Facial selectivity in the hydroboration of androst-4-enes

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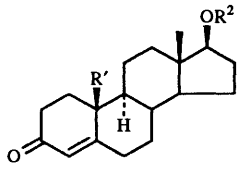
In the absence of an allylic hydroxy group, the stereochemistry of hydroboration of an androst-4-ene is determined by the presence and stereochemistry of the C-10 methyl group. Allylic hydroxy groups at C-3 direct the hydroboration/oxidation to the *anti*-face. In the case of the 3α-alcohol, this effect is in opposition to the normal hydration from the α-face of the steroid and leads to the 4β-alcohol. The stereochemistry of 4β,17β-diacetoxy-19-nor-5β-androstane was established by X-ray crystallography.

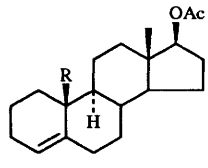
The hydration of alkenes by hydroboration and the subsequent oxidation of the borane with alkaline hydrogen peroxide, is a widely used synthetic reaction.[1] The hydration of an isolated steroidal alkene is reported[2] to proceed in an anti-Markownikoff sense from the α-face of the molecule. Although 19-nor steroids were not studied, the facial selectivity was attributed to steric hindrance on the β-face of the molecule by the angular methyl group. In smaller molecules an allylic hydroxy group has also been shown to affect the facial selectivity of the hydroboration of an alkene. Thus, the hydroboration of cyclohex-2-enols leads to the *trans*-1,2-diols.[3,4] The use of hydroboration in the synthesis of steroidal glycols requires an evaluation of the balance between the effect of the 10-methyl group and an allylic hydroxy group in determining the facial selectivity of the addition. In this paper we report on the facial selectivity of the hydroboration of the trisubstituted 4-enes, 17β-acetoxyandrost-4-ene **5**, 17β-acetoxy-19-norandrost-4-ene **6** and the retro-steroid, 17β-acetoxy-9β,10α-androst-4-ene **8** and of the effect of the pseudo-axial and equatorial 3α- and 3β-hydroxy groups on the stereochemistry of the reaction. In prior work the hydroboration and oxidation of cholest-4-ene has been reported[2] to give exclusively 5α-cholestan-4α-ol. The hydroboration of testosterone **1** gave 5α-androstane-3β,4α,17β-triol **13**.[5] The reduction of testosterone acetate under Cagliotti conditions (B_2H_6, Ac_2O) has been examined[6,7] thoroughly to optimize the conditions for preparing 17β-acetoxy-5α-androst-3-ene.

The alkenes were prepared as follows. 17β-Acetoxyandrost-4-ene **5**, free from isomeric 3-enes, was best obtained[8] by reduction of testosterone acetate **2** with sodium borohydride in trifluoroacetic acid–acetonitrile–acetic acid–methylene dichloride. 17β-Acetoxy-19-norandrost-4-ene **6** and the retro-steroid, 17β-acetoxy-9β,10α-androst-4-ene **8** were prepared in a similar manner from 19-nortestosterone acetate **4** and retrotestosterone acetate **7**, respectively. 17β-Acetoxyandrost-4-en-3β-ol **9**[9] was obtained by the reduction of testosterone acetate **2** with sodium borohydride† in methanol. 19-Norandrost-4-ene-3β,17β-diol **10** was obtained in a similar manner from 19-nortestosterone **3**. Inversion of the 3β-hydroxy group to form 17β-acetoxyandrost-4-en-3α-ol **11** using the normal Mitsunobu procedure[10] was accompanied by elimination to form a mixture of dienes. The best yields were obtained by using triphenylphosphine–chloroacetic acid and ethyl azodicarboxylate.[11] Selective hydrolysis of the resultant 3α-chloroacetate under mild conditions with aqueous methanolic potassium carbonate then gave 17β-acetoxyandrost-4-en-3α-ol **11**.

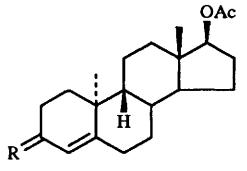
The hydration of the steroids was carried out by hydroboration with borane in tetrahydrofuran followed by oxidation with alkaline hydrogen peroxide. The results are given in Table 1. The structures of the products were established as follows. In contrast to the previous work with cholest-4-ene,[2] the hydroboration and oxidation of 17β-acetoxyandrost-4-ene **5** gave both 5α-androstane-4α,17β-diol **12** and 5β-androstane-4β,17β-diol **20**. Although the 4-H ^{1}H NMR resonances in each showed a similar multiplicity [δ_H 3.41, dt, J 4.6 and 10.8 Hz in **12**; δ_H 3.56, dt, J 4.6 and 10.8 Hz in **20**] arising from two diaxial and one axial:equatorial coupling, the epimers were distinguished by a nuclear Overhauser enhancement of 5% of the



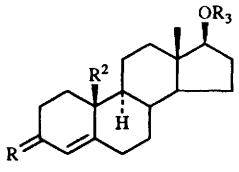
1 R^1 = Me, R^2 = H
2 R^1 = Me, R^2 = Ac
3 R^1 = R^2 = H
4 R^1 = H, R^2 = Ac



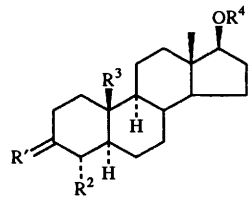
5 R = Me
6 R = H



7 R = O.
8 R = H_2.



9 R^1 = α-H, β-OH; R^2 = Me; R^3 = Ac
10 R^1 = α-H, β-OH; R^2 = R^3 = H
11 R^1 = α-H, β-H; R^2 = Me; R^3 = Ac

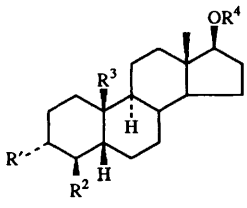


12 R^1 = H_2; R^2 = OH; R^3 = Me; R^4 = H
13 R^1 = α-H, β-OH; R^2 = OH; R^3 = Me; R^4 = H
14 R^1 = α-H, β-OAc; R^2 = OAc; R^3 = Me; R^4 = Ac
15 R^1 = α-OH, β-H; R^2 = R^4 = H; R^3 = Me
16 R^1 = α-H, β-OH; R^2 = R^4 = H; R^3 = Me
17 R^1 = H_2, R^2 = OH; R^3 = R^4 = H
18 R^1 = α-H, β-OH; R^2 = OH; R^3 = R^4 = H
19 R^1 = α-H, β-OAc; R^2 = OAc; R^3 = H; R^4 = Ac

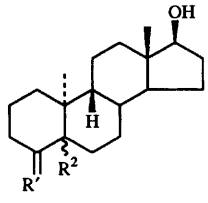
† Now more correctly named as sodium boranuide according to IUPAC rules of nomenclature. Editor.

Table 1 Hydroboration/oxidation of androst-4-enes

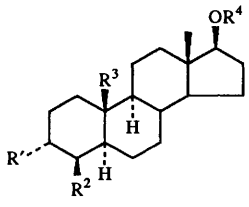
Substrate	Product	Yield (%)
17β-Acetoxyandrost-4-ene	**5**	
5α-Androstane-4α,17β-diol	**12**	81
5β-Androstane-4β,17β-diol	**20**	17
17β-Acetoxy-19-norandrost-4-ene	**6**	
19-Nor-5α-androstane-4α,17β-diol	**17**	35
19-Nor-5β-androstane-4β,17β-diol	**23**	38
17β-Acetoxy-9β,10α-androst-4-ene	**8**	
5α,9β,10α-Androstane-4α,17β-diol	**25**	14
5β,9β,10α-Androstane-4β,17β-diol	**26**	77
17β-Acetoxyandrost-4-en-3β-ol	**9**	
5α-Androstane-3β,4α,17β-triol	**13**	
isolated as the triacetate	**14**	65
19-Norandrost-4-ene-3β,17β-diol	**10**	
19-Nor-5α-androstane-3β,4α,17β-triol	**18**	
isolated as the triacetate	**19**	48
17β-Acetoxyandrost-4-en-3α-ol	**11**	
5α-Androstane-3α,17β-diol	**15** } as a 1:2 mixture	9
5α-Androstane-3β,17β-diol	**16** }	
17β-Ethoxy-5β-androstane-3α,4β-diol	**21**	21
5β-Androstane-3α,4β,17β-triol	**22**	63



20 $R^1 = R^4 = H$; $R^2 = OH$; R^3 Me
21 $R^1 = R^2 = OH$; $R^3 = Me$; $R^4 = Et$
22 $R^1 = R^2 = OH$; $R^3 = Me$; $R^4 = H$
23 $R^1 = R^3 = R^4 = H$; $R^2 = OH$
24 $R^1 = R^3 = H$; $R^2 = OAc$; $R^4 = Ac$



25 $R^1 = \alpha$-OH, β-H; $R^2 = \alpha$-H
26 $R^1 = \alpha$-H, β-OH; $R^2 = \beta$-H



27 $R^1 = Me$; $R^2 = \alpha$-H
28 $R^1 = Me$; $R^2 = \beta$-H
29 $R^1 = H$; $R^2 = \alpha$-H
30 $R^1 = H$; $R^2 = \beta$-H

4β-H signal (δ_H 3.41) in **12** on irradiation of the 19-H resonance. No effect was observed in **20**. The same method was used to distinguish between the isomers **25** and **26** obtained from the retro-steroid **8**. Irradiation of the 19-H resonance at δ_H 1.09 in **26** produced an NOE, enhancement of 5% of the C*H*(OH) resonance at δ_H 3.95. However, in the 19-nor series in which the epimers **17** and **23** were obtained in approximately equal amounts, there was no convenient NMR distinction and consequently the stereochemistry of the alcohols was established by X-ray crystallography. Suitable crystals were obtained from 4β,17β-diacetoxy-19-nor-5β-androstane **24** (see Fig. 1).

In order to confirm their stereochemistry at C-5 both 5α-androstane-4α,17β-diol **12** and 5β-androstane-4β,17β-diol **20** were separately oxidized to their corresponding diketones (**27** and **28**). These may be distinguished by the position of their 19-H proton resonances (δ_H 0.87 and 1.14, respectively). Equilibration of each with methanolic potassium hydroxide gave the same 3:1 mixture of 5α- and 5β-androstane-4,17-diones with *trans*- and *cis*-fused A/B ring junctions, respectively. The corresponding diketones, **29** and **30**, were also prepared in the 19-nor series. The *cis* A/B fused isomer **30** was converted by base into the *trans* fused 19-nor-5α-androstane-4,17-dione **29**.

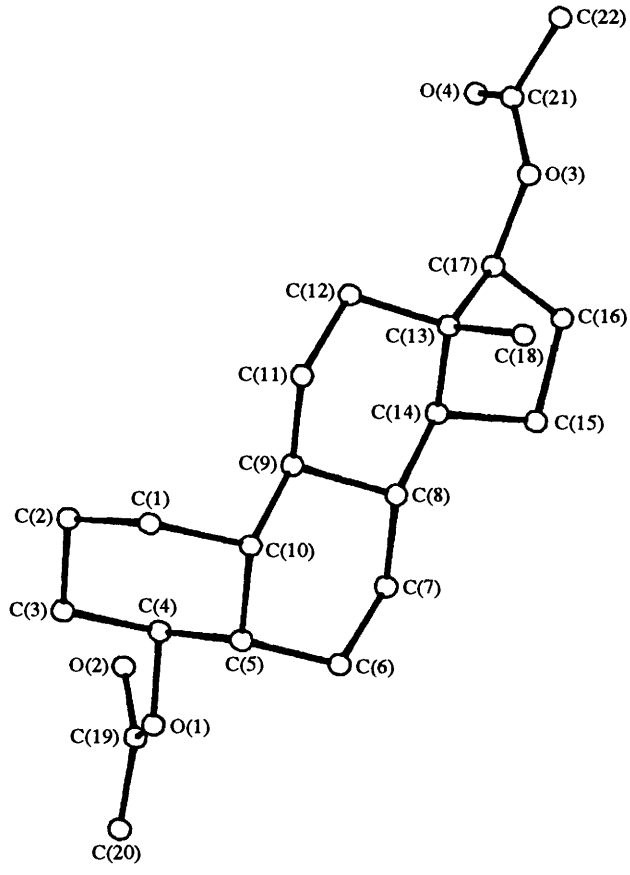
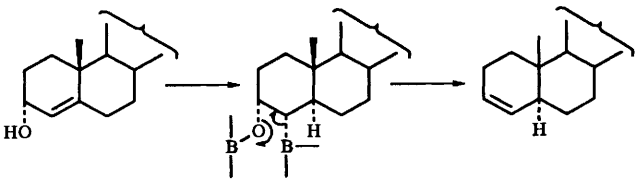


Fig. 1 X-Ray structure of 4β,17β-diacetoxy-19-nor-5β-androstane **24**

The stereochemistry of the products obtained from the C-3 alcohols was evident from the multiplicity of their C*H*(OH) ^1H NMR signals. Thus, the 4-H signal in **14** (the triol **13** was purified as its acetate) appeared as a double doublet (*J* 9.5 and 11.5 Hz), in which there was a large coupling (11.5 Hz) to the C-3α proton corresponding to a diaxial relationship. A similar



Scheme 1

situation was present in **18**. In the case of compound **21** decoupling of the proton resonance at δ_H 3.70 (dd, *J* 9.0 and 9.1 Hz, 4-H) collapsed the signal at δ_H 3.39 (ddd, *J* 5.8, 9.0 and 11.4 Hz, 3-H) to a double doublet (*J* 5.8 and 11.4 Hz). There is thus a diaxial relationship between these protons and hence a diequatorial relationship between the hydroxy groups. There was a similar coupling pattern in **22**.

A number of conclusions may be drawn from these results. Comparison of the results of hydroboration of 17β-acetoxyandrost-4-ene **5**, 17β-acetoxy-19-norandrost-4-ene **6** and 17β-acetoxy-9β,10α-androst-4-ene **8** reveals the stereochemical directing effect of the 10-methyl group. However, the allylic C-3 hydroxy groups direct hydroboration to the face of the alkene opposite to the hydroxy group. Although 17β-acetoxyandrost-4-ene and the 19-noralkene both gave some 4β-alcohol, a 3β-hydroxy group directed attack entirely to the α-face. On the other hand a 3α-hydroxy group directed the hydroboration entirely to the β-face despite the steric hindrance from the 10β-methyl group. The origin of this facial selectivity may be electronic or it may lie in the formation of bulky borate complexes from the alcohol which direct a second molecule of the borane to attack from the *trans* face. The formation of the 3α,17β- and 3β,17β-dihydroxy-5α-androstanes (**15** and **16**) may occur through an elimination reaction of the borane to form a 3-ene (see Scheme 1) which is then rehydroboronated. The ethyl ether in **21** presumably arose by reduction of the acetate.

Experimental

Light petroleum refers to the fraction bp 60–80 °C; silica for chromatography was Merck Kieselgel 60 type 9380. IR spectra were determined as Nujol mulls; ^{1}H NMR spectra were determined at 360 or 500 MHz in deuteriochloroform on Bruker WM 360 or AMX spectrometers; *J* values given in Hz. Borane (1 mol dm^{-3}) in tetrahydrofuran was used as supplied by Aldrich Chemicals. Extracts were dried over anhydrous sodium sulfate.

Preparation of 17β-acetoxyandrost-4-ene 5 [8]

Sodium borohydride (1.3 g) was added in portions with stirring and cooling to a previously cooled mixture of trifluoroacetic acid (8.0 cm^3), acetic acid (8.0 cm^3) and acetonitrile (8.0 cm^3). 17β-Acetoxyandrost-4-en-3-one (2.3 g)(2) in dry dichloromethane (40 cm^3) was added to the mixture which was then stirred at room temperature for 1 h. After this the reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined extracts were washed with water, dried and evaporated under reduced pressure to give 17β-acetoxyandrost-4-ene **5** (2.2 g), which crystallized from light petroleum as prisms, mp 89 °C (lit.,[8] 97 °C) ν_{max}/cm^{-1} 1732 and 1625; δ_H 0.80 (3 H, s, 18-H), 1.05 (3 H, s, 19-H), 2.10 (3 H, s), 4.56 (1 H, t, *J* 8.4, 17-H) and 5.31 (1 H, t, *J* 3.5, 4-H). 17β-Acetoxy-19-norandrost-4-ene **6**, mp 79–81 °C (lit.,[13] 81–82 °C) and 17β-*acetoxy*-9β,10α-*androst*-4-*ene* **8** were prepared in a similar manner. The latter crystallized from light petroleum as prisms, mp 51–53 °C (Found: C, 79.2; H, 10.0. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%); ν_{max}/cm^{-1} 1736 and 1660; δ_H 0.82 (3 H, s, 18-H) 1.14 (3 H, s, 19-H), 3.53 (1 H, t, *J* 8.4, 17-H) and 5.28 (1 H, br s, 4-H).

Preparation of 19-norandrost-4-ene-3β,17β-diol 10

17β-Hydroxy-19-norandrost-4-en-3-one **3** (2 g) in methanol (40 cm^3) was treated with sodium borohydride (500 mg) at 0 °C for 2 h. Acetic acid (0.4 cm^3) was added to the mixture which was then concentrated under reduced pressure. Water was added to the residue and the products were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated to give 19-*norandrost*-4-*ene*-3β,17β-*diol* **10** (1.87 g) which crystallized from ethyl acetate–light petroleum as needles, mp 143 °C (Found: C, 77.6; H, 10.4. $C_{18}H_{28}O_2$ requires C, 78.2; H, 10.2%); ν_{max}/cm^{-1} 3350; δ_H 0.77 (3 H, s, 18-H), 3.63 (1 H, t, *J* 8, 17-H), 4.14 (1 H, m, 3-H) and 5.38 (1 H, s, 4-H).

17β-Acetoxyandrost-4-en-3β-ol **9**, prepared from 17β-acetoxyandrost-4-en-3-one **2** under similar conditions crystallized from light petroleum as needles, mp 135–136 °C (lit.,[9] 135–136 °C) ν_{max}/cm^{-1} 3310 and 1735; δ_H 0.83 (3 H, s, 18-H), 1.10 (3 H, s, 19-H), 2.03 (3 H, s, 17-OAc), 4.13 (1 H, m, 3-H), 4.60 (1 H, t, *J* 8.4, 17-H) and 5.31 (1 H, br s, 4-H).

Preparation of 17β-acetoxy-3α-chloroacetoxyandrost-4-ene

Triphenylphosphine (3.0 g) and dry chloroacetic acid (1.2 g) were added to a solution of 17β-acetoxyandrost-4-en-3β-ol (2.0 g) in toluene (60 cm^3). Diethyl azodicarboxylate (1 cm^3) was then added dropwise to the mixture after which it was stirred overnight at room temperature. After evaporation of the solvent under reduced pressure from the mixture the residue was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave the *title compound* (1.4 g) which crystallized from ethyl acetate–light petroleum as needles, mp 128–130 °C (Found: C, 67.0; H, 7.7. $C_{23}H_{33}ClO_4$ requires C, 67.5; H, 8.1%); ν_{max}/cm^{-1} 1760, 1737 and 1651; δ_H 0.82 (3 H, s, 18-H), 1.01 (3 H, s, 19-H), 2.04 (3 H, s, OAc), 4.05 (2 H, s, $OCOCH_2Cl$), 4.58 (1 H, br s, 3β-H) and 5.45 (1 H, d, *J* 5, 4-H).

Preparation of 17β-acetoxyandrost-4-en-3α-ol 11

An aqueous solution (10 cm^3) of potassium carbonate (2.0 g) was added to a solution of 17β-acetoxy-3α-chloroacetoxyandrost-4-ene (1.0 g) in methanol (30 cm^3) and the mixture kept at room temperature for 1 h. After this acetic acid (1 cm^3) was added to the mixture which was then concentrated under reduced pressure and the product recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water, dried and evaporated. The residue was chromatographed on silica, eluting with 10% ethyl acetate–light petroleum, to give the *title compound* **11** (650 mg) which crystallized from ethyl acetate–light petroleum as needles, mp 108–110 °C (Found: C, 74.6; H, 9.4. $C_{21}H_{32}O_3 \cdot 0.5H_2O$ requires C, 73.9; H, 9.7%); ν_{max}/cm^{-1} 3230, 1730 and 1660; δ_H 0.81 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 2.04 (3 H, s, OAc), 4.07 (1 H, br s, 3β-H), 4.56 (1 H, t, *J* 8.7, 17α-H) and 5.47 (1 H, s, 4-H).

Hydroboration/oxidation experiments

(a) 17β-Acetoxyandrost-4-ene **5** (1.0 g) in dry tetrahydrofuran (30 cm^3) was treated with borane in tetrahydrofuran (1 mol dm^{-3}; 20 cm^3) at 0 °C under nitrogen. The reaction was followed by TLC until the formation of the borane was complete (4 h). The mixture was carefully diluted with water (10 cm^3) after which it was cooled to 0 °C and treated with sodium hydroxide (10%; 20 cm^3) followed by hydrogen peroxide (30%; 30 cm^3), added dropwise. The mixture was stirred overnight after which sodium sulfite (2 g) was added to it followed by acetic acid (1 cm^3), water (50 cm^3), dil. hydrochloric acid (50 cm^3) and ethyl acetate (100 cm^3). The mixture was stirred for a further 15 min after which the organic layer was separated, washed with water and brine, dried and evaporated under reduced pressure to give a residue. This was chromatographed on silica, eluting with 20% ethyl acetate–light petroleum to give

5α-androstane-4α,17β-diol **12** (746 mg) which crystallized from ethyl acetate–light petroleum as plates, mp 232–234 °C (lit.,[12] mp 235–237 °C); ν_{max}/cm^{-1} 3600 and 3453; δ_H 0.72 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 3.41 (1 H, dt, *J* 4.6 and 10.8, 4β-H) and 3.59 (1 H, t, *J* 8.6, 17α-H). Further elution with the same solvent system gave 5β-androstane-4β,17β-diol **20** (162 mg) which crystallized from acetone as prisms, mp 178–181 °C (lit.,[12] mp 177–178 °C); ν_{max}/cm^{-1} 3585 and 3448; δ_H 0.71 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 3.56 (1 H, dt, *J* 4.6 and 10.8, 4α-H) and 3.85 (1 H, t, *J* 8.6, 17α-H).

(b) 17β-Acetoxyandrost-4-en-3β-ol **9** (2 g) in dry tetrahydrofuran (50 cm^3) was treated with borane in tetrahydrofuran (1 mol dm^{-3}; 40 cm^3) at 0 °C under nitrogen for 4 h (TLC control) after which the mixture was carefully diluted with water (10 cm^3) and cooled to 0 °C. Sodium hydroxide (10%; 20 cm^3) was then added to the mixture followed by hydrogen peroxide (30%; 40 cm^3), added dropwise. The mixture was stirred overnight after which sodium sulfite (2 g) added followed by acetic acid (1 cm^3), water (50 cm^3), dil. hydrochloric acid (50 cm^3) and ethyl acetate (100 cm^3) were added to it. The mixture was stirred for a further 15 min after which the organic layer was separated, washed with water and brine, dried and evaporated under reduced pressure. The residue (1.93 g) was treated with acetic anhydride (4 cm^3) in pyridine (10 cm^3) overnight and the mixture worked up to provide a product which was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave *3β,4α,17β-triacetoxy-5α-androstane* **14** (1.70 g) which crystallized from ethyl acetate as needles, mp 124–126 °C (Found: C, 69.0; H, 9.1. $C_{25}H_{38}O_6$ requires C, 69.1; H, 8.8%); ν_{max}/cm^{-1} 1750 and 1730; δ_H 0.78 (3 H, s, 18-H), 0.92 (3 H, s, 19-H), 2.00, 2.03 and 2.04 (each 3 H, s, OAc), 4.58 (1 H, t, *J* 8.4, 17α-H), 4.76 (1 H, ddd, *J* 5.5, 9.4, and 11.5, 3α-H) and 4.97 (1 H, dd, *J* 9.5 and 11.5, 4β-H).

(c) 17β-Acetoxyandrost-4-en-3α-ol **11** (600 mg) in dry tetrahydrofuran (25 cm^3) was treated with borane in tetrahydrofuran, (1 mol dm^{-3}; 25 cm^3) at 0 °C under nitrogen for 4 h (TLC control) after which the mixture was diluted with water (10 cm^3) and cooled to 0 °C. Sodium hydroxide (10%; 15 cm^3) was then added to the mixture followed by hydrogen peroxide (30%; 20 cm^3) added dropwise. The mixture was stirred overnight after which sodium sulfite (2 g) was added to it followed by acetic acid (1 cm^3), water (50 cm^3), dil. hydrochloric acid (50 cm^3) and ethyl acetate (100 cm^3). The mixture was stirred for a further 15 min after which the organic layer was separated, washed with water and brine, dried and evaporated. The residue was chromatographed on silica, eluting with 15% ethyl acetate–light petroleum to give a mixture (55 mg) of 5α-androstane-3α,17β- and 3β,17β-diols **15** and **16**, in the ratio 3:2. They were identified by comparison of the ^1H NMR spectrum with those of authentic samples. Further elution with 25% ethyl acetate–light petroleum gave *17β-ethoxy-5β-androstane-3α,4β-diol* **21** (125 mg), mp 209–212 °C (Found: C, 75.0; H, 10.8. $C_{21}H_{36}O_3$ requires C, 74.95; H, 10.7%); ν_{max}/cm^{-1} 3583 and 3431; δ_H 0.74 (3 H, s, 18-H), 0.97 (3 H, s, 19-H), 1.17 (3 H, t, *J* 7.0, OCH_2CH_3), 3.29 (1 H, t, *J* 8.5, 17-H), 3.39 (1 H, ddd, *J* 5.8, 9.0 and 11.4, 3-H), 3.50 (2 H, m, OCH_2CH_3) and 3.70 (1 H, dd, *J* 9.0, 9.1, 4-H). Further elution with the same solvent system gave *5β-androstane-3α,4β,17β-triol* **22** (345 mg), mp 225–227 °C (Found: C, 70.0; H, 10.3. $C_{19}H_{32}O_3 \cdot H_2O$ requires C, 69.9; H, 10.5%); ν_{max}/cm^{-1} 3470 and 3338; δ_H 0.73 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 3.60 (1 H, t, *J* 8.5, 17-H), 3.45 (1 H, ddd, *J* 5.8, 8.9 and 11.4, 3β-H), 3.66 (1 H, dd, *J* 8.9 and 9.0, 4α-H).

(d) 17β-Acetoxy-19-norandrost-4-ene **6** (1 g) was treated with borane in tetrahydrofuran as above. The product was chromatographed on silica, eluting with 20% ethyl acetate–light petroleum to give *19-nor-5α-androstane-4α,17β-diol* **17** (318 mg) which crystallized from ethyl acetate–light petroleum as needles, mp 209–212 °C (Found: C, 77.1; H, 11.1. $C_{18}H_{30}O_2$ requires C, 77.6; H, 10.9%); ν_{max}/cm^{-1} 3415; δ_H 0.72 (3 H, s, 18-H), 3.20 (1 H, dt, *J* 4.3, 9.9, 4β-H), 3.66 (1 H, t, *J* 8.6, 17α-H). Further elution gave *19-nor-5β-androstane-4β,17β-diol* **23** (349 mg) as prisms, mp 159–161 °C (Found: C, 77.3; H, 10.9. $C_{18}H_{30}O_2$ requires C, 77.6; H, 10.9%); ν_{max}/cm^{-1} 3300; δ_H 0.75 (3 H, s, 18-H), 3.65 (1 H, dt, *J* 4.1 and 11.0, 4-H) and 3.82 (1 H, t, *J* 8.5, 17-H). The *diacetate*, prepared with acetic anhydride in pyridine, had mp 109–110 °C (Found: C, 83.7; H, 10.9. $C_{22}H_{34}O_4$ requires C, 84.0; H, 10.9%); ν_{max}/cm^{-1} 1740; δ_H 0.78 (3 H, s, 18-H), 2.03 (6 H, s, OAc), 4.59 (1 H, dd, *J* 7.9 and 9.0, 17-H) and 5.10 (1 H, dt, *J* 5.0 and 11.1, 4-H).

(e) 19-Norandrost-4-ene-3β,17β-diol **10** (1.5 g) was treated with borane in tetrahydrofuran as above and the product (1.32 g) was treated with acetic anhydride (3 cm^3) in pyridine (7 cm^3) at room temperature overnight. The solution was poured into dil. hydrochloric acid and the steroids were recovered in ethyl acetate and chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave *3β,4α,17β-triacetoxy-19-nor-5α-androstane* **19** (1.1 g) which crystallized from ethyl acetate–light petroleum as plates, mp 233 °C (Found: C, 68.5; H, 8.6. $C_{24}H_{36}O_6$ requires C, 68.6; H, 8.5%); ν_{max}/cm^{-1} 1737; δ_H 0.79 (3 H, s, 18-H), 2.00 (3 H, s), 2.02 (6 H, s,) (3 × OAc), 4.59 (1 H, t, *J* 8, 17α-H) and 4.75 (2 H, m, 3- and 4-H). When the spectrum was determined in C_6D_6 this signal was resolved to δ 4.93 (1 H, t, *J* 10, 4-H), 5.02 (1 H, ddd, *J* 4.9, 10 and 11.5, 3-H).

(f) 17β-Acetoxy-9β,10α-androst-4-ene **8** (1.0 g) was treated with borane in tetrahydrofuran as above. The product was chromatographed on silica, eluting with 20% ethyl acetate–light petroleum to give *5α,9β,10α-androstane-4α,17β-diol* **25** (130 mg), mp 151–153 °C (Found: C, 77.7; H, 10.9. $C_{19}H_{32}O_2$ requires C, 78.0; H, 11.0%); ν_{max}/cm^{-1} 3520 and 3453; δ_H 0.76 (3 H, s, 18-H), 0.92 (3 H, s, 19-H), 3.48 (1 H, dt, *J* 4.5 and 11.0, 4-H) and 3.68 (1 H, t, *J* 8.6, 17-H). Further elution gave *5β,9β,10α-androstane-4β,17β-diol* **26** (709 mg) mp 181–183 °C (Found: C, 77.6; H, 10.8. $C_{19}H_{32}O_2$ requires C, 78.0; H, 11.0%); ν_{max}/cm^{-1} 3613 and 3443; δ_H 0.76 (3 H, s, 18-H), 1.09 (3 H, s, 19-H), 3.68 (1 H, t, *J*, 8.8, 17-H) and 3.95 (1 H, dt, *J* 4.6 and 10.9, 4-H). Irradiation at δ 1.09 produced an NOE enhancement of 5% at δ_H 3.95 m.

Oxidation of 5α-androstane-4α,17β-diol 12

The diol **12** (100 mg) in acetone (25 cm^3) was treated with Jones' reagent (0.8 cm^3) at room temperature for 20 min after which methanol was added to the mixture to destroy the excess of the reagent and the solution was concentrated under reduced pressure. Water was added to the residue and the steroids were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water, dried and evaporated to give 5α-androstane-4,17-dione **27** (80 mg) which crystallized from light petroleum as needles, mp 163–165 °C (lit.,[13] 162–164 °C); ν_{max}/cm^{-1} 1739 and 1707; δ_H 0.77 (3 H, s, 18-H), 0.87 (3 H, s, 19-H). Under similar conditions (i) 5β-androstane-4β,17β-diol **20** gave *5β-androstane-4,17-dione* **28** which crystallized from light petroleum as needles, mp 158–160 °C (Found: C, 78.85; H, 10.1. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%); ν_{max}/cm^{-1} 1740 and 1703; δ_H 0.85 (3 H, s, 18-H) and 1.14 (3 H, s, 19-H). (ii) 19-Nor-5α-androstane-4α,17β-diol **17** gave *19-nor-5α-androstane-4,17-dione* **29** which crystallized from ethyl acetate–light petroleum as plates, mp 149–151 °C (Found: C, 78.4; H, 9.1. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.5%); ν_{max}/cm^{-1} 1734 and 1704; δ_H 0.88 (3 H, s, 18-H). (iii) 19-Nor-5β-androstane-4β,17β-diol **23** gave *19-nor-5β-androstane-4,17-dione* **30** which crystallized from light petroleum as needles, mp 93–95 °C (Found: C, 78.3; H, 9.1. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.5%); ν_{max}/cm^{-1} 1733 and 1705; δ_H 0.88 (3 H, s, 18-H).

Equilibration experiments

(i) 5α-Androstane-4,17-dione **27** (200 mg) in methanol (5 cm^3) was treated with aqueous potassium hydroxide [200 mg in

water (0.5 cm^3)] under reflux for 1 h. The solution was acidified with dil. hydrochloric acid, concentrated under reduced pressure and the steroids recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated to give a 3:1 mixture of 5α- and 5β-androstane-4,17-dione, **27** and **28**, based on the intensity of the 18-H and 19-H ^1H NMR signals at δ_H 0.77, 0.87 and 1.14. (ii) Under similar conditions 5β-androstane-4,17-dione (40 mg) gave the same mixture of **27** and **28**. (iii) 19-Nor-5β-androstane-4,17-dione **30** (30 mg) under similar conditions gave 19-nor-5α-androstane-4,17-dione **29** (25 mg), mp 148–150 °C, identified by its IR and ^1H NMR spectra. The 19-nor-5α-androstane-4,17-dione **29** was recovered unchanged.

X-Ray crystal structure determination of compound 24

Crystal data. $C_{22}H_{32}O_4$, M 360.5, monoclinic, space group P_{21} (No 4), a = 7.481(2), b = 10.855(7), c = 13.256(9) Å, α = 90°, β = 100.91(4), γ = 90°, V = 1057.0 (Å^3), Z = 2, D_c = 1.13 g cm^{-3}, $F(000)$ = 392, monochromated Mo-Kα radiation, λ = 0.710 69 Å, μ = 0.71 cm^{-1}.

Data collection. Data were collected using a crystal, 0.3 × 0.3 × 0.1 mm on an Enraf-Nonius CAD_4 diffractometer. Reflections were measured using a θ–2θ scan. The data reflection ranges were (θ min. and max.) h 0–8, k 0–12, l −15–15. A total of 2105 reflections were measured of which 1962 were unique reflections and 1070 significant reflections with $|F^2| > 3\sigma(F^2)$ were used in the refinement where $\sigma(F^2) = \{\sigma^2(I) + (0.04\ I)^2\}^{\frac{1}{2}}/L_p$. The maximum change in the standard reflections was 0.6%. There was no correction for decay or absorption.

Structure solution and refinement

The structure was solved by direct methods using SHELXS-86. Non-hydrogen atoms were refined anisotropically by full matrix least-squares using the Enraf-Nonius MoLEN program. Hydrogen atoms were held fixed at calculated positions with $U_{iso} = 1.3\ U_{eq}$ for the parent atom except that the hydrogen atoms attached to C(20) and C(22) (the acetoxy methyl groups) were omitted. The final residuals were R = 0.085 and R' = 0.106, S = 4.07 amu. The number of variables was 234, $(\Delta/\sigma)_{max}$ 0.02; $(\Delta_\rho)_{max,min}$(e Å^{-3}) = +0.28, −0.22. The absolute structure was assigned from the known origin of the material.

The fractional atomic co-ordinates, bond lengths and angles and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.†

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