2\text{-C}^*\text{H}_2$.

A cyclic (ring) structure for any compound herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the cyclic compound. In formulas depicting such compounds, a substituent attached to a carbon atom below the plane of the ring is identified as being in the alpha (α) configuration and is indicated by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "....". The corresponding substituent attached above the plane of the ring is identified as being in the beta (β) configuration.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as $\text{-C(=R)}_i\text{-}$ might be bivalent and be defined as oxo or keto (thus forming a carbonyl group -CO-) or as two separately attached monovalent variable substituents $\alpha\text{-R}_{i-1}$ and $\beta\text{-R}_{i-k}$. When a bivalent variable, R_i , is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the forms " $\alpha\text{-R}_{i-1};\beta\text{-R}_{i-k}$ " or some variant thereof. In such a case both $\alpha\text{-R}_{i-1}$ and $\beta\text{-R}_{i-k}$ are attached to the carbon atom to yield $\text{-C}(\alpha\text{-R}_{i-1})(\beta\text{-R}_{i-k})\text{-}$. For example, when the bivalent variable R_6 , $\text{-C(=R)}_6\text{-}$ is defined to consist of two monovalent variable substituents, two monovalent variable substituents are $\alpha\text{-R}_{6-1};\beta\text{-R}_{6-2}, \dots, \alpha\text{-R}_{6-9};\beta\text{-R}_{6-10}$, etc, yielding $\text{-C}(\alpha\text{-R}_{6-1})(\beta\text{-R}_{6-2}), \dots, \text{-C}(\alpha\text{-R}_{6-9})(\beta\text{-R}_{6-10})\text{-}$, etc. Likewise, for the bivalent variable R_{11} , $\text{-C(=R)}_{11}\text{-}$, two monovalent variable substituents are $\alpha\text{-R}_{11-1};\beta\text{-R}_{11-2}$. For a ring substituent for which separate α and β orientations do not exist (e.g. due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the α and β designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula $\text{-C}_1(\text{R})_i\text{H-C}_2(\text{R})_j\text{H-}$ (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa (-O-) and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group -X-Y- , then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y. Thus, by convention the designation "... R_i and R_j are taken together to form $\text{-CH}_2\text{-CH}_2\text{-O-CO-}$..." means a lactone in which the carbonyl is bonded to C_2 . However, when designated "... R_j and R_i are taken together to form $\text{-CH}_2\text{-CH}_2\text{-O-CO-}$ the convention means a lactone in which the carbonyl is bonded to C_1 .

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as " $\text{C}_1\text{-C}_4$ ", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, " $\text{C}_1\text{-C}_4$ alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus $\text{C}_2\text{-C}_4$ alkoxy carbonyl describes a group $\text{CH}_3\text{-(CH}_2\text{)}_n\text{-O-CO-}$ where n is zero, one or 2. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "Ci-Cj" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention $(\text{C}_1\text{-C}_3)\text{alkoxy carbonyl}$ has the same meaning as $\text{C}_2\text{-C}_4$ alkoxy carbonyl because the " $\text{C}_1\text{-C}_3$ " refers only to the carbon atom content of the alkoxy group. Similarly while both $\text{C}_2\text{-C}_6$ alkoxy alkyl and $(\text{C}_1\text{-C}_3)\text{alkoxy(C}_1\text{-C}_3)\text{alkyl}$ define alkoxy alkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

II. DEFINITIONS

STEROID refers to the steroid nucleus as set forth in CHARTS A, B and C.

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

HPLC refers to high pressure liquid chromatography.

THF refers to tetrahydrofuran.

LDA refers to lithium diisopropylamide.

Saline refers to an aqueous saturated sodium chloride solution.

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

ϕ refers to phenyl (C_6H_5).

Ether refers to diethyl ether.

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

Androstenedione refers to androst-4-ene-3,17-dione.

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 examples 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

3,17 α -Dihydroxyandrosta-3,5,9(11)-triene-17 β -carbox aldehyde 3-methyl 17-trimethylsilyloxy diether (III)

17 β -Cyano-3,17 α -dihydroxyandrosta-3,5,9(11)-triene 3-methyl 17-trimethylsilyloxy diether (II, 17.46 g) is dissolved in methyl t-butyl ether (50 ml) and THF (5.7 ml). The resulting solution is cooled to -28°. Diisobutylaluminum hydride (12.6 ml) is dissolved in methyl t-butyl ether (26.6 ml) and this solution is cooled to -30° before being added dropwise to the steroid mixture. The addition is done over 35 min and the reaction temperature is maintained between -25 and -30°. Following the addition, the mixture is allowed to warm to 0° slowly over 2.5 hr at which time the reaction is complete as measured by TLC.

Methanol (5.5 ml) is added dropwise while maintaining the temperature between 0 and 10°. After stirring, the resulting cloudy mixture for 10 min a solution of aqueous acetic acid (50%, 66 ml) is slowly added while maintaining the temperature below 25°. After stirring the resulting two-phase mixture at 25° for 0.5 hr, toluene (70 ml) is added and the mixture is distilled under vacuum at 30° until 50 ml of distillate are collected. The two phases are separated and the aqueous fraction is extracted with toluene (2 x 15 ml). The combined organic phases are washed twice with water (20 ml), then with saturated sodium bicarbonate (20 ml), then with water again (20 ml), and then finally with saline (20 ml). After drying over anhydrous magnesium sulfate (1 g) and silica gel (5 g), the mixture is filtered and the solvent is removed under reduced pressure to give an oily residue. TLC and HPLC indicate that the product is >95% pure.

The product is crystallized by dissolving it in a minimum of ethyl acetate and adding methanol until it becomes cloudy. After gentle heating and then cooling to 25° seed crystals are added and the mixture is then left at -15° for 15 hr. Filtration gives a solid which is crystallized to give the title compound, mp = 90-92°.

A second crop can be obtained following silica gel chromatography of the mother liquor eluting with hexane/acetone (98/2), NMR ($CDCl_3$) 0.1, 0.65, 1.15, 3.6, 5.2, 5.3, 5.5 and 9.65 δ .

EXAMPLE 2

21-Bromo-17 α -hydroxypregna-4,9(11)-diene-3,20-dione 17-trimethylsilyloxy ether (IV)

5 3,17 α -Dihydroxyandrosta-3,5,9(11)-triene-17 β -carboxaldehyde 3-methyl 17-trimethylsilyloxy diether (III, EXAMPLE 1, 1.18 g) is dissolved in THF (1.2 ml) and hexane (2.3 ml) is added. After degassing with nitrogen, the solution is cooled to -35° and methylene bromide (0.22 ml) is added. A solution of lithium diisopropylamide in THF/hexane (1M, ~2:1) is then added dropwise over 10 min maintaining the temperature between -30 and -35°. The resulting mixture is then stirred for 1/2 hr during which time the temperature is allowed to climb to -10°. The mixture is then transferred to a flask containing hydrochloric acid (3N, 7 ml) and methylene chloride (3 ml) which is previously cooled to -20°. A 10° exotherm is observed during this addition. The resulting mixture is then allowed to warm up to 20-25°. After a total hydrolysis time of 1.5 hr methylene chloride (30 ml) is added and the two layers are separated. The aqueous phase is extracted with methylene chloride (5 ml) and the combined organic fractions are washed successively with water (10 ml), sodium bicarbonate (10%, 10 ml) and saline (10 ml). After drying over anhydrous magnesium sulfate (-1 g) and filtering through a short column of silica gel (-5 g, eluting with about 10 ml methylene chloride), the solvent is removed to give the title compound, mp = 155-156°; NMR (CDCl₃) 0.15, 0.55, 1.35, 4.1, 4.3, 5.6 and 5.7 δ .

EXAMPLE 3

20 3,3,17 α -Trihydroxyandrost-5-ene-17 β -carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether (III)

Following the general procedure of EXAMPLE 1 and making non-critical variations but starting with 17 β -cyano-3,3,17 α -trihydroxyandrost-5-ene 3,3-ethylene ketal 17-trimethylsilyloxy ether (II) the title compound is obtained, mp = 128-134°.

EXAMPLE 4

30 21-Bromo-17 α -hydroxypregn-4-ene-3,20-dione 17-trimethylsilyloxy ether (IV)

Following the general procedure of EXAMPLE 2 and making non-critical variations but starting with 3,3,17 α -trihydroxyandrost-5-ene-17 β -carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether (III, EXAMPLE 3) the title compound is obtained, NMR (CDCl₃) 0.15, 0.6, 1.15, 4.1, 4.3 and 5.75 δ ; TLC (methylene chloride/methanol, 98/2) R_f = 0.64; TLC (methylene chloride/acetone, 95/5) R_f = 0.68.

EXAMPLE 5

40 3,3,17 α -Trihydroxyandrosta-5,9(11)-diene-17 β -carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether (III)

Following the general procedure of EXAMPLE 1 and making non-critical variations but starting with 17 β -cyano-3,3,17 α -trihydroxyandrosta-5,9(11)-diene 3,3-ethylene ketal 17-trimethylsilyloxy ether (II) the title compound is obtained, mp = 131-134°.

EXAMPLE 6

45 21-Bromo-17 α -hydroxypregna-4,9(11)-diene-3,20-dione 17-trimethylsilyloxy ether (IV)

Following the general procedure of EXAMPLE 2 and making non-critical variations but starting with 3,3,17 α -trihydroxyandrosta-5,9(11)-diene-17 β -carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether (III, EXAMPLE 5) the title compound is obtained.

CHART A

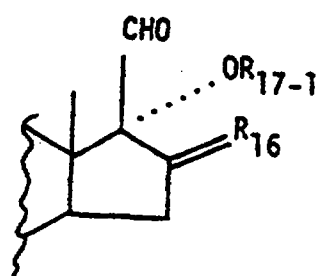
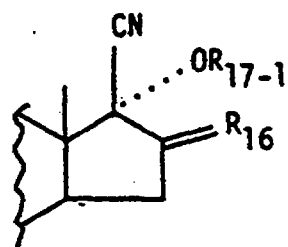
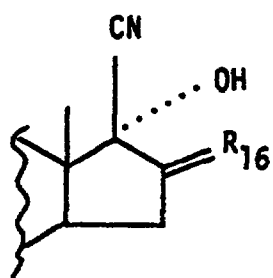


CHART A - Continued

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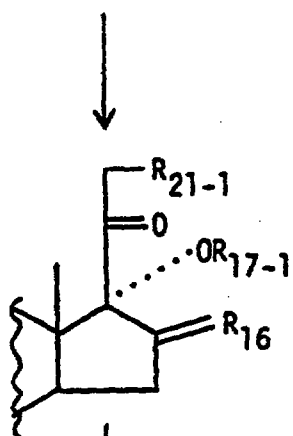
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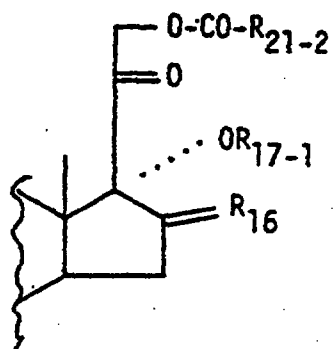
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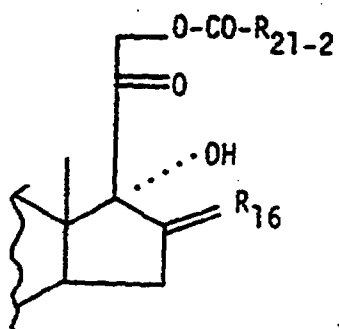
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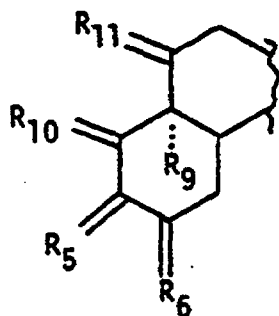
(IV)



(V)



(VI)

CHART B

(A/B/C)

where:

(A-I) R_5 is $R_{5-1}:R_{5-2}$, R_6 is $R_{6-1}:R_{6-2}$, R_{10} is $\alpha-R_{10-1}:\beta-R_{10-2}$ where one of R_{6-1} and R_{6-2} is -H, -F, -Cl, -Br, -CH₃ and the other taken together with one of R_{6-1} and R_{6-2} forms a second bond between C₆ and C₈, R_{10-2} is -CH₃, R_{10-1} and the other of R_{6-1} and R_{6-2} taken together are -CH₂-CH₂-C(R_{3-1})=CH- or -CH=CH-C(R_{3-1})=CH- where R_{3-1} is C₁-C₆ alkoxy, -O- ϕ where ϕ is optionally substituted with 1 C₁-C₄ alkyl or -N(R_{3-2})(R_{3-6}) where R_{3-2} is C₁-C₃ alkyl, R_{3-6} is C₁₋₃ alkyl or ϕ , where the R_{3-2} and R_{3-6} may be cyclized to form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine, morpholine, piperazine;

(A-II) R_5 is $R_{5-3}:R_{5-4}$, R_6 is $R_{6-3}:R_{6-4}$ and R_{10} is $\alpha-R_{10-3}:\beta-R_{10-4}$, where one of R_{6-3} and R_{6-4} is -H, -F, -Cl, -Br, -CH₃ and the other taken together with one of R_{6-3} and R_{6-4} forms a second bond between C₆ and C₈, R_{10-4} is -CH₃, R_{10-3} and the other of R_{6-3} and R_{6-4} taken together are -CH₂-CH₂-C($\alpha-R_{3-3}$)($\beta-R_{3-4}$)-CH₂, where one of R_{3-3} and R_{3-4} is -H and the other of R_{3-3} and R_{3-4} is -OH or -OR₃₋₅ where R_{3-5} is C₁-C₆ alkyl, -CH₂- ϕ or -Si(R_{3-7})₂(R_{3-8}) where R_{3-7} and R_{3-8} are C₁₋₄ and ϕ , and where R_{3-3} and R_{3-4} taken together are -O-CH₂-C(CH₃)₂-CH₂-O- or -O-(CH₂)_{n1}-O- where n_1 is 2 or 3;

(C-I) R_{11} is $R_{11-1}:R_{11-2}$ where one of R_{11-1} and R_{11-2} taken together with R_9 to form a second bond between C₉ and C₁₁ and the other of R_{11-1} and R_{11-2} is -H;

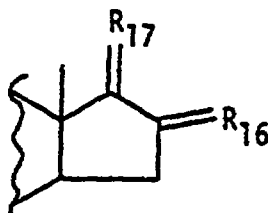
(C-II) R_{11} is $\alpha-H:\beta-O-$, where $\beta-O-$ is taken together with R_9 to form a β -epoxide between C₉ and C₁₁;

CHART B - Continued

(C-III) R_9 is -H and R_{11} is -O-CH₂-C(CH₃)₂-CH₂-O- or -O-(CH₂)_{n2}-O- where n_2 is 2 or 3, $\alpha-R_{11-3}:\beta-R_{11-4}$ where one of R_{11-3} and R_{11-4} is -H and the other of R_{11-3} and R_{11-4} is -H, -OH or -OR₁₁₋₅ where R_{11-5} is C₁-C₆ alkyl, -CH₂- ϕ or -Si(R_{11-6})₂(R_{11-7}) where R_{11-6} and R_{11-7} are C₁₋₄ and ϕ .

CHART C

The six partial structural formulas of CHART A can be represented by

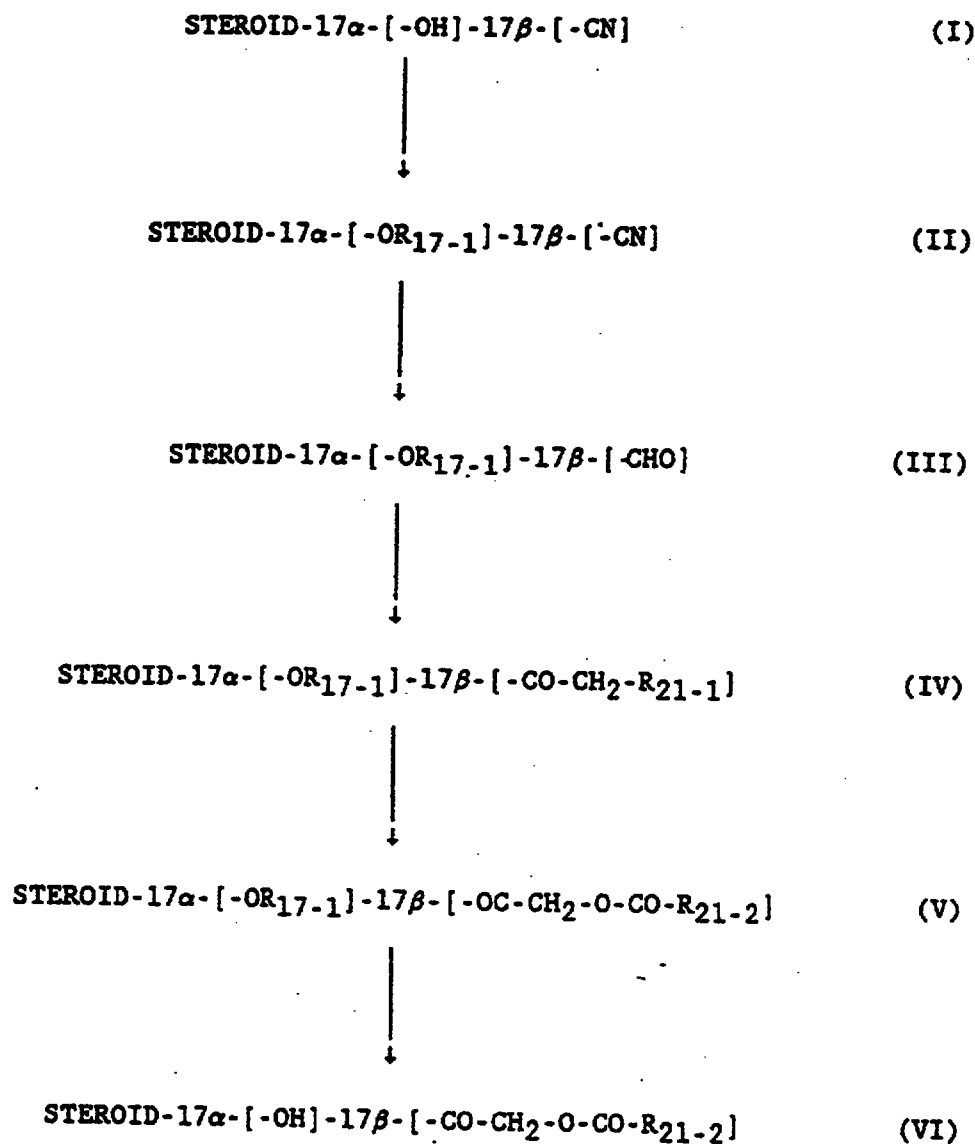


(VII)

where R_{16} is $\alpha-R_{16-1}:\beta-R_{16-2}$ where one of R_{16-1} and R_{16-2} is -H and the other of R_{16-1} and R_{16-2} is -H, -CH₃ or -OH;

where for the cyanohydrin (I) R_{17} is $\alpha-OH:\beta-CN$,

for the protected cyanohydrin (II) R_{17} is $\alpha\text{-OR}_{17-1};\beta\text{-CN}$,
 for the protected aldehyde (III) R_{17} is $\alpha\text{-OR}_{17-1};\beta\text{-CHO}$,
 for the protected 21-halo steroid (IV) R_{17} is $\alpha\text{-OR}_{17-1};\beta\text{-CO-CH}_2\text{-R}_{21-1}$,
 for the protected 21-ester (V) R_{17} is $\alpha\text{-OR}_{17-1};\beta\text{-CO-CH}_2\text{-O-CO-R}_{21-2}$ and
 for the corticoid (VI) R_{17} is $\alpha\text{-OH};\beta\text{-CO-CH}_2\text{-O-CO-R}_{21-2}$.

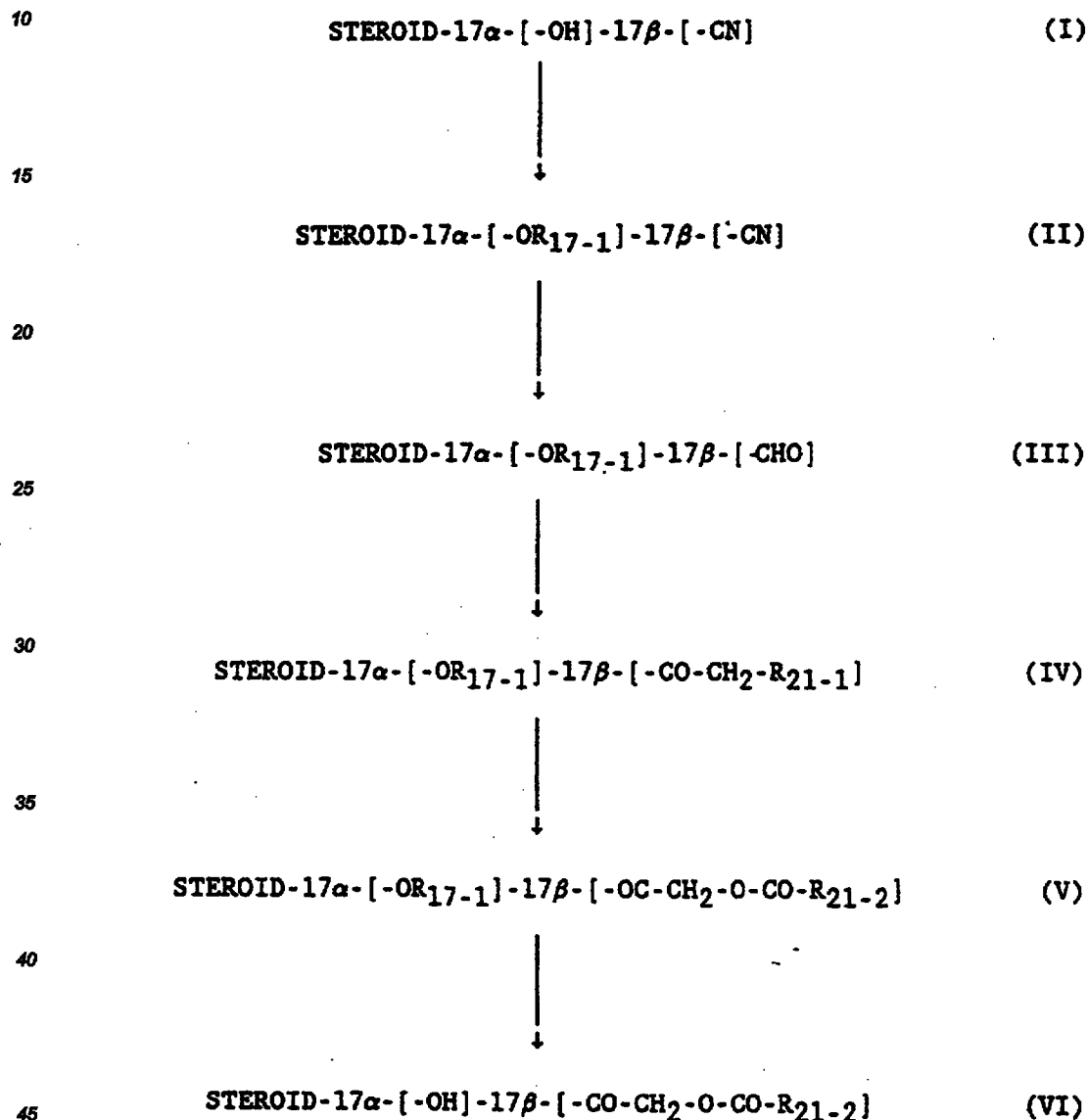
CHART D

STEROID refers to the steroid nucleus as set forth in CHARTS A, B and C.

Claims

1. A process for the preparation of a protected aldehyde of formula (III)

for the protected cyanohydrin (II) R_{17} is $\alpha\text{-OR}_{17-1}:\beta\text{-CN}$,
 for the protected aldehyde (III) R_{17} is $\alpha\text{-OR}_{17-1}:\beta\text{-CHO}$,
 for the protected 21-halo steroid (IV) R_{17} is $\alpha\text{-OR}_{17-1}:\beta\text{-CO-CH}_2\text{-R}_{21-1}$,
 for the protected 21-ester (V) R_{17} is $\alpha\text{-OR}_{17-1}:\beta\text{-CO-CH}_2\text{-O-CO-R}_{21-2}$ and
 for the corticoid (VI) R_{17} is $\alpha\text{-OH}:\beta\text{-CO-CH}_2\text{-O-CO-R}_{21-2}$.

CHART D

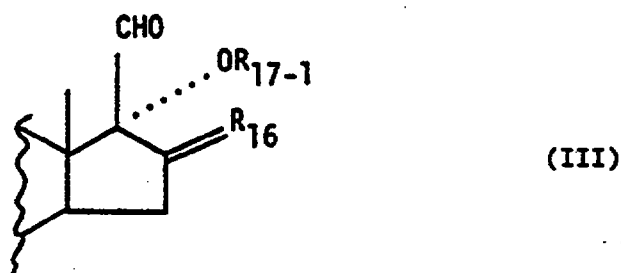
STEROID refers to the steroid nucleus as set forth in CHARTS A, B and C.

50 **Claims**

1. A process for the preparation of a protected aldehyde of formula (III)

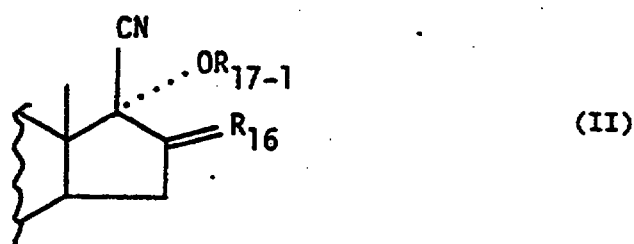
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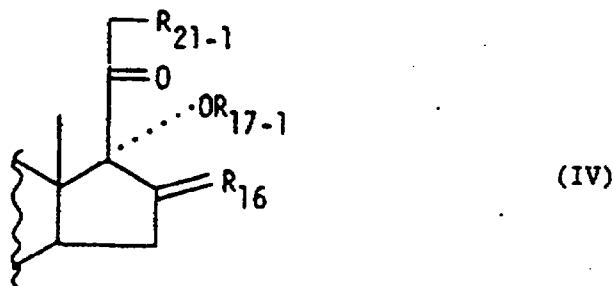
where R_{16} is $\alpha-R_{16-1}-\beta-R_{16-2}$ where one of R_{16-1} and R_{16-2} is -H and the other of R_{16-1} and R_{16-2} is -H, -CH₃ or -OH;

R_{17-1} is -Si-(R_{17-2})₂(R_{17-3}) where R_{17-2} and R_{17-3} are C₁-C₄ alkyl or ϕ , and which comprises
(1) contacting a protected cyanohydrin of formula (II)



where R_{16} and R_{17-1} are as defined above with at least one hydride equivalent of a reducing agent in the presence of an ether and
(2) hydrolyzing the reaction mixture of step (1).

2. A process according to claim 1 where the reducing agent is an aluminum hydride.
3. A process according to claim 1 where the reducing agent is selected from diisobutylaluminium hydride, lithium aluminium hydride, sodium bis (2-methoxyethoxy) aluminium hydride and lithium tri-terbutoxyaluminium hydride.
4. A process according to claim 1, where the reducing agent is diisobutylaluminium hydride.
5. A process according to any preceding claim, where 1.2 to 2.0 equivalents of reductant agent are used.
6. A process according to any preceding claim, where the ether is selected from tetrahydrofuran, ether, methyl t-butyl ether and mixtures thereof.
7. A process according to any preceding, where the hydrolysis is performed with aqueous acid.
8. A process according to claim 7, where the acid is a carboxylic acid.
9. A process for the preparation of a protected 21-halo steroid of formula (IV)



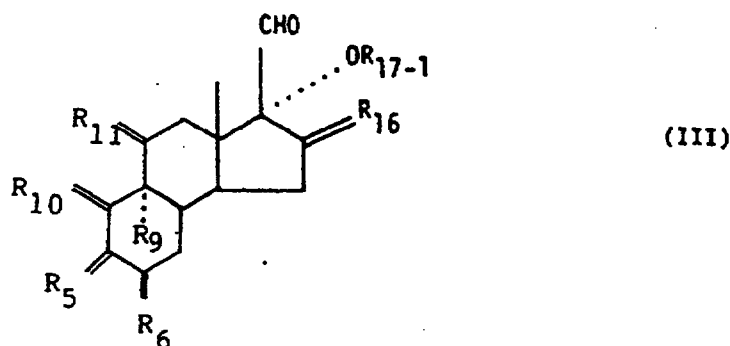
where R_{16} and R_{17-1} are as defined in claim 1; and



R_{21-1} is Cl or Br;

which comprises contacting a protected aldehyde of formula III as defined in claim 1 with an amide of the formula Metal-N-(R_1)₂ where Metal is lithium, sodium, potassium or magnesium and R_1 is H, C₁-C₆ alkyl or -Si(R_2)₃ where R_2 is C₁-C₆ alkyl, in the presence of a compound of the formula CH₂(R_{21-1})₂ where R_{21-1} is as defined above.

10. A process according to claim 9, where the amide is selected from lithium diisopropylamide, lithium diethylamide, lithium piperidide and lithium dicyclohexylamide.
11. A process according to claim 9, where the amide is lithium diisopropylamide.
12. A process according to any of claims 9 to 11, where <3 equivalents of the strong base are used.
13. A process according to any of claims 9 to 12, where R_{21-1} is Br.
14. A process according to any of claims 9 to 13, which comprise the prior step of preparing the protected aldehyde (III) by a process according to any of claims 1 to 8.
15. A protected aldehyde of the formula



where R_{16} and R_{17-1} are as defined in claim 1;

(A-I) R_5 is R_{5-1} : R_{5-2} , R_6 is R_{6-1} : R_{6-2} and R_{10} is α - R_{10-1} : β -CH₃, where one of R_{6-1} and R_{6-2} is H, F, Cl, Br or CH₃ and the other taken together with one of R_{5-1} and R_{5-2} forms a second bond between C₅ and C₆, and R_{10-1} and the other of R_{5-1} and R_{5-2} taken together are -CH₂-CH₂-C(R_{3-1})=CH- or -CH=CH-C(R_{3-1})=CH- where R_{3-1} is C₁-C₆ alkyloxy, -O- ϕ where ϕ is optionally substituted with one C₁-C₄ alkyl or -N(R_{3-2})(R_{3-3}) where R_{3-2} is C₁-C₃ alkyl and R_{3-3} is C₁₋₃ alkyl or ϕ , or where the R_{3-2} and R_{3-3} are cyclised to form a heterocyclic ring selected from pyrrolidine, piperidine, morpholine and piperazine; or

(A-II) R_5 is R_{5-3} : R_{5-4} , R_6 is R_{6-3} : R_{6-4} and R_{10} is α - R_{10-3} : β -CH₃, where one of R_{6-3} and R_{6-4} is H, F, Cl, Br or CH₃ and the other taken together with one of R_{5-3} and R_{5-4} forms a second bond between C₅ and C₆, and R_{10-3} and the other of R_{5-3} and R_{5-4} taken together are -CH₂-CH₂-C(α - R_{3-3})(β - R_{3-4})-CH₂- where one of R_{3-3} and R_{3-4} is H and the other is OH or OR₃₋₅ where R_{3-5} is C₁-C₆ alkyl, -CH₂- ϕ or -Si(R_{3-7})₂(R_{3-8}) where R_{3-7} and R_{3-8} are C₁₋₄ or ϕ , or R_{3-3} and R_{3-4} taken together are -O-CH₂-C(CH₃)₂-CH₂-O- or -O-(CH₂)_{n1}-O- where n_1 is 2 or 3; and

(C-I) R_{11} is R_{11-1} : R_{11-2} where one of R_{11-1} and R_{11-2} taken together with R_9 forms a second bond between C₉ and C₁₁ and the other of R_{11-1} and R_{11-2} is H;

(C-II) R_{11} is α -H: β -O-, where β -O- is taken together with R_9 to form a β -epoxide between C₉ and C₁₁; or

(C-III) R_9 is H and R_{11} is -O-CH₂-C(CH₃)₂-CH₂-O-, -O-(CH₂)_{n2}-O- where n_2 is 2 or 3, or α - R_{11-3} : β - R_{11-4} where one of R_{11-3} and R_{11-4} is H and the other is H, OH or OR₁₁₋₅ where R_{11-5} is C₁-C₆ alkyl, -CH₂- ϕ or -Si-(R_{11-6})₂(R_{11-7}) where R_{11-6} and R_{11-7} are C₁₋₄ or ϕ .

16. A protected aldehyde according to claim 15, where R_{17-1} is trimethylsilyl.

17. A protected aldehyde according to claim 15 or claim 16, where

(A-I) said one of R_{6-1} and R_{6-2} is H and R_{10-1} and said other of R_{5-1} and R_{5-2} taken together are -



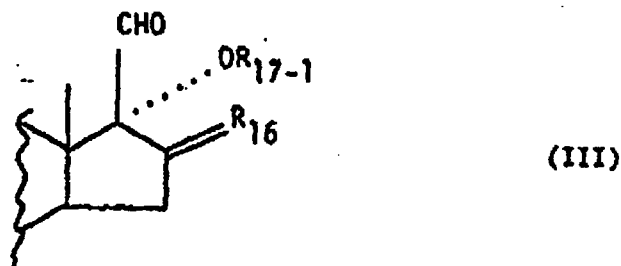
$\text{CH}_2\text{-CH}_2\text{-C(R}_{3-1}\text{)=CH-}$ where R_{3-1} is $\text{C}_1\text{-C}_8$ alkyloxy or $\text{-O-}\phi$ where ϕ is optionally substituted with one $\text{C}_1\text{-C}_4$ alkyl; or

(A-II) said one of R_{6-3} and R_{6-4} is H and R_{3-3} and R_{3-4} are taken together.

18. A protected aldehyde according to any of claims 15 to 17, where R_{11} is $\text{R}_{11-1}\text{:R}_{11-2}$ or H:H.
19. A protected aldehyde according to any of claims 15 to 18, where R_{16} is H:H.
20. A protected aldehyde according to claim 15, which is
 3,17 α -dihydroxyandrosta-3,5,9(11)-triene-17 β -carboxaldehyde 3-methyl 17-trimethylsilyloxy diether,
 3,3,17 α -trihydroxyandrost-5-ene-17 β -carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether, or
 3,3,17 α -trihydroxyandrosta-5,9(11)-diene-17 β -carboxaldehyde 3,3-ethylene ketal 17-trimethylsilyloxy ether.
21. A process according to any of claims 1 to 14, wherein the protected aldehyde (III) is as defined in any of claims 15 to 20.

Patentansprüche

1. Verfahren zur Herstellung eines geschützten Aldehyds der Formel (III)

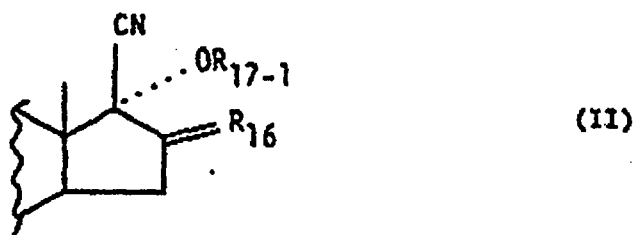


worin bedeuten:

R_{16} $\alpha\text{-R}_{16-1}\text{:}\beta\text{-R}_{16-2}$, worin einer der Reste R_{16-1} und R_{16-2} für -H und der andere der Reste R_{16-1} und R_{16-2} für -H, -CH_3 oder -OH steht,

R_{17-1} -Si-(R_{17-2})₂(R_{17-3}), worin R_{17-2} und R_{17-3} für $\text{C}_1\text{-C}_4$ Alkyl oder ϕ stehen, dadurch gekennzeichnet, daß man

- (1) ein geschütztes Cyanhydrin der Formel (II)



worin R_{16} und R_{17-1} die zuvor angegebene Bedeutung besitzen,

in Gegenwart eines Ethers mit mindestens einem Hydridäquivalent eines Reduktionsmittels in Berührung bringt und

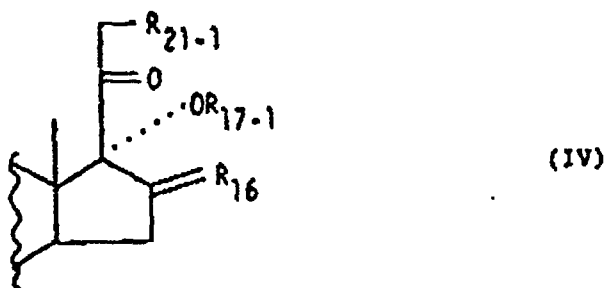
(2) das Reaktionsgemisch aus Stufe (1) hydrolysiert.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Reduktionsmittel aus einem Aluminiumhydrid besteht.
3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Reduktionsmittel aus Diisobutylaluminium-



umhydrid, Lithiumaluminiumhydrid, Natrium-bis-(2-methoxyethoxy)-aluminiumhydrid und Lithium-tri-tert.-butoxyaluminiumhydrid ausgewählt ist.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Reduktionsmittel aus Diisobutylaluminiumhydrid besteht.
5. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß 1,2 bis 2,0 Äquivalente Reduktionsmittel verwendet werden.
6. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Ether aus Tetrahydrofuran, Ether, Methyl-tert.-butylether und Mischungen derselben ausgewählt ist.
7. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Hydrolyse mit einer wäßrigen Säure durchgeführt wird.
8. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß die Säure aus einer Carbonsäure besteht.
9. Verfahren zur Herstellung eines geschützten 21-Halogensteroids der Formel (IV)

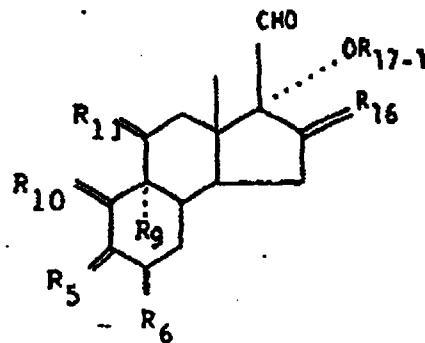


worin R_{16} und R_{17-1} die in Anspruch 1 angegebene Bedeutung besitzen und R_{21-1} für Cl oder Br steht,

dadurch gekennzeichnet, daß man einen geschützten Aldehyd der Formel (III) gemäß Anspruch 1 mit einem Amid der Formel Metall-N- $(R_1)_2$, worin Metall für Lithium, Natrium, Kalium oder Magnesium steht, und $R_1=H$, C_1-8 Alkyl oder $-Si(R_2)_3$ mit R_2 gleich C_1-C_8 Alkyl, in Gegenwart einer Verbindung der Formel $CH_2(R_{21-1})_2$, worin R_{21-1} die zuvor angegebene Bedeutung besitzt, in Berührung bringt.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß das Amid aus Lithiumdiisopropylamid, Lithiumdiethylamid, Lithiumpiperidid und Lithiumdicyclohexylamid ausgewählt ist.
11. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß das Amid aus Lithiumdiisopropylamid besteht.
12. Verfahren nach einem der Ansprüche 9 bis 11, dadurch gekennzeichnet, daß <3 Äquivalente der starken Base verwendet werden.
13. Verfahren nach einem der Ansprüche 9 bis 12, dadurch gekennzeichnet, daß R_{21-1} für Br steht.
14. Verfahren nach einem der Ansprüche 9 bis 13, dadurch gekennzeichnet, daß ihm die Herstellung des geschützten Aldehyds (III) nach einem Verfahren gemäß der Ansprüche 1 bis 8 vorgeschaltet ist.
15. Geschützter Aldehyd der Formel:





(III)

worin R_{16} und R_{17-1} die in Anspruch 1 angegebene Bedeutung besitzen;

(A-I) $R_5 = R_{5-1}:R_{5-2}$, $R_6 = R_{6-1}$ und $R_{10} = \alpha-R_{10-1}: \beta-CH_3$, worin einer der Reste R_{6-1} und R_{6-2} H, F, Cl, Br oder CH_3 bedeutet und der andere zusammen mit einem der Reste R_{5-1} und R_{5-2} eine zweite Bindung zwischen C_5 und C_6 bildet und R_{10-1} und der andere der Reste R_{5-1} und R_{5-2} zusammengenommen für $-CH_2-CH_2-C(R_{3-1})=CH-$ oder $-CH=CH-C(R_{3-1})=CH-$ mit R_{3-1} gleich C_1-C_6 Alkyloxy, $-O-\phi$, worin ϕ gegebenenfalls mit einem C_1-C_4 Alkyl substituiert ist, oder $-N(R_{3-2})(R_{3-6})$ mit R_{3-2} gleich C_1-C_3 Alkyl und R_{3-6} gleich C_1-C_3 Alkyl oder ϕ oder worin die Reste R_{3-2} und R_{3-6} unter Bildung eines heterocyclischen Rings aus der Gruppe Pyrrolidin, Piperidin, Morpholin und Piperazin cyclisiert sind, stehen oder

(A-II) $R_5 = R_{5-3}:R_{5-4}$, $R_6 = R_{6-3}:R_{6-4}$ und $R_{10} = \alpha-R_{10-3}: \beta-CH_3$, worin einer der Reste R_{6-3} und R_{6-4} H, F, Cl, Br oder CH_3 bedeutet und der andere zusammen mit einem der Reste R_{6-3} und R_{6-4} eine zweite Bindung zwischen C_5 und C_6 bildet, und R_{10-3} und der andere der Reste R_{6-3} und R_{6-4} zusammengenommen $-CH_2-CH_2-C(\alpha-R_{3-3})(\beta-R_{3-4})-CH_2-$, worin einer der Reste R_{3-3} und R_{3-4} H darstellt und der andere OH oder OR_{3-5} mit R_{3-5} gleich C_1-C_6 Alkyl, $-CH_2-\phi$ oder $-Si(R_{3-7})_2(R_{3-8})$, mit R_{3-7} und R_{3-8} gleich C_1-4 oder ϕ , oder R_{3-3} und R_{3-4} zusammen $-O-CH_2-C(CH_3)_2-CH_2-O-$ oder $-O-(CH_2)_{n1}-O-$ mit $n_1 = 2$ oder 3 bedeuten und

(C-I) $R_{11} = R_{11-1}:R_{11-2}$, worin einer der Reste R_{11-1} und R_{11-2} zusammen mit R_9 eine zweite Bindung zwischen C_9 und C_{11} bildet und der andere der Reste R_{11-1} und R_{11-2} H bedeutet;

(C-II) $R_{11} = \alpha-H:\beta-O-$, worin $\beta-O$ zusammen mit R_9 ein β -Epoxid zwischen C_9 und C_{11} bildet; oder

(C-III) $R_9 = H$ und $R_{11} = -O-CH_2-C(CH_3)_2-CH_2-O-$, $-O-(CH_2)_{n_2}-O-$ mit $n_2 = 2$ oder 3, oder $\alpha-R_{11-3}: \beta-R_{11-4}$, worin einer der Reste R_{11-3} und R_{11-4} für H steht und der andere H, OH, oder OR_{11-5} mit R_{11-5} gleich C_1-C_6 Alkyl, $-CH_2-\phi$ oder $-Si-(R_{11-6})_2(R_{11-7})$, worin R_{11-6} und R_{11-7} für C_1-4 oder ϕ stehen, bedeutet.

16. Geschützter Aldehyd nach Anspruch 15, worin R_{17-1} für Trimethylsilyl steht.

17. Geschützter Aldehyd nach Anspruch 15 oder Anspruch 16, worin (A-I) einer der Reste R_{6-1} und R_{6-2} für H steht und R_{10-1} und der andere der Reste R_{5-1} und R_{5-2} zusammen für $-CH_2-CH_2-C(R_{3-1})=CH-$ mit R_{3-1} gleich C_1-C_6 Alkyloxy oder $-O-\phi$, wobei ϕ gegebenenfalls mit einem C_1-C_4 Alkyl substituiert ist, oder (A-II) der eine der Reste R_{6-3} und R_{6-4} für H steht und R_{3-3} und R_{3-4} zusammengefaßt sind.

18. Geschützter Aldehyd nach einem der Ansprüche 15 bis 17, worin $R_{11} = R_{11-1}:R_{11-2}$ oder H:H.

19. Geschützter Aldehyd nach einem der Ansprüche 15 bis 18, worin $R_{16} = H:H$.

20. Geschützter Aldehyd nach Anspruch 15, nämlich

3,17 α -Dihydroxyandrosta-3,4,9(11)-trien-17 β -carboxaldehyd-3-methyl-17-trimethylsilyloxydiether

oder
3,3,17 α -Trihydroxyandrost-5-en-17 β -carboxaldehyd-3,3-ethylenketal-17-trimethylsilyloxyether

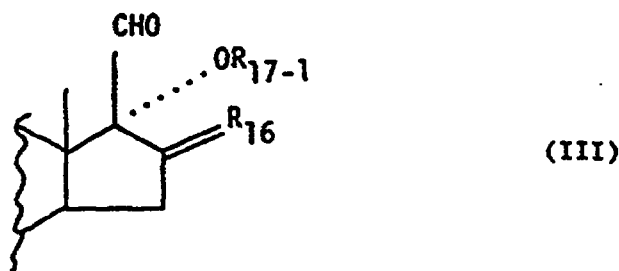
oder
3,3,17 α -Trihydroxyandrosta-5,9(11)-dien-17 β -carboxaldehyd-3,3-ethylenketal-17-trimethylsilyloxyether.

21. Verfahren nach einem der Ansprüche 1 bis 14, worin der geschützte Aldehyd (III) entsprechend einem der Ansprüche 15 bis 20 definiert ist.



Revendications

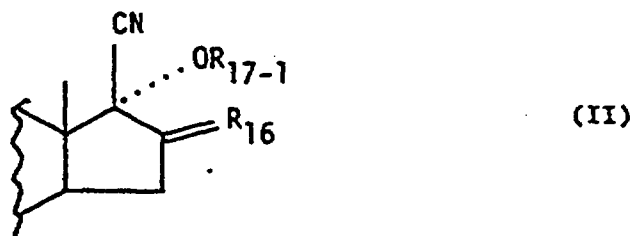
1. Procédé de production d'un aldéhyde protégé de formule (III)



dans laquelle R_{16} est un groupe $\alpha-R_{16-1}:\beta-R_{16-2}$ où l'un de R_{16-1} et R_{16-2} représente -H et l'autre représente -H, $-\text{CH}_3$ ou $-\text{OH}$;

R_{17-1} est un groupe $-\text{Si}-(R_{17-2})_2(R_{17-3})$ où R_{17-2} et R_{17-3} sont des groupes alkyle en C_1 à C_4 ou phényle, et qui consiste

- (1) à faire entrer une cyanhydrine protégée de formule (II)

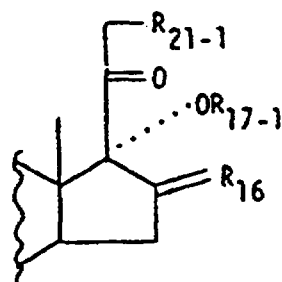


dans laquelle R_{16} et R_{17-1} sont tels que définis ci-dessus, en contact avec au moins un équivalent d'hydrure d'un agent réducteur en présence d'un éther et

(2) à hydrolyser le mélange réactionnel de l'étape (1).

2. Procédé suivant la revendication 1, dans lequel l'agent réducteur est un hydrure d'aluminium.
3. Procédé suivant la revendication 1, dans lequel l'agent réducteur est choisi entre l'hydrure de diisobutylaluminium, l'hydrure de lithium et d'aluminium, l'hydrure de sodium et de bis(2-méthoxyéthoxy)aluminium et l'hydrure de lithium et de tri-tertiobutoxyaluminium.
4. Procédé suivant la revendication 1, dans lequel l'agent réducteur est l'hydrure de diisobutylaluminium.
5. Procédé suivant l'une quelconque des revendications précédentes, dans lequel on utilise 1,2 à 2,0 équivalents d'agent réducteur.
6. Procédé suivant l'une quelconque des revendications précédentes, dans lequel l'éther est choisi entre le tétrahydrofurane, l'éther, l'éther de méthyle et de tertibutyle et des mélanges de ces éthers.
7. Procédé suivant l'une quelconque des revendications précédentes, dans lequel l'hydrolyse est conduite avec un acide aqueux.
8. Procédé suivant la revendication 7, dans lequel l'acide est un acide carboxylique.
9. Procédé de production d'un 21-halogéno-stéroïde protégé de formule (IV)





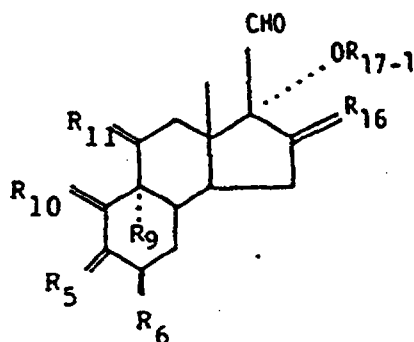
(IV)

dans laquelle R_{16} et R_{17-1} sont tels que définis dans la revendication 1 ; et

R_{21-1} représente Cl ou Br ;

qui consiste à faire entrer un aldéhyde protégé de formule III tel que défini dans la revendication 1 en contact avec un amide de formule Métal-N-(R_1)₂ où Métal désigne le lithium, le sodium, le potassium ou le magnésium et R_1 représente H, un groupe alkyle en C₁ à C₆ ou -Si(R_2)₃ où R_2 est un groupe alkyle en C₁ à C₆, en présence d'un composé de formule CH₂(R_{21-1})₂ dans laquelle R_{21-1} est tel que défini ci-dessus.

10. Procédé suivant la revendication 9, dans lequel l'amide est choisi entre le diisopropylamidure de lithium, le diéthylamidure de lithium, le dérivé de lithium du pipéridine et le dicyclohexylamidure de lithium.
11. Procédé suivant la revendication 9, dans lequel l'amidure est le diisopropylamidure de lithium.
12. Procédé suivant l'une quelconque des revendications 9 à 11, dans lequel on utilise moins de 3 équivalents de la base forte.
13. Procédé suivant l'une quelconque des revendications 9 à 12, dans lequel R_{21-1} représente Br.
14. Procédé suivant l'une quelconque des revendications 9 à 13, qui comprend l'étape préalable de préparation de l'aldéhyde protégé (III) par le procédé suivant l'une quelconque des revendications 1 à 8.
15. Aldéhyde protégé de formule



(III)

dans laquelle R_{16} et R_{17-1} sont tels que définis dans la revendication 1 ;

(A-I) R_5 représente $R_{5-1}:R_{5-2}$, R_6 représente $R_{6-1}:R_{6-2}$ et R_{10} représente $\alpha-R_{10-1}:\beta-CH_3$, où l'un de R_{5-1} et R_{5-2} représente H, F, Cl, Br ou CH_3 et l'autre, conjointement avec l'un de R_{5-1} et R_{5-2} , forme une seconde liaison entre les atomes C₅ et C₆, et R_{10-1} et l'autre de R_{5-1} et R_{5-2} , pris conjointement, représentent un groupe -CH₂-CH₂-C(R_{3-1})=CH- ou -CH=CH-C(R_{3-1})=CH- où R_{3-1} est un groupe alkyloxy en C₁ à C₆, -O- ϕ où ϕ est facultativement substitué avec un radical alkyle en C₁ à C₄ ou -N(R_{3-2})(R_{3-3}) où R_{3-2} est un radical alkyle en C₁ à C₃ et R_{3-3} est un radical alkyle en C₁ à C₃ ou ϕ , ou bien les groupes R_{3-2} et R_{3-3} sont cyclisés pour former un noyau hétérocyclique choisi entre les noyaux de pyrrolidine, pipéridine, morpholine et pipérazine ; ou

(A-II) R_5 est un groupe $R_{5-3}:R_{5-4}$, R_6 est un groupe $R_{6-3}:R_{6-4}$ et R_{10} est un groupe $\alpha-R_{10-3}:\beta-CH_3$, où l'un de R_{5-3} et R_{5-4} représente H, F, Cl, Br ou CH_3 et l'autre, pris conjointement avec l'un de R_{5-3} et



- R_{5-4} , forme une seconde liaison entre les atomes C_5 et C_6 , et R_{10-3} et l'autre de R_{5-3} , et R_{5-4} , pris conjointement, forment un groupe $-CH_2-CH_2-C(\alpha-R_{3-3})(\beta-R_{3-4})-CH_2-$ où l'un de R_{3-3} et R_{3-4} représente H et l'autre représente OH ou un groupe OR_{3-5} dans lequel R_{3-5} représente un radical alkyle en C_1 à C_6 , $-CH_2-\phi$ ou $-Si(R_{3-7})_2(R_{3-8})$ où R_{3-7} et R_{3-8} représentent un groupe alkyle en C_1 à C_4 ou ϕ ,
 5 ou bien R_{3-3} et R_{3-4} pris conjointement forment un groupe $-O-CH_2-C(CH_3)_2-CH_2-O-$ ou $-O-(CH_2)_{n1}-O-$ où n_1 a la valeur 2 ou 3 ; et
 (C-I) R_{11} est un groupe $R_{11-1}:R_{11-2}$ dans lequel l'un de R_{11-1} et R_{11-2} pris conjointement avec R_9 forme une seconde liaison entre les atomes C_9 et C_{11} et l'autre représente H ;
 10 (C-II) R_{11} est un groupe $\alpha-H:\beta-O-$, où $\beta-O-$ forme conjointement avec R_9 un β -époxyde entre les atomes C_9 et C_{11} ; ou bien
 (C-III) R_9 représente H et R_{11} est un groupe $-O-CH_2-C(CH_3)_2-CH_2-O-$, $-O-(CH_2)_{n2}-O-$ où n_2 a la valeur 2 ou 3, ou bien $\alpha-R_{11-3}:\beta-R_{11-4}$ où l'un de R_{11-3} et R_{11-4} représente H et l'autre représente H, OH ou un groupe OR_{11-5} dans lequel R_{11-5} est un radical alkyle en C_1 à C_6 , $-CH_2-\phi$ ou
 15 $-Si-(R_{11-6})_2(R_{11-7})$ où R_{11-6} et R_{11-7} représentent un radical alkyle en C_1 à C_4 ou ϕ .
16. Aldéhyde protégé suivant la revendication 15, dans lequel R_{17-1} est le groupe triméthylsilyle.
17. Aldéhyde protégé suivant la revendication 15 ou la revendication 16, dans lequel
 20 (A-I) l'un des groupes R_{5-1} et R_{5-2} en question représente H et R_{10-1} et l'autre des groupes R_{5-1} et R_{5-2} forment, conjointement, un groupe $-CH_2-CH_2-C(R_{3-1})=CH-$ où R_{3-1} est un groupe alkyloxy en C_1 à C_6 ou $-O-\phi$, où ϕ est facultativement substitué avec un radical alkyle en C_1 à C_4 ; ou bien
 (A-II) l'un de R_{5-3} et R_{5-4} représente H, et R_{3-3} et R_{3-4} sont considérés ensemble.
18. Aldéhyde protégé suivant l'une quelconque des revendications 15 à 17, dans lequel R_{11} est un groupe
 25 $R_{11-1}:R_{11-2}$ ou H:H.
19. Aldéhyde protégé suivant l'une quelconque des revendications 15 à 18, dans lequel R_{16} représente H:H.
20. Aldéhyde protégé suivant la revendication 15, qui est
 30 le 17-triméthylsilyloxy-diéther 3-méthylque de 3,17 α -dihydroxyandrost-3,5,9(11)-triène-17 β -carboxaldéhyde,
 le 17-triméthylsilyloxyéther du 3,3-éthylènecétal de 3,3,17 α -trihydroxyandrost-5-ène-17 β -carboxaldéhyde ou
 35 le 17-triméthylsilyloxyéther du 3,3-éthylènecétal de 3,3,17 α -trihydroxyandrost-5,9(11)diène-17 β -carboxaldéhyde.
21. Procédé suivant l'une quelconque des revendications 1 à 14, dans lequel l'aldéhyde protégé (III) est tel que défini dans l'une quelconque des revendications 15 à 20.

