Synthesis of 13α-Steroids. A New Route to 16-Substituted 13α-Androstanes

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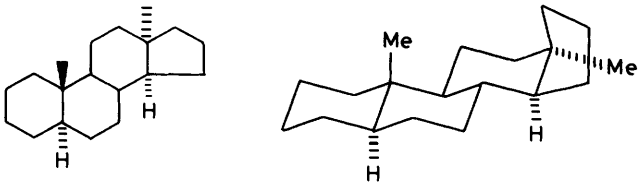
1,4-Addition of MeMgI on D-homo-18-norandrost-13(17a)-en-17-one (**3**) yields stereospecifically D-homo-13α-androstan-17-one (**4**). Ring-D contraction leads to a compound having a 13α-androstane skeleton: the Favorskii rearrangement of bromo ketone (**9**) yields 13α-androstane-16α- and 16β-carboxylic acids (**8**) and (**14**). Ketone (**4**) is oxidized by Tl^{III} to (**8**). The transformation of these carboxylic acids into methyl ketones, alcohols, and, finally, 13α-androstan-16-one is described.

Steroids having the 13α-androstane skeleton (**1**), characterized by a *cis* junction of the C- and D-ring and by an equatorial stereochemistry of the C-18 angular methyl group with regard to the C-ring, were first described in 1941 by Butenandt.[1,2] They were obtained by photochemical epimerization of the natural 17-keto steroids.



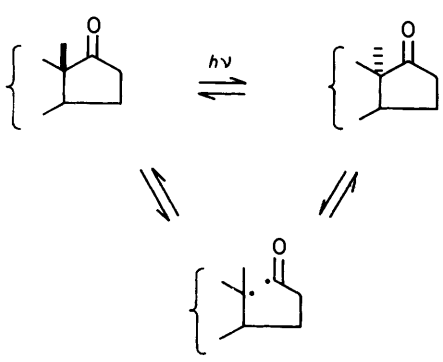
(**1**)

This skeleton does not occur in natural steroids, and the absence of biological activity of the first synthetic compounds[1,2] probably accounts for the fact that only a small number of compounds in this series have been described up to now.

The important work of Nambara *et al.*[3] has, nevertheless, shown that certain derivatives possess biological activity. Furthermore, these steroids having an unusual skeleton can constitute a convenient model for conformational analysis or reaction mechanism studies.[4]

Three routes to the 13α-steroids have been reported in the literature:

(1) Homolysis of the C-13, C-14 bond (Norrish type-I fragmentation[5]) and epimerization at C-13, being induced by photochemical irradiation of 17-keto steroids. This reversible reaction[6] affords an equilibrium mixture in which the 13α-derivative is favoured relative to the 13β-derivative (ratio 2:1) (Scheme 1).



Scheme 1.

There are obvious disadvantages to this synthetic method: the separation of the two isomers is often laborious and the yields are poor. The photoequilibration is also limited to 17-keto steroid derivatives.

(2) The epimerization of 5α,13β,17β-pregnane-3,20-dione into 5α,13α,17α-pregnane-3,20-dione (67%), in hyperacidic media, permits direct access to steroids of the 13α-series having a side chain.[7a,b]

(3) Finally, the oxime of a 17-keto steroid, treated with acetic anhydride and pyridine, affords in two steps 13α-androstan-17-one[7c] by epimerization of the C-13 carbon.

We have looked for a method for synthesizing 13α-steroids based on stereospecific introduction of the C-18 angular methyl in 18-norsteroids.

Specific introduction of an angular methyl with a *cis* junction[8] can be achieved by 1,4-addition of methylmagnesium iodide, catalysed by $Cu(OAc)_2$ (in fact cuprate addition), to an α,β ethylenic ketone (enone) such as (**2**). This stereospecificity has been confirmed in many cases.[9–11]

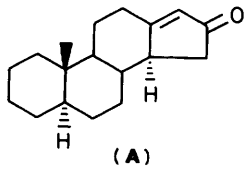
Moreover, type-(**3**) D-homo-18-norsteroids are relatively accessible.[12,13] The previous reaction, applied to such a compound, must afford a D-homoandrostan-17-one for which many methods exist for subsequent ring contraction,[14,15] giving products with differing functionality in the D ring (Scheme 2).†

We now report the synthesis of D-homo-13α-androstan-17-one and the employment of two methods for D-ring contraction which leads to various 13α-androstane derivatives.

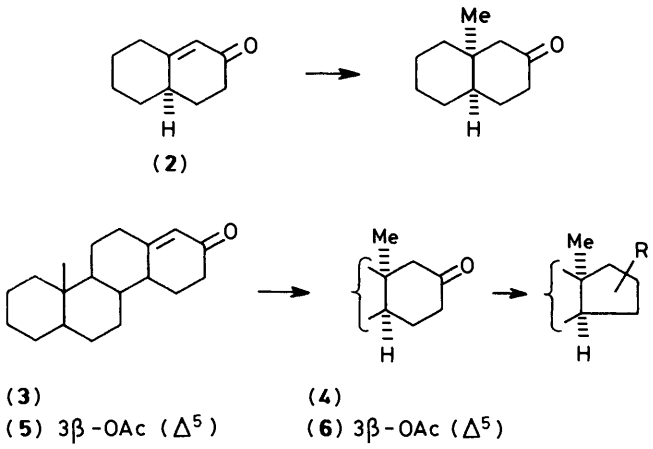
The enone (**5**),[12b] treated with methylmagnesium bromide in tetrahydrofuran in the presence of copper(II) acetate, afforded the saturated 13α-ketone (**6**) (83%).

The 13α-stereochemistry of the new asymmetric centre was established by circular dichroism (c.d.) and nuclear magnetic resonance: the positive c.d. ($\lambda_{max.}$ 293 nm, $\Delta\varepsilon$ +0.36) of ketone (**6**) was only consistent with a *cis* junction of the C- and D-ring. The 'octant' diagram shows that a *trans* junction would produce a negative c.d. In the ^1H n.m.r. spectrum (60 MHz), the C-18 methyl protons in (**6**) resonated at δ 0.95. In the case of a *trans* C/D junction, the chemical shift of the C-18 methyl protons was estimated to be at δ 0.72 according to the Zürcher and the

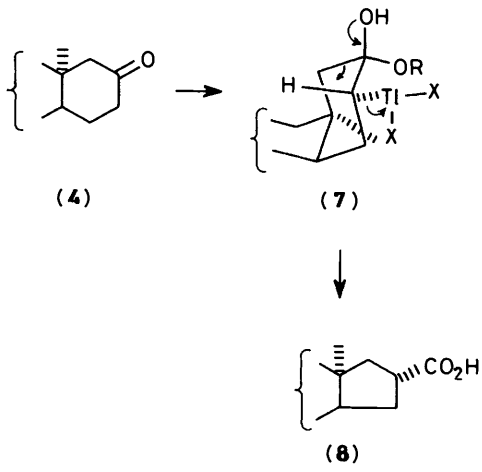
† It may be possible to apply the same reaction to an enone such as (**A**). However, the synthesis of such a compound is difficult and would afford a 16-keto steroid, this having fewer synthetic possibilities than a ketone of the D-homo series.



(**A**)



Scheme 2.



Scheme 3.

equivalent positions rules.[16,17] Finally the C-18 methyl protons chemical shift, measured in benzene, was at δ 0.77, from which a solvent effect $\Delta^{CDCl_3}_{C_6H_6}$ 0.18 p.p.m. coroborates the β and axial position of the angular methyl with regard to the carbonyl group.[18]

In the same conditions, the enone (**3**)[13] afforded D-homo-13α-androstan-17-one (**4**); the stereochemistry of compound (**4**) was confirmed by physical characteristics [especially c.d.: $\lambda_{max.}$ 289 nm, Δε +0.36; δ_H ($CDCl_3$) 0.92, 18-H_3].

Contraction of the D-*Ring of* D-*Homo-13α-androstan-17-one* (**4**).—Two methods for the D-ring contraction of D-homo-13α-androstan-17-one were studied on the monofunctional model (**4**). By each of these methods a cyclopentane D-ring is produced, substituted by a carboxylic acid function.

(1) *Oxidation of ketone* (**4**) *with thallium*(III) *salts.* Oxidation of cyclic olefins with Tl^{III} salts afforded ring-contracted aldehydes.[19] By a similar reaction, a cyclohexanone leads, in acidic medium, to a cyclopentane carboxylic acid[20] (the enol is, in fact, oxidized). This reaction has been recently applied in steroidal series: cholestan-3-one affords stereoselectively A-nor-2α-cholestanecarboxylic acid.[21]

Treating ketone (**4**) with thallium triacetate in acetic acid afforded a complex mixture, the acidic fraction of which contained as its major component 13α-androstane-16α-carboxylic acid (**8**) (20% yield). The mixture did not contain the 16β-isomer.

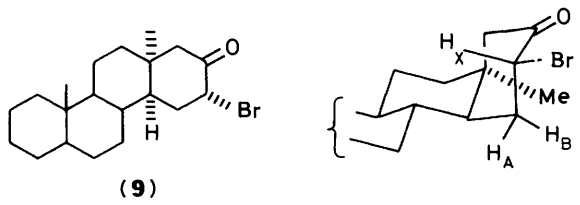
This acid is similar to one of those obtained by Favorskii rearrangement (*vide infra*), the structure of which was established independently.

The structure is in agreement with the proposed reaction mechanism: the thallium triacetate addition to the enol of (**4**) (probably Δ^{16}),* by the α face, ('convex' side of the molecule) would afford the intermediate (**7**), the stereochemistry of which is favourable for a pinacol-type rearrangement. It gave stereospecifically the acid (**8**) with reversed configuration at carbon 16 (Scheme 3).

(2) *Favorskii rearrangement.*

Rearrangement of bromocyclohexanones in basic medium leads to cyclopentanecarboxylic acids.[22] This reaction, applied to bromo ketones derived from 3-keto steroids, is known[15,23] to produce A-norsteroids. In the case of a D-homoandrostan-17-one one should observe formation of a five-membered D-ring.

Treatment of ketone (**4**) with trimethyl(phenyl)ammonium perbromide (PTT),[24] afforded 16α-bromo-D-homoandrostan-17-one (**9**). Its i.r. spectrum showed a signal at 1 730 cm^{-1}, characteristic of an equatorial bromocyclohexanone.[25]



Moreover, in the ^1H n.m.r. spectrum, the signal for the methine hydrogen on the bromine-substituted carbon appeared as a quadruplet at δ 4.63, corresponding to the X part of an ABX spectrum in which $J_{AX} + J_{BX} = 20$ Hz (H_A and H_B being the hydrogens at C-15). This value corresponded to the sum of the two constants J_{aa} and J_{ae}.[17] This provided strong evidence for the presence of bromine at C-16 (if it was at C-17, H_X would appear as a singlet), and for H_X to be axial (Br was equatorial). In the opposite case, $J_{AX} + J_{BX}$ would be ~ 10 Hz.

We know[26] that the Favorskii rearrangement is generally stereospecific in non-polar solvents, and non-stereospecific in polar solvents. In the case of a bromo ketone, in a non-polar solvent, we would expect, considering the stereochemistry of the bromine atom, to obtain the two acids (**8**) and (**10**). In a polar solvent, the formation of a dipolar intermediate[27] (which can precede or follow that of cyclopropanone) would lead to the loss of stereospecificity and the four acids (**8**), (**14**), (**10**), and (**11**) would be formed.

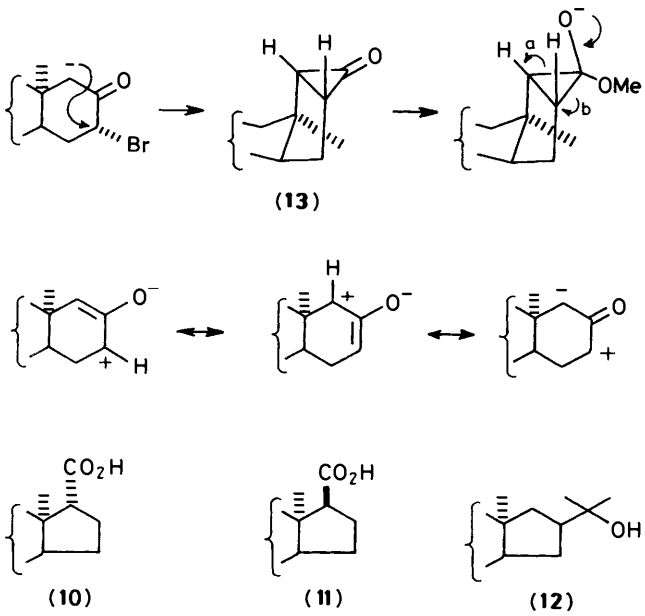
The yields are generally better when polar solvents are used. On the other hand, the determination of the stereochemistry of acids at C-16 and -17 should be made easier if pairs of epimers are to hand. Bromo ketone (**9**) was therefore treated by sodium methoxide in anhydrous methanol.

The separation of reaction products was difficult.† Repeated chromatography (silica gel columns) of the acidic fraction afforded 13α-androstane-16α-carboxylic acid (**8**) (21%) and 13α-androstane-16β-carboxylic acid (**14**) (21%).

The intermediate fractions contained several minor by-

* In neutral medium, (**4**) was brominated at C-16. In acidic medium, the major enol should also be Δ^{16}.

† Contrary to expectation the esters' separation was more difficult than for the acids. Nevertheless the R_F-values of the acids were very similar and the compounds were practically invisible on fluorescent silica gel sheets.



Scheme 4.

products, in addition to a mixture of the two acids (**8**) and (**14**). Considering these last fractions, the yield of C-16 epimeric acids was *ca.* 60%.

It was not possible, in spite of a systematic search, to show the presence of the C-17 acids (**10**) and (**11**), which were at best produced in trace amounts.

This result confirms the importance[28] of steric factors on the direction of opening unsymmetrical cyclopropanones in basic media; a half-benzylic mechanism being very unlikely in the case of bromo ketone (**9**),[29] the structure of the products obtained depends on the direction of opening of the cyclopropanone (**13**) (Scheme 4). The very important steric decompression which comes with opening of (**13**) according to path **a** (to give acids at C-16) by far dominates the electronic effects which would favour the opening according to path **b** (opening according to **a** leads to a neopentyl anion) and assures the regioselectivity of the reaction, affording exclusively acids at C-16.

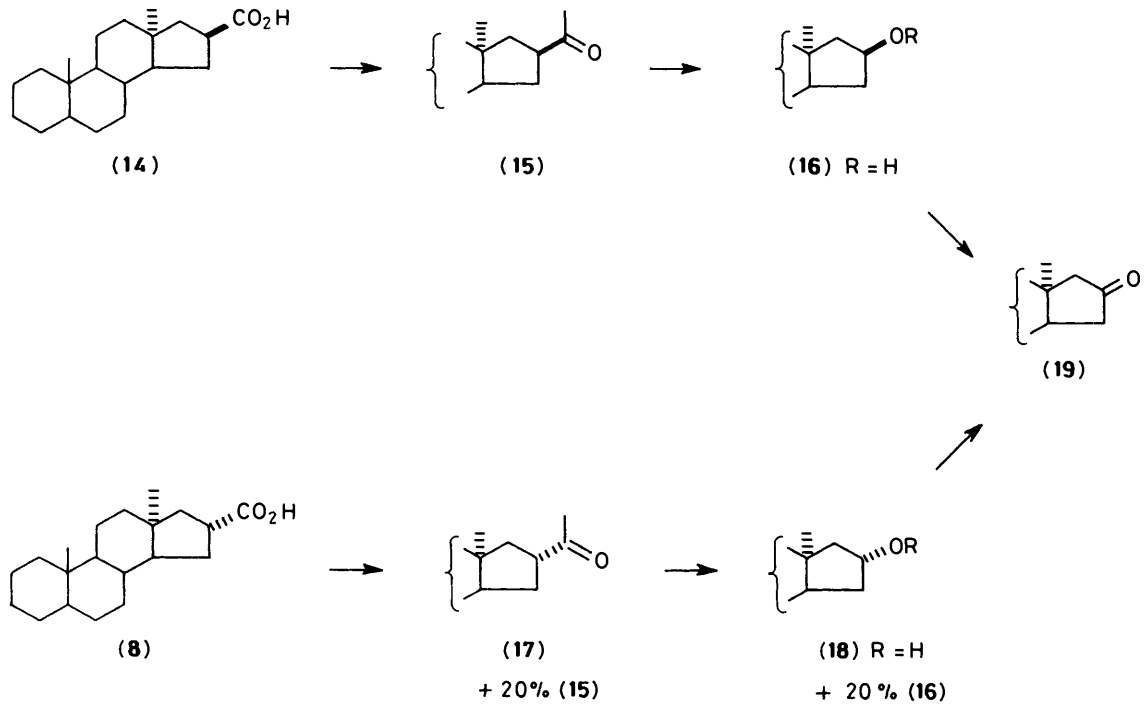
It was not possible, on the basis of physical and spectrometric characteristics, to assign to the two isolated acids (or to their methyl esters) a structure among the four possible ones (**8**), (**10**), (**11**), and (**14**).

The nature of the steroidal skeleton, the position (16 or 17) and the stereochemistry (α or β) of the CO_2H group had to be known. Thus the series of transformations acid ⟶ methyl ketone ⟶ acetate ⟶ alcohol ⟶ ketone (Scheme 5) was realized.

The CO_2H group position on the D-ring was the same as that of the carbonyl group (which can be at either C-16 or C-17) in the final ketone. The ketones were easily identified. The two isolated acids afforded 13α-androstan-16-one (**19**). They were therefore C-16 acids. On the other hand, their stereochemistry, easily established by n.m.r. spectroscopy, was that of the intermediary alcohol (**16**) or (**18**).

The reaction of methyl-lithium in anydrous benzene with acid (**14**)[30] afforded 16β-acetyl-13α-androstane (**15**) (70%) stereospecifically, and the tertiary alcohol (**12**) (Scheme 4) (25%). The equilibration (in basic medium) of ketone (**15**) gave a mixture of 16α- and 16β-epimeric ketones in an estimated (n.m.r.) 50:50 ratio (comparison of C-18 and C-19 angular methyl groups).

Independently of the latter evidence, they could not be 17α- and 17β-acetyl-13α-androstane: computed chemical shifts ($CDCl_3$) of the C-18 and C-19 methyl protons of 17α- and 17β-acetyl-13α-androstane could be made from data for compounds belonging to the 3β-OH, Δ^5 series described by Nambara[3d] or from derivatives described by Jacquesy *et al.*[7] It afforded values very different from those observed for (**15**) and (**17**). On the other hand, the equilibration of compounds acetylated at C-17



Scheme 5.

gave a 92:8 mixture in favour of the 17α-epimer,[3d] very far from the observed composition for (**15**) and (**17**).*

Methyl ketone (**15**), treated with *m*-chloroperbenzoic acid (MCPBA) in 1,2-dichlorethane and refluxed with sodium hydrogen carbonate afforded, with retention of configuration,[31] the 16β-acetate, which was saponified.

13α-Androstan-16β-ol (**16**) [60% from (**14**)] was obtained and its stereochemistry established by n.m.r. spectroscopy (see next section).

Oxidation of this alcohol with Jones' reagent afforded 13α-androstan-16-one (**19**). This compound possessed a band at 1 740 cm^{-1} (cyclopentanone) in the i.r. and a strong positive c.d. ($\lambda_{max.}$ 296 nm, $\Delta\varepsilon$ +2.71) in agreement with the 'octant' rule and comparable with that of the 3β-acetoxy derivative.[3b]

Moreover, the mass spectrum of its ethylene acetal presented two main fragments, *m/z* 139 and 247, characteristic of the fragmentation of 16-keto steroid ethylene acetals.[32]

Treatment of compound (**8**) with methyl-lithium in benzene afforded in ~55% yield a mixture of 16α- and 16β-acetyl-13α-androstane in 80:20 ratio in favour of the epimer (**17**) having the 16α stereochemistry.

Equilibration, in basic medium, gave a 50:50 mixture of the two epimers, identical with that obtained by equilibration of 16β-ketone (**15**) produced from acid (**14**). Acid (**8**) therefore corresponded to the C-16 epimer of (**14**).

Obtention of a 80:20 mixture of the two epimers (**17**) and (**15**) resulted from partial epimerization of epimer (**17**) during the extraction. The two methyl ketones were inseparable by column chromatography and the following reactions were done on the 80:20 mixture. N.m.r. determinations could doubtless have been obtained, the α isomer being the most abundant and the β isomer (**15**) being already obtained.

Baeyer–Villiger reaction gave, under previously described conditions and after saponification, an 80:20 mixture of 13α-androstan-16α- and -16β-ol (50% yield).

In the same way, a 1:1 mixture of the methyl ketones afforded the 16α- and 16β-alcohol in 1:1 ratio. The relationship acid ⟶ methyl ketone ⟶ alcohol was therefore unambiguous, 16α- and 16β-alcohols not having been separated. Finally, oxidation of the 80:20 mixture gave 13α-androstan-16-one (**19**).

Nuclear Magnetic Resonance.—Chemical shifts of C-18 and C-19 methyl protons in new compounds and Zürcher increments of the different functional groups are collected in Tables 1 and 2.

Stereochemistry determination of 13α-*androstan*-16α-*and*-16β-*ol.* 16α- and 16β-Stereochemistry were attributed to alcohols (**18**) and (**16**) respectively from the chemical-shift values of the methyl group and from the solvent-effect shift $\Delta^{CDCl_3}_{C_5H_5N}$ it underwent. The C-18 methyl protons in alcohol (**17**) were deshielded (0.23 p.p.m.), corresponding to a 1,3 *cis*-arrangement of methyl and OH groups in a five-membered ring: this value was very close to that observed (0.24 p.p.m.) for the C-18 methyl protons of 5α-androstan-16β-ol, in the normal series.[33]

There was no effect on the C-18 methyl protons of the 16β-alcohol, as in the case of the 16α-OH group in the normal series (0.01 p.p.m.).

On the other hand, solvent effects $\Delta^{CDCl_3}_{C_5H_5N}$ are known to be important for steroidal alcohols and to decrease rapidly on removal of the OH group and the observed angular methyl.[34]

The values, obtained for 16α- and 16β-epimers (corrected by the skeleton solvent effect,[34c] equal to 0.03 p.p.m. for the 13α-androstane C-18 methyl) were −0.19 and −0.03 p.p.m. respectively (see Table 1 and Figure).

* The examination of molecular models showed that this 1:1 composition is quite consistent with the steric hindrance, nearly equivalent, of the α and β faces of the D-ring.

Table 1. Chemical shifts (δ_H) of C-18 and C-19 methyl protons in the 13α-androstane series

	$CDCl_3$		C_6H_6		C_5H_5N	
Compounds	18-H_3	19-H_3	18-H_3	19-H_3	18-H_3	19-H_3
13α-Androstane (**1**)	0.87	0.71	0.93	0.71	0.90	0.70
16α-OH (**18**)	1.10	0.68			1.32	0.68
16β-OH (**16**)	0.87	0.73			0.93	0.68
16-Keto (**19**)	1.03	0.71	0.77	0.55		
16α-acetyl (**17**)	0.87	0.73	0.92	0.73		
16β-acetyl (**15**)	0.93	0.69	0.87	0.70		
16α-CO_2H (**8**)	0.97	0.72				
16β-CO_2H (**14**)	0.92	0.72				

Table 2. Zürcher increments in the 13α-androstane series, in $CDCl_3$ (p.p.m. and Hz at 60 MHz)

	18-H_3		19-H_3	
Substituents	p.p.m.	Hz (60 MHz)	p.p.m.	Hz (60 MHz)
13α-Androstane (**1**)	0.87	52.4	0.71	42.7
16α-OH (**18**)	0.23	14	−0.03	−1.5
16β-OH (**16**)	0	0	0.03	1.5
16-keto (**19**)	0.16	9.5	0	0
16α-acetyl (**17**)	0	0	0.02	1
16β-acetyl (**15**)	0.07	4	−0.03	−1.5
16α-CO_2H (**8**)	0.10	6	0	0
16β-CO_2H (**14**)	0.05	3	0	0

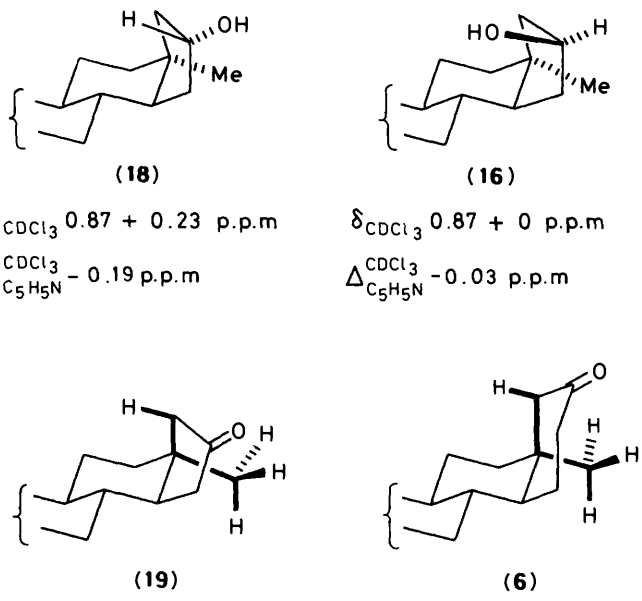


Figure.

This result established without ambiguity the stereochemistry of the two alcohols obtained from acids (**8**) and (**14**) and therefore the stereochemistry of the latter.

13α-*Androstan*-16-*one* (**19**). The carbonyl group at C-16 induced a strong solvent-effect shift $\Delta^{CDCl_3}_{C_6H_6}$ 0.32 p.p.m. on the C-18 methyl protons, in agreement with the empirical rule of Connolly and McCrindle.[35]

On the other hand, the C-18 angular methyl protons appeared as a doublet (^4J 0.8 Hz). Some examples of tertiary methyl undoubling, by long-distance coupling (in W with an axial hydrogen α to a carbonyl group) are found in the literature

(ref. 34*c* and cited refs). 3β-Acetoxy-D-homo-13α-androst-5-en-17-one (**6**) also showed the same effect (Figure).

This new access to 13α-steroids, based on stereospecific introduction of a 13α angular methyl on a D-homo-18-norandrost-13(17a)-en-17-one to obtain a D-homo-13α-androstan-17-one, was therefore attainable. Most of these 13α-steroids are indeed difficult to obtain by the equilibration methods described in the literature, which can be applied only to compounds functionalized at C-17.

Experimental

M.p.s were determined using a Reichert hot-stage micro apparatus and are uncorrected. I.r. spectra were run in CCl_4 and CS_2 on a Perkin-Elmer 377 spectrophotometer. Optical rotations were measured in 1,4-dioxane on a Perkin-Elmer 141 polarimeter. C.d. curves were determined in ethanol (except where otherwise indicated) on a Roussel-Jouan dichrograph.* Mass spectra were recorded on a Varian CH5 spectrometer,† using electron-impact ionization (70 eV). Analyses were performed by the Microanalysis Service of the CNRS. ^1H N.m.r. spectra were recorded on Jeol C 60H and Perkin-Elmer R-24 spectrometers. Chemical shifts are reported in p.p.m. relative to tetramethylsilane as internal reference.‡

D-*Homo*-13α-*androstan*-17-*one* (**4**).—A solution of methylmagnesium iodide was prepared from magnesium (1.8 g) and iodomethane (4.8 ml) in ether (60 ml). The solution was cooled to −8 °C, and a solution of the ketone (**3**)[13] (1.8 g) and copper(II) acetate (600 mg) in THF (40 ml) was added dropwise. The resulting mixture was stirred at room temperature for 2 h, refluxed for 3 h, hydrolysed with aqueous ammonium chloride, and extracted with ether. The combined extracts were dried (Na_2SO_4) and evaporated. Silica gel column chromatography afforded the *saturated ketone* (**4**) (1 g, 50%), m.p. 131—133 °C (recrystallized three times from aqueous MeOH) (Found: C, 83.0; H, 11.4. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%); $\nu_{max.}(CCl_4)$ 1 720 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.92 (3 H, s, 18-H_3) and 0.78 (3 H, s, 19-H_3); $\lambda_{max.}(\Delta\varepsilon)$ 289 nm (+0.36); Λ 33 nm (*c* 0.360 in EtOH).

3β-*Acetoxy*-D-*homo*-13α-*androst*-5-*en*-17-*one* (**6**).—In analogous conditions, the ketone (**5**)[12] (3 g) and the Grignard reagent prepared from magnesium (4.5 g) and iodomethane (28 g, 12.3 ml) gave a crude product (3 g), which was reacetylated at C-3β [Ac_2O (7 ml), pyridine (30 ml), 24 h, room temperature]. Preparative t.l.c. on alumina sheets afforded the *saturated ketone* (**6**) (2.5 g, 85%), m.p. 129—130 °C (recrystallized three times from ether–pentane) (Found: C, 76.9; H, 9.3. $C_{22}H_{32}O_3$ requires C, 76.70; H, 9.36%); $\nu_{max.}(CCl_4)$ 1 715 (cyclohexanone) and 1 740 cm^{-1} (acetate); $[\alpha]_D^{20}$ −106° (*c* 0.721 in dioxane); $\lambda_{max.}(\Delta\varepsilon)$ 260 (0.07), 293 (0.36), and 323 nm; Λ 38 nm (*c* 1.03 in dioxane); $\delta_H(CDCl_3)$ 0.95 (3 H, d, *J* 0.7 Hz, 18-H_3), 1.04 (3 H, s, 19-H_3), 4.58 (1 H, m, 3α-H), and 5.38 (1 H, m, 6-H); $\delta_H(C_6H_6)$ 0.77 (3 H, d, *J* 0.8 Hz, 18-H_3) and 0.81 (3 H, s, 10-Me).

13α-*Androstane*-16α-*carboxylic Acid* (**8**) *by Action of Thallium Triacetate on Compound* (**4**).—A solution of D-homo-13α-androstan-17-one (**4**) (600 mg) and thallium triacetate ·15H_2O (5 g) in acetic acid (20 ml) was stirred at 80 °C for 2 h. After cooling, the reaction mixture was diluted with water (150 ml) and extracted with ether. The combined extracts were dried (Na_2SO_4) and evaporated. The crude product was methylated with diazomethane. Chromatography (silica gel column) of the product of three identical reactions afforded the uncrystallized methyl ester of acid (**8**) (370 mg, 56%); $\nu_{max.}(CCl_4)$ 1 735 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.70 (3 H, s, 19-H_3), 0.97 (3 H, s, 18-H_3), and 3.65 (3 H, s, CO_2Me). Saponification of this ester with 5% methanolic KOH gave the 16α-*carboxylic acid* (**8**) (130 mg, 37%), m.p. 176—179 °C (recrystallized three times from ether–pentane) (Found: C, 78.6; H, 10.6. $C_{20}H_{32}O_2$ requires C, 78.89; H, 10.59%); $\nu_{max.}(CCl_4)$ 1 755 cm^{-1} (C=O); $\delta_H(CDCl_3)$ (Table 1).

16α-*Bromo*-D-*homo*-13α-*androstan*-17-*one* (**9**).—PTT (4.5 g) was added to a solution of D-homo-13α-androstan-17-one (**4**) (3 g) in anhydrous THF (250 ml). The mixture was kept for 75 min at room temperature, poured into 5% aqueous $NaHCO_3$ (600 ml) and extracted (ether), and the extracts were dried (Na_2SO_4) and evaporated to give crude product (**9**) (3.2 g, 84%), m.p. 172—174 °C (recrystallized three times from aqueous MeOH) (Found: C, 65.3; H, 8.7. $C_{20}H_{31}BrO$ requires C, 65.39; H, 8.50%); $\nu_{max.}(CCl_4)$ 1 730 cm^{-1} (C=O); $[\alpha]_D^{20}$ +12° (*c* 0.420 in dioxane); $\lambda_{max.}(\Delta\varepsilon)$ 293 nm (0.67); Λ 36 nm (*c* 0.568 in EtOH); $\delta_H(CDCl_3)$ 0.95 (3 H, s, 18-H_3) and 4.63 (1 H, q, $J_{AX} + J_{BX}$ 20 Hz, 16-H).

Favorskii Rearrangement of Bromo Ketone (**9**).—A solution of bromo ketone (**9**) (3.2 g) in 2M-sodium methoxide in anhydrous methanol (270 ml) was stirred for 15 h at room temperature. Water (100 ml) was added. The mixture was refluxed for 1 h, acidified with 1M-H_2SO_4, and extracted with ether, and the extract was dried (Na_2SO_4) and evaporated. The crude product (3 g), after repeated chromatography on a silica gel column, monitored by n.m.r. spectroscopy and t.l.c., yielded 16β-acid (**14**) (550 mg, 21%), 16α-acid (**8**) (550 mg, 21%), and fractions consisting of either minor products or mixtures of these two acids.

13α-*Androstane*-16β-*carboxylic acid* (**14**). The analytical sample was recrystallized three times from ether–pentane (long needles), m.p. 150—153 °C (Found: C, 78.7; H, 10.7. $C_{20}H_{32}O_2$ requires C, 78.89; H, 10.59%); $\nu_{max.}(CCl_4)$ 1 750 and 1 705 cm^{-1} (C=O monomer and dimer); $[\alpha]_D^{20}$ −47° (*c* 0.205 in dioxane); $\delta_H(CDCl_3)$ (Table 1).

13α-*Androstane*-16α-*carboxylic acid* (**8**). The analytical sample was recrystallized three times from ether–pentane, m.p. 177—179 °C; mixed m.p. 176—179 °C [with the acid obtained by oxidation of ketone (**4**) with thallium triacetate] (Found: C, 78.7; H, 10.6%); $\nu_{max.}$ and δ_H identical with those of this acid; $[\alpha]_D^{20}$ −49° (*c* 0.213 in dioxane).

16β-*Acetyl*-13α-*androstane* (**15**).—A solution of methyllithium in ether (1 ml) was added to a solution of the 16β-acid (**14**) (220 mg) in anhydrous benzene (25 ml). The mixture was stirred for 1 h at room temperature, poured into water, and extracted with ether, and the extract was washed (water), dried (Na_2SO_4), and evaporated. The residue (220 mg), purified by silica gel column chromatography, afforded 16β-*acetyl*-13α-*androstane* (**15**) (150 mg, 70%), m.p. 70—72 °C (recrystallized three times from ether–hexane) (Found: C, 83.2; H, 11.5. $C_{21}H_{34}O$ requires C, 83.38; H, 11.33%); $\nu_{max.}(CCl_4)$ 1 720 cm^{-1} (C=O); $[\alpha]_D^{20}$ −55.5° (*c* 0.293 in dioxane); $\lambda_{max.}(\Delta\varepsilon)$ 227 nm (+0.24); Λ 28 nm (*c* 0.153 in EtOH); $\delta_H(CDCl_3)$ 2.15 (3 H, s, COMe); $\delta_H(C_6H_6)$ 1.78 (3 H, s, COMe); see also Table 1.

The structure (**12**) was assigned to the tertiary alcohol (60 mg, 25%) which was then eluted; $\nu_{max.}(CCl_4)$ 3 625 cm^{-1} (OH); $\delta_H(CDCl_3)$ 0.95 (3 H, s, 18-H_3), 0.73 (3 H, s, 19-H_3), and 1.32 (6 H, s, CMe_2); *m/z* 318 (M^+).

16α-*Acetyl*-13α-*androstane* (**17**).—In the same conditions, 16α-acid (**8**) (70 mg) gave, after chromatography, an 80:20

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mixture (established by n.m.r.) of 16α-methyl ketone (**17**) and 16β-methyl ketone (**15**) (38 mg, 55%), and a tertiary alcohol mixture. Separation of the two methyl ketones was found to be impossible. In spite of several attempts, ketone (**17**) could not be obtained without being contaminated with (**15**), the 16α-ketone being epimerized very rapidly when extracted. For (**17**), $\nu_{max.}(CCl_4)$ 1 720 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.17 (3 H, s, COMe); see also Table 1.

Equilibration of Ketones (**15**) *and* (**17**).—The 80:20 mixture (65 mg) was refluxed for 15 min in 2% methanolic NaOH (6 ml). The reaction mixture was poured into water, and extracted with ether, and the extract was dried (Na_2SO_4) and evaporated. A 50:50 mixture (evaluated by n.m.r. spectroscopy on the well separated signals of the C-18 and C-19 protons) was obtained (60 mg, 92%).

In the same conditions, the 16β-methyl ketone (**15**) (20 mg) afforded an identical mixture (20 mg, quantitative yield).

13α-*Androstan*-16β-*ol* (**16**).—A solution of 16β-acetyl-13α-androstane (**15**) (145 mg), $NaHCO_3$ (450 mg), and MCPBA (540 mg) in 1,2-dichlorethane (50 ml), was refluxed for 12 h. The mixture was poured into water, and extracted with CH_2Cl_2, and the extract was washed (aq. K_2CO_3), dried (Na_2SO_4), and evaporated. 16β-Acetoxy-13α-androstane (**16**; R = Ac) (140 mg, 92%), $\delta_H(CDCl_3)$ 0.88 (3 H, s, 18-H_3), 0.73 (3 H, s, 19-H_3), and 2.0 (3 H, s, OAc), was obtained.

This ester (65 mg) was saponified by refluxing for 1 h with NaOH (500 mg) and water (1 ml) in MeOH (10 ml). The mixture was poured into water, acidified with dil. HCl, and extracted with ether, and the extract was washed (aq. K_2CO_3), dried (Na_2SO_4), and evaporated. Silica gel chromatography of the crude product (60 mg) afforded uncrystallized 13α-androstan-16β-ol (**16**; R=H) (30 mg, 51%); $\nu_{max.}(CCl_4)$ 3 620 cm^{-1} (OH); $[\alpha]_D^{20}$ −27° (*c* 0.295 in dioxane); $\delta_H(CDCl_3$ and $C_5H_5N)$ 4.50 (1 H, m, 16-H); see also Table 1; *m/z* 276 (M^+, 5%), 261 (1), 258 (14), 243 (43), and 217 (100).

13α-*Androstan*-16α-*ol* (**18**).—16α-Acetyl-13α-androstane (**17**) and 16β-acetyl-13α-androstane (**15**) (80:20 mixture; 60 mg), submitted to the same sequence of reactions (Baeyer–Villiger and saponification), yielded a 80:20 mixture of 13α-androstan-16α-ol (**18**; R=H) and 13α-androstan-16β-ol (**16**; R=H) (33 mg, 60%). These two compounds were not separable. I.r., n.m.r., and mass spectra showed compounds (**16**) and (**18**) to be isomers at C-16: $\nu_{max.}(CCl_4)$ 3 620 cm^{-1} (OH); $[\alpha]_D^{20}$ −22° (*c* 0.322 in dioxane) for the mixture: this value permitted us to estimate $[\alpha]_D^{20}$ −20° for pure (**18**); $\delta_H(CDCl_3$ and $C_5H_5N)$ 4.45 (1 H, m, 16-H); see also Table 1; *m/z* 276 (M^+, 23%), 261 (9), 258 (26), 243 (83), and 217 (100).

In the same way, the 50:50 mixture of methyl ketones (**15**) and (**17**) (resulting from their equilibration) (60 mg) afforded a 50:50 mixture of alcohols (**16**) and (**18**) (33 mg, 60% yield).

13α-*Androstan*-16-*one* (**19**).—13α-Androstan-16β-ol (**16**) (30 mg) dissolved in acetone (5 ml) was oxidized with 4M Jones' reagent (0.1 ml) (3 min at room temperature). The reaction mixture was poured into water, and extracted with ether, and the extract was dried (Na_2SO_4) and evaporated. 13α-Androstan-16-one (**19**) (not crystallized) was obtained (30 mg, quantitative yield), $\nu_{max.}(CCl_4)$ 1 740 cm^{-1} (C=O); $[\alpha]_D^{20}$ +73° (*c* 0.234 in dioxane); $\lambda_{max.}(\Delta\varepsilon)$ 296 nm (+2.71); Λ 37 nm (*c* 0.616 in EtOH); $\delta_H(CDCl_3$ and $C_6H_6)$ see Table 1.

The same reaction performed on the one hand on the 80:20 mixture of 13α-androstan-16α-ol (**18**) and -16β-ol (**16**) (20 mg) and on the other hand on the 50:50 mixture [from (**15**) ⇌ (**17**) equilibration] yielded 13α-androstan-16-one (**19**) as the only product, which was confirmed by t.l.c. and i.r., n.m.r. spectroscopy. The mass spectrum of 16, 16-ethylenedioxy-13α-androstane [prepared from 13α-androstan-16-one (**19**) (30 mg), ethyleneglycol (0.5 ml), toluene-*p*-sulphonic acid (10 mg), and benzene (5 ml) under reflux for 36 h with water separator] showed *m/z* 318 (M^+, 3%), 303 (2), 247 (2), 162 (100), and 139 (12).

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