## 19-Hydroxy-5 $\beta$ ,19-cyclosteroids: synthesis, isomerization and ring opening

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19(*R*/*S*)-Hydroxy-5 $\beta$ ,19-cyclosteroids have been synthesised from the 19-formyl 4-en-3-one by reductive cyclization with zinc in aqueous acetic acid. Treatment of the aldehyde with lithium in liquid ammonia also gave the 19(*R*)-hydroxy-5 $\beta$ ,19-cyclosteroid together with the 17 $\beta$ -hydroxy analogue. The 19(*R*)-alcohol is isomerized to the 19(*S*)-alcohol in either dilute acidic or basic media *via* the 3-hydroxy-3,5-cyclosteroid. The 19(*S*)-alcohol is in equilibrium with its 3-hemiketal. Treatment of the 19(*R*)-alcohol with methanolic HCl gave the 19(*R*)- and 19(*S*)-methyl ethers, the 3-methyl ether 19-ketal and the 3 $\alpha$ -methoxy-3 $\beta$ ,5 $\beta$ -cyclosteroid. Further rearrangements of the 19(*R*)- and 19(*S*)-alcohols take place on more vigorous treatment with acid or base to give cyclopropanol ring-opened aldehydes including a 5 $\beta$ -methyl-A-norsteroid. Metal hydride reduction of the 3-ketone in the 19(*R*)-alcohol gave only the 3 $\beta$ -alcohol whereas the 19(*S*)-alcohol gave both the 3 $\alpha$ - and 3 $\beta$ -alcohols. Acid treatment of the 3 $\beta$ -alcohols gave products with retention of configuration at C-5 and C-19 while base-catalysed ring opening gave inversion at C-5. Ring opening mainly involved breaking of the 5,19-bond, however, the 19(*S*)-alcohol also resulted in 10,19-bond cleavage. Structures were established by NMR measurements.

### Introduction

Recently we reported the first synthesis of 19-monosubstituted derivatives of  $5\beta$ ,19-cyclosteroids, namely, 19(R/S)-chloro- $5\beta$ ,19-cycloandrostane<sup>1</sup> and 19(R/S)-hydroxy- $5\beta$ ,19-cycloandrostane.<sup>2</sup> In this report details of the synthesis, isomerization, metal hydride reduction, and acid and base catalysed cyclo-propanol ring transformations of the 19(R/S)-hydroxy- $5\beta$ ,19-cycloandrostanes are presented.

19(R/S)-Hydroxy-5 $\beta$ ,19-cycloandrostanes were prepared as part of our studies on mechanism-based inhibitors of the steroid enzyme, aromatase, based on their potential metabolic conversion into a reactive cyclopropane intermediate.<sup>3</sup> Aromatase inhibition or inactivation is of therapeutic importance because malignant cell growth in many female breast cancers is dependent on endogenous estrogen levels.<sup>4</sup>

The synthesis of unsubstituted 5 $\beta$ ,19-cyclosteroids has been reported by addition of the Simmons–Smith reagent to the steroid 5(10)-double bond,<sup>5</sup> reduction of the 19,19-dibromo-5 $\beta$ ,19-cyclosteroid,<sup>6</sup> elimination of a 19-methanesulfonate 4-ene with hydride ion<sup>7</sup> or a 5-ene with pyridine<sup>8</sup> or acetate ion,<sup>9</sup> reductive elimination of a C-19 sulfonate or halogen in the steroid 4-en-3-one with Li– or Na–NH<sub>3</sub>,<sup>9-11</sup> or zinc in aqueous acetic acid.<sup>7,12,13</sup> A unique rearrangement of the steroid 19-diethyl-[2-chloro-1,1,2-difluoroethyl]-amine derivative gave the C-1 unsaturated 5 $\beta$ ,19-cyclosteroid.<sup>14</sup> Treatment of the 19-methanesulfonate 1,4-dien-3-one with biphenyl in tetrahydrofuran (THF) also gave the C-1 unsaturated 5 $\beta$ ,19-cyclosteroid.<sup>15</sup>

### **Results and discussion**

19-Formylandrost-4-ene-3,17-dione **1**, prepared by pyridinium dichromate oxidation of 19-hydroxyandrost-4-ene-3,17-dione, on treatment with zinc in aqueous acetic acid gave a mixture of the 19(R/S)-hydroxy- $5\beta$ ,19-cycloandrostane derivatives (Scheme 1). The major product was the 19(R)-alcohol **2a** (62.5%) an the minor product 19(S)-alcohol **3a** (0.56%), the latter obtained after chromatographic separation. The 19(S)-alcohol **3a** was in equilibrium with its intramolecular hemiketal

**4**. The formation also of a small amount of estr-5(10)-ene-3,17dione **5a** (3.3%) was probably initiated by H<sub>2</sub>O attack on the 19aldehyde. Bond formation between carbons 5 and 19 occurs readily as shown by the facile reductive cyclizations to the 19unsubstituted 5 $\beta$ ,19-cyclosteroids.<sup>7-15</sup> Radical or anion formation at C-5, expected from treatment of the unsaturated ketone with zinc in aqueous acetic acid, locates the C-5 bonding orbital in an advantageous position to add to the 19-carbonyl group as shown in Scheme 2. Cyclization to the 19(*R*)-alcohol may be favoured by repulsion between the  $\pi$ -orbitals in ring A and the carbonyl oxygen. Acetylation or trimethylsilylation of the 19(*R*)- and 19(*S*)-alcohols, **2a** and **3a**/**4**, gave the corresponding acetates, **2b** and **3b**, and silyl ethers, **2c** and **3c**, respectively.

Treatment of the aldehyde **1** with lithium in ammonia gave the reductive cyclization product **2a** (11%) as obtained with zinc in aqueous acetic acid together with the corresponding 17βalcohol analogue **6a** (34%), and the 5(10)-olefin **5a** (11%) together with its 17β-alcohol analogue **5b** (12%). The 17βalcohol **6a** was further characterized as the diacetate **6b**.

A detailed NMR analysis has determined the conformation of ring A in the 19(R)- and 19(S)-substituted derivatives.<sup>16</sup> Ring A in the 19(R)-isomers, in which a hydrogen is located over ring A, takes up a boat conformation. The 19(S)-isomers, with a larger substituent over ring A, adopt an inverted boat conformation.

The unsaturated 19-aldehyde **1** is a vinylogous  $\beta$ -keto aldehyde. Reductive cyclization of the aldehyde to a cyclopropanol is comparable to cyclopropane-1,2-diol formation in the abnormal Clemmensen reduction of  $\beta$ -diketones. The diol has been shown to be an intermediate in the abnormal Clemmensen reduction.<sup>17</sup> Reusch *et al.*<sup>18</sup> have synthesised a number of substituted decalin cyclopropanol derivatives by an analogous intramolecular reductive cyclization.

Treatment of the 19(R)-alcohol **2a** with dilute solutions of either concentrated HCl–THF or KOH–MeOH at 20 °C for 1–4 h caused isomerization to the thermodynamically more stable 19(S)-alcohol **3a**/4. In this homoenolic system<sup>19</sup> isomerization can occur through an initial 19(R)-cyclopropanol ring opening to the 3-hydroxy-3,5-cyclosteroid followed by ring opening





Scheme 1 Reagents: i, Zn-HOAc-H<sub>2</sub>O; ii, Li-NH<sub>3</sub>; iii, KOH-MeOH or HCl-THF; iv, Ac<sub>2</sub>O-DMAP-CH<sub>2</sub>Cl<sub>2</sub>; v, Me<sub>3</sub>Si-imidazole-CH<sub>2</sub>Cl<sub>2</sub>; vi, Ac2O-pyridine; vii, Ac2O-DMAP-Et3N-CH2Cl2



Scheme 2 Reductive cyclization of the steroid 19-formyl 4-en-3-one (M = Li, Zn)

again and reclosure to the more stable 19(S)-alcohol (see Scheme 3). Acid- and base-catalysed rearrangements of similar equilibrating cyclopropanol derivatives have been studied in detail by Reusch et al.20 Steric strain by the 19(R)-hydroxy group together with hemiketal formation shifts the equilibrium toward the 19(S)-alcohol 3a/4. Protonation of the ketone can similarly initiate the isomerization process. Treatment of the 19(R)-alcohol 2a with concentrated HCl in MeOH gave the following four products: (i) the 19(R)-methyl ether 7 (18%), (ii) the 19(S)-methyl ether 8 (28%), (iii) the 3-methoxy ketal 9 (28%) and (iv) the  $3\alpha$ -methoxy- $3\beta$ ,  $5\beta$ -cyclosteroid **10** (3%) (Scheme 4). Isolation of both the 19(R)- and 19(S)-methyl ethers, 7 and 8, demonstrates that the 19(S)- to 19(R)-alcohol isomerization occurs under the conditions in which the  $3\alpha$ -methoxy- $3\beta$ , $5\beta$ cyclosteroid derivative 10 is formed. Therefore, formation of the 3-methoxy-3β,5β-cyclosteroid **10** supports isomerization occurring through the 3-hydroxy-3,5-cyclopropanol as shown in Scheme 3. The small amount of 19(S)-alcohol 3a/4 isolated from the zinc in aqueous acetic acid treatment of the 19aldehyde 1 probably results from acidic isomerization rather than direct reductive cyclization.

Treatment of the 19(S)-alcohol 3a/4 with sodium hydride and iodomethane gave the 19(S)-methyl ether 8 and the 3-methoxy ketal 9 (Scheme 4). When the 19(R)-alcohol 2a was treated with a larger excess of NaH the  $4\alpha$ -methyl compound **11**, derivable from the product 8 above, was obtained together with the 3methoxy ketal 9. Isomerization of the 19(R)-alcohol 2a to the 19(S)-alcohol 3a/4 occurs rapidly under the reaction conditions



3-hydroxy-3,5-cyclosteroid

Scheme 3 Isomerization of 19(R)- and 19(S)-hydroxy-5,19-cyclosteroids

as only derivatives of the 19(S)-isomer were isolated. Formation of  $4\alpha$ -methyl compound **11** established that enolization occurred towards C-4 and that stereoelectronic requirements permit methylation to occur at that position, probably from the less hindered  $\alpha$ -face, more readily than at C-2.

More vigorous acidic or basic treatment of the 19(R)-alcohol 2a led to further rearrangement products (Scheme 4). When the 19(R)-alcohol 2a was heated under reflux with toluene-psulfonic acid in benzene the major product was the 5βandrostan-19-al 12 together with the unstable  $5\beta$ -methyl-Anorsteroid aldehyde 13. Under these acidic conditions protonation of the cyclopropanol 5,19-bond led to the aldehyde 12. The A-norsteroid **13** can be formed by ring opening through  $\beta$ -face protonation of the 3,4-bond in the intermediate 3-hydroxy-3,5cyclosteroid (see Scheme 3). The 19(R)-alcohol **2a** under reflux with KOH-MeOH gave the A-norsteroid 13 as the major product; however, because it proved to be unstable the reaction mixture was treated directly with sodium borohydride to give the corresponding C-19 alcohol 14.

Metal hydride reduction of the C-3 carbonyl group was carried out on the 19(R)- and 19(S)-alcohols, 2a and 3a/4, to determine the effect of the cyclopropanol ring on the stereochemistry of reduction to the C-3 alcohols. These alcohols were



Scheme 4 Reagents: i, HCl-MeOH; ii, NaH-MeI-DMF; iii, *p*-TsOH-benzene; iv, 0.5 M KOH-MeOH; v, NaBH<sub>4</sub>

then employed to examine the course of the cyclopropanol ring opening in the absence of the carbonyl group. Lithium tri-tertbutoxyaluminium hydride (LTBAH) reduction of the 19(R)alcohol **2a** gave the 19(R)-diolone **6a** (44%) and the 19(R)-triol 15 (35%) (Scheme 5). The C-3 ketone was resistant to  $\beta$ -face attack by the reagent, probably because of steric hindrance from the 19-H. Furthermore  $\alpha$ -face attack was relatively slow compared with reduction of the C-17 ketone. Similar treatment of the 19(S)-alcohol 3a/4 gave the 19(S)-diolone 16a/17 further characterized as the diacetate 16b (Scheme 5). Resistance of the C-3 ketone to reduction may result from intramolecular hemiketal formation with the 19-hydroxy group. Treatment of the 19(R)-alcohol **2a** with sodium borohydride gave only the 19(R)-triol 15. Similar sodium borohydride treatment of the 19(S)-alcohol 3a/4 gave two epimeric alcohols, the 19(S)-triols **18** (62%) and **19** (12%). While the  $3\beta$ -hydroxy group in the 19(S)-triol 18 is formed by  $\alpha$ -face attack of the reagent on the less sterically hindered face of the molecule the  $3\alpha$ -hydroxy group in the 19(S)-triol **19** requires attack on the more sterically hindered  $\beta$ -face.  $\beta$ -Face attack may occur either directly on the



**Scheme 5** *Reagents:* i, LTBAH–THF; ii, NaBH<sub>4</sub>MeOH; iii, Ac<sub>2</sub>O–pyridine

ketone or by an initial reaction of the reagent with the C-19 alcohol followed by intramolecular reduction. Attempts to purify the 19(*S*)-triol **19** led to its decomposition whereas the 19(*S*)-triol **18** proved to be more stable. The greater stability of the 19(*S*)-triol **18** may result from hydrogen bonding between the C-3 and C-19 alcohols not possible with the 19(*S*)-triol **19**.

Treatment of the triols 15 and 18 (Scheme 6) obtained from reduction of the 19(R/S)-alcohols, 2a and 3a/4, respectively, under acidic or basic conditions gave no A-norsteroid derivable from a 3-hydroxy-3,5-cyclosteroid (Scheme 3). Since this intermediate requires the C-3 ketone, it is not possible to form with the C-3 alcohols and, therefore, the absence of an A-norsteroid is consistent with its formation through a 3-hydroxy-3,5cyclosteroid. Treatment of the 19(R)-triol 15 with KOH-MeOH under reflux for 24 h gave the  $5\alpha$ , 19 $\beta$ -aldehyde **20** which was directly reduced with sodium borohydride to the more stable alcohol 21 (Scheme 6). Similar base treatment of the 19(R)-alcohol 2a gave the A-norsteroid 13 (Scheme 4). When the 19(R)-triol 15 was treated with HCl-THF for 24 h the unstable 56,196-aldehyde 22 obtained was directly reduced with sodium borohydride to the corresponding alcohol 23. Treatment of the 19(S)-triol 18 with KOH-MeOH gave the unstable isomeric aldehydes 20 and 24 which were immediately reduced to the isomeric hydroxymethyl alcohols, 21 and 25.

The 19(*R*)-alcohol **15** on KOH–MeOH treatment (24 h reflux) gave the C-5 inversion product **20/21** (10 $\beta$ -CH<sub>2</sub>OH/5 $\alpha$ -H) in 48% yield. Similar treatment (72 h reflux) of the 19(*S*)-alcohol **18** gave not only **20/21** in 30% yield but also the 10 $\beta$ -H/5 $\beta$ -CH<sub>2</sub>OH product **24/25** isolated in 15% yield.

Gibson and De Puy<sup>21</sup> have reviewed the ring opening of cyclopropanols under both acidic and basic conditions. Generally under acidic conditions cyclopropanol ring opening proceeds with retention of configuration while under basic conditions ring opening results in inversion. In agreement with their conclusion the 19(*R*)-triol **15** under acidic conditions retained



Scheme 6 Reagents and conditions: i. 0.5 M KOH-MeOH, 24-72 h; ii, NaBH<sub>4</sub>-MeOH; iii, HCl-THF, 24 h

the 5 $\beta$  stereochemistry while under basic conditions C-5 inversion occurred (Scheme 6). Inversion also occurred on base treatment of the 19(*S*)-triol **18**. Under acidic conditions ring opening following protonation of the cyclopropanol retained the 5 $\beta$  stereochemistry giving a mixture of 5,19- and 10,19-cyclopropane ring-opened products. Formation of an intermediate homoenolate anion, under basic conditions, can result in inversion at C-5 consistent with the observed stereochemistry. Inversion at C-5 leads to the thermodynamically more stable *trans* ring junction.

Trimethylsilylation of the saturated dione **2b** gave a mixture of the 2- and 3-enol silyl ethers **6a** (H-2/4, 6.1:1) which was treated with Pd(OAc)<sub>2</sub> (1.2 equiv.) to give the unsaturated ketone **27a**. Similar treatment of the isomeric saturated dione **3b** also gave a mixture of the 2- and 3-enol silyl ethers **26b** (H-2/4, 2.3:1), but in a different ratio. Treatment of the enol silyl ethers with Pd(OAc)<sub>2</sub> gave the unsaturated ketone **27b**.  $5\beta$ , 19-



Scheme 7 Reagents: i, TMSOTf-Pr $_2^i{\rm EtN}$  or Et\_3N; ii, Pd(OAc)\_2-MeCN

Cycloandrost-1-ene-3,17-dione **28** was prepared as previously reported for NMR comparison.<sup>14</sup> Attempts to hydrolyse these unsaturated esters to the 19-alcohol analogues were unsuccessful.

### Nuclear magnetic resonance analysis

COSY and HSQC spectra were used for a complete assignment of the carbon and proton spectra of compounds **2a**, **2b**, **3b**, **6**, **9–15**, **18**, **19**, **21**, **23**, **25** (see Tables 1 and 2). Spectra for compounds **2c**, **3a/4**, **3c**, **5a**, **5b**, **6a**, **6b**, **7**, **8**, **16a/17**, **16b**, **20** and **22** were assigned by comparison with their analogues above and with literature values.<sup>22</sup>

Irradiation of the cyclopropyl proton (19-H) in the 19(R)alcohol **2a** resulted in NOEs to the 1 $\beta$ -H (3.2%), 2 $\beta$ -H (2.4%) and 4 $\beta$ -H (4.1%). In the 19(R)-acetate **2b** irradiation gave NOEs with the 1 $\beta$ -H (3.0%), 2 $\beta$ -H (4.5%) and 4 $\beta$ -H (2.3%). Four-bond couplings (J < 1 Hz) between the 19-H and the 9-H were observed in the COSY spectrum in both compounds. These data clearly demonstrate that the 19-H is located over ring A and also serves to identify the  $\beta$  hydrogens in ring A.

Irradiation of the 19-H in the 19(*S*)-acetate **3b** revealed NOEs to the 7 $\beta$ -H (1.4%), the 8-H (11.8%) and the 6 $\beta$ -H (2.1%), demonstrating that the 19-H is located over ring B and identifying the  $\beta$  hydrogens in ring B.

The <sup>1</sup>H NMR spectrum of the ketone/hemiketal mixture **3a**/**4** in [ ${}^{2}H_{6}$ ]acetone showed signals assigned to the 19(*R*)-H at 3.31 and 3.60 ppm (2.5:1) corresponding to the 19(*S*)-alcohol **3a** and hemiketal **4**, respectively. Two 10-Me signals (the stronger at 0.89 and weaker at 0.86 ppm) were also present. Two carbonyls, 212.29 and 219.28 corresponding to the C-3 and C-17 carbonyl groups, respectively, were observed in the <sup>13</sup>C NMR spectrum.

The structures of compounds **7** and **8** were assigned by comparison with the corresponding acetates **2b** and **3b**. The structure of compound **10** was consistent with the complete <sup>1</sup>H and <sup>13</sup>C NMR assignments obtained from the 2D measurements.

Examination of rows extracted from the HSQC spectrum of compound **10** showed that both the  $6\alpha$ -H and  $6\beta$ -H lacked the expected coupling to the 5-H and that the  $2\alpha$ -H and  $2\beta$ -H lacked any couplings to protons attached to C-3, implying that C-3 and C-5 must be quaternary. An isolated highfield doublet of doublets (H-4 $\alpha$ ), 0.32 ppm, (J=1.5, 5.4 Hz) coupled to a doublet at 0.84 ppm (4 $\beta$ -H) and to the 2 $\alpha$ -H was also observed. These data strongly suggest a 3,5-cyclosteroid structure. Irradiation of the 19-H resulted in NOEs to the  $1\beta$ -H (1.3%) and to the lowfield cyclopropyl proton (3.5%). The latter NOE identifies this as the *endo* cyclopropyl proton ( $4\beta$ -H). Irradiation of the exo cyclopropyl proton (4 $\alpha$ -H) resulted in NOEs to, the  $6\alpha$ -H (4.1%) and the C-4 methoxy group (2.4%). Irradiation of the C-3 methoxy group resulted in an NOE to the 4α-H (2.0%). These data are only consistent with the proposed 3β,5β-cyclosteroid 10.

Irradiation of the 19-H in the  $4\alpha$ -methyl derivative **11** showed NOE with the 7 $\beta$ -H (5.1%) and 8-H (11%). Therefore the 19-H must be located over ring B. Irradiation of the 19-methoxy protons revealed NOEs to the 4-H (2.5%). The NOE between the 19-methoxy group and the 4-H is consistent with the  $4\alpha$ -methyl stereochemistry.

Examination of the 4 $\alpha$ -H, 4 $\beta$ -H and 5-H multiplets in the aldehyde **12** clearly showed that the 5-H is axial to ring A but equatorial to ring B (no axial coupling with the C-6 protons), as required for 5 $\beta$  stereochemistry. Irradiation of the aldehyde peak (19-H) resulted in an NOE to both the 5-H (4.1%) and the 1 $\beta$ -H (1.5%). Irradiation of the 4 $\alpha$ -H resulted in an NOE to the 7 $\alpha$ -H (5.6%) an the 9-H (5.7%). These results are in agreement with the 5 $\beta$  structure **12** proposed.

Irradiation of the 5-methyl group in the A-norsteroid **14** revealed NOEs to the high field 19-proton (4.0%), the  $6\beta$ -H (3.2%) and the  $1\beta$ -H (4.9%). Irradiation of the highfield 19-

Compd.	13-Me	19-H	Other
2a <sup>b,c</sup>	0.90	3.30	0.80 (m, 7α-H), 2.31d (4β-H), 2.49d (4α-H), J <sub>AB</sub> 17.3
2b <sup>b, c</sup>	0.91	4.03	2.14 (s, OAc), 2.50d <sup>d</sup> (4 $\alpha$ -H), 2.55d <sup>d</sup> (4 $\beta$ -H) $J_{AB}$ 17.7
2c	0.87	3.12	0.16 (s, SiMe <sub>3</sub> ), 2.31d (4 $\beta$ -H), 2.50d (4 $\alpha$ -H) $J_{AB}$ 16.7
3b <sup>b, c</sup>	0.92	3.88	2.09 (m, 16α-H), 2.08 (s, OAc), 2.25d (4β-H), 2.38d (4α-H), J <sub>AB</sub> 16.5
<b>3c</b> <sup>c</sup>	0.92	3.15	0.17 (s, SiMe <sub>3</sub> ), 0.73 (m, 7 $\alpha$ -H), 2.09d (4 $\beta$ -H), 2.53d (4 $\alpha$ -H) $J_{AB}$ 16.3
6a <sup>b, e, f</sup>	0.77	3.21	2.22 (m, 2 $\beta$ -H), 2.34d (4 $\beta$ -H), 2.49d (4 $\alpha$ -H) J <sub>AB</sub> 17.0
6b	0.82	4.00	2.04 (s, 17-OAc), 2.14 (s, 19-OAc), 3.48d <sup><i>d</i></sup> (4 $\alpha$ -H), 2.55d <sup><i>d</i></sup> (4 $\beta$ -H) $J_{AB}$ 17.9, 4.63 (dd, J7.8, 9.0) (17 $\alpha$ -H)
7°	0.90	2.86	0.81 (m, 7 $\alpha$ -H), 2.38d (4 $\beta$ -H), 2.53d (4 $\alpha$ -H) $J_{AB}$ 17.1, 3.38 (s, 19-MeO)
<b>8</b> <sup>c</sup>	0.92	2.93	0.72 (m, 7 $\alpha$ -H), 2.25d (4 $\beta$ -H), 2.53d (4 $\alpha$ -H) $J_{AB}$ 16.3, 3.34 (s, 19-MeO)
9 <sup><i>b,c</i></sup>	0.86	3.61	3.33 (s, 3-MeO)
10 <sup>b,g</sup>	0.89	4.11	0.32 (dd, J1.7, 5.4, 4β-H), 0.84 (d, J5.4, 4α-H), 3.27 (s, 3-MeO), 3.45, 3.48 [s, 19-(MeO) <sub>2</sub> CH]
11 <sup>b,c</sup>	0.91	2.97	0.66 (m, 7α-H), 1.12 (d, J6.6, 4α-Me), 2.27d, 2.29d, 2-H <sub>2</sub> ), 2.61 (q, J6.7, 4β-H), 3.37 (s, 19-MeO)
12 <sup>b,c</sup>	0.98	9.63	2.65 (dd, J13.7, 14.6, 4α-H)
13	0.88 <sup>d</sup>	9.94	0.90 <sup><i>d</i></sup> (s, 5-Me)
14 <sup>b,e,f</sup>	0.80	3.73d, 3.81d, J <sub>AB</sub> 11.5	1.02 (s, $5\beta$ -Me), 2.27 (m, 2-H <sub>2</sub> )
15 <sup>b,f,h</sup>	0.73	3.11	2.15 (m, 1β-H), 3.50 (m, 3α-H)
16b <i>°</i>	0.83	3.87	2.04, 2.07 (s, 17-OAc, 19-OAc), 2.25d (4β-H), 2.40d, (4α-H), J <sub>AB</sub> 16.4, 4.62 (t, J8.3, 17α-H)
18 <sup>b,f,h</sup>	0.73	3.11	3.69 (m, $3\alpha$ -H) <sup><i>j</i></sup>
19 <sup><i>b,f,h</i></sup>	0.73	2.97	1.30 (dd, J8.1, 13.0, 4-axial-H), 1.95 (m, 16 $\alpha$ -H), 2.20 (dd, J5.0, 13.2, 4-equatorial-H), 3.57 (m, 3 $\beta$ -H) <sup>j</sup>
20 <sup><i>f</i>,<i>h</i></sup>	0.65	10.0	2.38 (dt, J 3.4, 13.4, 1 $\beta$ -H), 3.55 (m, 3 $\beta$ ) <sup><i>j</i></sup>
<b>21</b> <sup>b,f,h</sup>	0.77	3.74d, 3.86d, J <sub>AB</sub> 11.7	2.30 (dt, $J$ 3.4, 13.4, 1 $\beta$ -H), 3.54 (m, 3 $\beta$ -H) <sup><i>j</i></sup>
<b>22</b> <sup>f,h</sup>	0.79	9.58	2.31 (m, 5 $\beta$ -H), 4.05 (br s, 3 $\beta$ -H)
23 <sup>b,f,h</sup>	0.71	3.45d, 3.85d, J <sub>AB</sub> 11.1	2.19 (m, 5 $\beta$ -H), 4.01 (br s, 3 $\beta$ -H)
25 <sup>b,f,h</sup>	0.73	3.40d, 3.91d, J <sub>AB</sub> 11.2 <sup><i>i</i></sup>	4.03 (br s, 3β-H)
27a	0.87	3.64	2.19 (s, 19-COMe), 2.45 (d, J18.6, 4β-H), 2.83 (d, J18.6, 4α-H), 5.80 (d, J10.2, 1-H), 7.14 (d, 10.2, 2-H)
27b	0.95	3.94	1.90 (s, 19-COMe), 2.34 (d, J18.4, 4β-H), 2.77 (d, J18.4, 4α-H), 5.97 (d, J10.2, 1-H), 6.77 (d, J10.2, 2-H)
<b>28</b> <sup>b</sup>	0.90	0.35d, 1.16d, $J_{AB}$ 4.3	2.50d (4 α-H), 2.87d (4 β-H), $J_{\rm AB}$ 18.4, 5.76 (d, $J$ 10.2, 1-H), 7.28 (d, J 10.2, 2-H)

<sup>*a*</sup> For solutions in CDCl<sub>3</sub> (residual C*H*Cl<sub>3</sub> peak  $\delta$  7.26 as internal standard) on a Bruker AM300 instrument unless otherwise indicated. *J* Values are given in Hz. <sup>*b*</sup> Determined by 2-D analysis on a Bruker AMX500 instrument. <sup>*c*</sup> ~2.45 (dd, *J* ~8.4, 19.3, 16β-H). <sup>*d*</sup> Interchangeable. <sup>*e*</sup> CDCl<sub>3</sub>-CD<sub>3</sub>OD (1:1). <sup>*f*</sup> ~3.57 (t, *J* ~8.5, 17*a*-H). <sup>*g*</sup> CD<sub>3</sub>COCD<sub>3</sub>. <sup>*b*</sup> CD<sub>3</sub>OD. <sup>*i*</sup> 5β-CH<sub>2</sub>OH. <sup>*j*</sup> Overlapping with the 17*a*-H.

proton showed NOEs to the 1 $\beta$ -H (5.4%), the 5-methyl group (7.3%) and the 13-methyl group (1.8%) whereas irradiation of the lowfield 19-proton gave an NOE with the 11 $\beta$ -H (6.3%). These NOE effects are consistent with a  $\beta$  orientation for both the 19-CH<sub>2</sub>OH and the 5-methyl group in compound **14**.

The structure of the diolone **6a** is based on the agreement of its carbon and proton spectra with those observed for the 19(R)-alcohol **2a** and published values.<sup>22</sup>

The presence of NOEs in the triol **15** between the 19-H and the 1 $\beta$ -H (1.7%), the 2 $\beta$ -H (6.5%) and the 4 $\beta$ -H (4.8%) establishes that the 19-H is located over ring A. From the coupling constants it is clear that the 1 $\beta$ -H is equatorial while the 2 $\beta$ -H and the 4 $\beta$ -H are axial (*J* 6.2, 6.2 and 13.0 Hz). Because the 3proton shows axial couplings to the 2 $\beta$ -H (*J* 12.0 Hz) and the 4 $\alpha$ -H (*J* 10.3 Hz) the 3-H must be  $\alpha$  and the 3-alcohol  $\beta$ . NOE effects consistent with this assignment were also observed from the 3-H to the 1 $\alpha$ -H (2.3%), the 4 $\alpha$ -H (4.8%) and the 4 $\beta$ -H (2.6%) and from the 1 $\beta$ -H to the 1 $\alpha$ -H (16%), the 2 $\beta$ -H (2.1%), the 11 $\alpha$ -H (3.7%) and the 19-H (3.6%).

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **16a/17** were indicative of a ketone/hemiketal mixture like **3a/4** and the compound was characterized as the diacetate **16b** which showed proton and carbon spectra in agreement with the 19(*S*)-acetate **3b**.

The triol **18** showed NOEs from the 19-H to the  $6\beta$ -H (2.3%), the  $7\beta$ -H (1%) and the 8-H (10.6%) confirming that the 19-H is located over ring B. Although it is clear from the multiplet structure of the 3-H that the 3-hydroxy group must be axial with the 3-H equatorial, conformational possibilities in ring A preclude an unambiguous assignment of the C-3 stereochemistry. However, based on the assignment of the 3a-alcohol configuration to compound **19** (see below), obtained from the same reaction mixture, the triol **18** is assigned to the 3 $\beta$ -alcohol. Furthermore, on acid treatment compound **18** gave the same ring-opened product **23** obtained from the triol **15** hence confirming the 3 $\beta$ -OH configuration.

The stereochemistry at C-19 in compound **19** was determined from NOEs observed from the 19-H to the  $6\beta$ -H (3.2%), the 7 $\beta$ -H (1.2%) and the 8-H (10%). A small NOE of 0.5% was also observed to the equatorial 4-proton, suggesting that the  $4\alpha$ -H must be axial. Further NOEs were obtained from the 3-H to the  $4\beta$ -H (4.8%) and the axial 1-proton (3.8%) and from the  $4\beta$ -H to the 3-H (5.1%) and the equatorial 2-proton (3.0%). These data are consistent only with a  $2\alpha_3\alpha$ -half chair conformation with the 1 $\beta$ -H,  $2\alpha$ -H and  $4\alpha$ -H (*J* 8.0 Hz) to the 3-H and it follows that the 3-H is  $\beta$  and therefore the 3-hydroxy group is  $\alpha$ .

In compound **21** the 5-H was observed to have axial couplings to both the  $6\beta$ -H and the  $4\beta$ -H, consistent only with  $\alpha$  stereochemistry at C-5. Irradiation of the lowfield 19-proton resulted in NOEs to the 8-H (10%), while irradiation of the highfield 19-proton resulted in NOEs to the 2 $\beta$ -H (5.2%), 4 $\beta$ -H (7.8%). These data imply  $\beta$  stereochemistry at C-10. Consistent with a normal chair conformation for ring A in a 5 $\alpha$ -steroid,<sup>22</sup> both the 2 $\beta$ -H and the 4 $\beta$ -H are observed to be axial. Because the 3-proton is also axial with couplings of 11.2 and 12.2 Hz to the 2 $\beta$ -H and 4 $\beta$ -H, respectively, the 3-hydroxy group is  $\beta$ .

In compound **23**, irradiation of the lowfield 19-proton resulted in NOEs to the 5-H (2.2%), the 6β-H (3.6%) the 8-H (7.2%), in agreement with β stereochemistry at both C-10 and C-5. Irradiation of the 5-H resulted in NOEs to the 4β-H (2.5%), the 6α-H (1.6%), the 6β-H (5.2%) and to the lowfield 19proton (1%), confirming the above conclusion. Irradiation of the highfield 19-proton resulted in an NOE to the 11β-H (6.7%). An axial coupling was observed between the 5-H and the 4α-H (*J* 13.2 Hz), while axial–equatorial couplings were observed between the 4α-H and the 3-H (*J* 4.1 Hz) and between the 3-H and the 2α-H (*J* ~3.5 Hz). Therefore, the C-3 hydroxy group must have β stereochemistry. The <sup>13</sup>C chemical shifts for ring A and B in compounds **22** and **23** are consistent with the stereochemistry assigned at C-5 and C-10.<sup>22</sup>

In compound **25**, from examination of the 1 $\alpha$ -H, 1 $\beta$ -H and 10-H multiplets extracted from the HSQC spectrum, it is clear that the 10-H is axial to ring B but equatorial to ring A. Irradiation of the highfield 5-hydroxymethyl proton resulted in NOEs to the 1 $\beta$ -H (1.3%), the 6 $\alpha$ -H (3.9%), the 10-H (0.8%). Irradiation of the lowfield 5-hydroxymethyl proton resulted in NOEs to the 1 $\beta$ -H (3.4%) and the 10-H (3.0%). These data establish

 Table 2
 <sup>13</sup>C NMR chemical shifts <sup>a</sup>

Carbon 5														
	2a "	2b <sup>b</sup>	<b>2c</b> <sup>c</sup>	<b>3b</b> <sup><i>b,d</i></sup>	<b>3c</b> <sup><i>c</i></sup>	6a <sup>b,e</sup>	<b>6b</b> <sup><i>f</i></sup>	7	8	9 <sup><i>b</i></sup>	10 <sup><i>b</i>,<i>g</i></sup>	11 <sup>b</sup>	12 <sup><i>b</i></sup>	13
1	27.61	22.47	27.31	23.12	20.88	28.05	27.49 <sup>7</sup>	27.83	20.98	23.59	27.68	20.16	28.31	22.70
2	36.28	36.41	36.41	36.37	36.16	36.64	36.26	36.25	35.94	30.31	28.25	35.63	35.39	32.56
3 2	212.31	210.59	212.38	212.02	214.01	215.17	210.87	212.17	213.12	105.45	72.05	214.66	209.72	218.16 <sup>7</sup>
4	47.89	47.20	48.21	43.10	42.86	48.43	47.27	48.09	42.55	36.69	18.72	40.56	41.49	
5	21.19	21.14	20.75	24.44	23.24	21.02 <i>1</i>	21.01	20.86 <sup>7</sup>	23.97	24.66	37.68 <sup>7</sup>	27.89	37.62	53.05 <sup>m</sup>
6	25.71	26.60 <sup>7</sup>	26.31	31.68	31.59	25.95	26.52′	26.05	31.49	25.38	27.21	24.83	27.38	30.21
7	26.23	25.87 <i>1</i>	26.40	25.70	26.08	27.33	27.52′	36.30	25.96	25.97	30.57	26.03	24.58	26.80
8	36.83	36.82	36.73	35.79	36.06	37.33	36.95	36.64	35.94	35.93	36.89 <sup>7</sup>	35.81	35.78	35.68
9	46.47	46.32	46.54	45.53	47.80	46.77	46.17	46.52	44.50	45.16	49.35	44.58	39.92	45.73
10	25.33	24.75	24.61	27.92	28.77	25.64'	24.79	25.56′	29.31	25.97	52.26	30.72	50.36	58.82 <sup>m</sup>
11	24.23	23.79	23.42	24.10	24.65	24.62	24.04	24.23	24.59	24.66	23.81	24.71	20.59	20.97
12	32.20	31.97	32.13	31.48	32.17	37.64	37.25	32.16	32.09	31.30	33.48	31.54	31.81	31.66
13	48.68	48.45	48.67	48.26	48.22	44.12	43.47	48.61	48.20	47.94	48.31	48.28	47.80	47.57
14	51.16	50.92	51.07	50.26	50.26	51.10	50.28	51.00	50.25	50.43	53.26	50.30	51.44	51.19
15	21.62	21.62	21.54	21.55	21.55	23.37	23.29	21.62	21.50	21.65	22.38	21.51	21.68	21.51
16	35.63	35.74	35.81	35.73	35.73	30.13	26.65 <sup>7</sup>	35.82	35.67	35.69	36.10	35.72	35.78	35.68
17 2	221.22	220.40	221.22	220.36	220.36	81.68	82.48	221.14	220.22	220.58	217.80	220.27	220.41	219.89 <sup>7</sup>
18	14.35	14.11	14.08	14.14	14.14	11.55	12.27	14.25	14.12	13.90	14.33	14.14	13.71	13.78
19	63.40	64.21	64.05	62.13	60.37	63.58	64.20	71.83	68.39	65.60		69.09	204.51	204.80
3-Me										50.14	55.87			
19-OMe	58.27 58.98						58.66	58.66	58.20		58.27	58.41		
4-Me												10.18		
5-Me														21.22

Carbon	14 <sup>b,e</sup>	15 <sup><i>b,h</i></sup>	16b <i>'</i>	18 <sup><i>b,h</i></sup>	19 <sup><i>b,h</i></sup>	<b>20</b> <sup><i>h</i></sup>	<b>21</b> <sup><i>b,h</i></sup>	22 <sup>h</sup>	23 <sup>b,h</sup>	25 <sup>b, h</sup>	27a <sup>,j</sup>	27b <sup><i>k</i></sup>	<b>28</b> <sup>b</sup>
1	23.94	30.54	23.22	25.58	24.91	32.11	32.50	22.47	24.37	18.05	152.21	145.00	156.18
2	33.37	31.03	36.46	30.96	32.73	32.69	32.67	29.13	28.18	27.17	129.99	127.14	124.37
3	224.22	68.32	212.16	67.01	68.23	71.14	71.78	66.52	67.58	67.89	195.26	195.21	196.69
4		45.55	43.17	38.32	40.24	40.48	39.30	33.42	34.27	34.93	41.92	40.42	44.90
5	53.89 <i>1</i>	23.09	24.41	23.08	25.13	44.77	46.55	30.93	30.13	39.09	23.52	24.69	21.81
6	30.82	30.30	31.77	36.22	35.78	29.43	29.37	27.04	27.29	35.79	26.70	31.36 <sup>7</sup>	32.66
7	27.80	28.78	26.38	28.05	27.74	33.24	32.96	26.95	26.71	27.38	24.97	24.95	25.10
8	36.63	38.57	35.90	37.82	37.79	38.30	37.32	37.89	36.91	42.42	36.76	36.24	35.81
9	46.87	52.53	45.37	50.22	50.13	53.95	56.62	39.76	40.98	40.64	43.85	44.16	44.09
10	42.98 <sup>7</sup>	26.77	27.90	27.59	27.43	52.91	40.35	37.89	40.53	41.69	27.76	30.89	27.95
11	22.48	25.43	24.36	23.31	25.55	22.53	23.51	21.90	21.78	27.17	23.39	23.96	24.73
12	37.13	38.79	36.78	38.08	38.12	37.88	38.67	38.26	38.55	38.15	31.73	31.45 <i>1</i>	31.46
13	48.14	44.97	43.22	44.71	44.78	43.91	44.25	44.18	44.17	44.03	48.33	48.33	48.27
14	52.01	52.26	49.61	51.21	51.21	52.44	52.83	52.36	52.93	51.56	50.64	50.28	49.94
15	23.11	24.22	23.22	24.05	24.04	24.16	24.34	24.25	24.27	24.14	21.47	21.56	21.60
16	30.00	30.78	27.48	30.66	30.66	30.56	30.66	30.69	30.72	30.71	35.57	35.66	35.70
17	81.41	82.62	82.49	82.47	82.49	82.30	82.55	82.39	82.49	82.64	219.86	219.90	220.18
18	11.27	12.05	12.33	11.86	11.85	11.51	11.87	11.51	11.67	11.60	14.00	14.21	14.12
19 3-OMe	64.18	64.54	62.19	60.61	60.73	210.43	60.68	208.31	66.17	71.56	70.12	61.25	31.31
19-OMe													

4-Me 5-Me 21.32

<sup>*a*</sup> For solution in CDCl<sub>3</sub> (residual CHCl<sub>3</sub> peak at  $\delta_{\rm C}$  77.0 internal standard) unless otherwise indicated on a Bruker AM300 instrument. <sup>*b*</sup> Determined by 2-D analysis on a Bruker AMX500 instrument. <sup>*c*</sup> -0.35 (s, SiMe<sub>3</sub>). <sup>*d*</sup> 20.53 (19-OCO*C*H<sub>3</sub>), 171.14 (19-O*C*OCH<sub>3</sub>). <sup>*e*</sup> CDCl<sub>3</sub>: CD<sub>2</sub>OD (1:1). <sup>*f*</sup> 20.92 (19-OCO*C*H<sub>3</sub>), 170.74 (19-O*C*OCH<sub>3</sub>), 21.14 (OCO*C*H<sub>3</sub>), 171.05 (17-O*C*OCH<sub>3</sub>). <sup>*s*</sup> CD<sub>3</sub>COCD<sub>3</sub>. <sup>*b*</sup> CD<sub>3</sub>OD. <sup>*i*</sup> 20.25 (19-OCO*C*H<sub>3</sub>), 171.13 (19-O*C*OCH<sub>3</sub>), 21.14 (17-OCO*C*H<sub>3</sub>), 171.08 (17-O*C*OCH<sub>3</sub>). <sup>*j*</sup> 20.76 (19-CO*Me*), 169.93 (19-*C*OMe). <sup>*k*</sup> 20.32 (19-CO*Me*), 170.70 (19-*C*OMe). <sup>*l*</sup> Mumbers are interchangeable within the column.

that the 5-hydroxymethyl group is located at C-5 rather than C-10, and that both the C-5 and C-10 stereochemistry is  $\beta$ .

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **27a** and **27b** showed new signals consistent with the introduction of a double bond at C-1. NMR assignments for the 19-unsubstituted compound **28**, based on COSY and NOE measurements, were made for comparison.

### Aromatase inhibition

The 19(R/S)-substituted androstane-3,17-dione derivatives **2a**, **3a/4**, **27a** and **27b** did not show aromatase inhibitory activity.<sup>23</sup> NMR measurements show that the A ring conformation of the saturated 19(R)- and 19(S)-alcohols **2a** and **3a** are in a 'boat' or

'twist' form, respectively.<sup>16</sup> The location of the 19-H would be most favourably located in the R-epimer for aromatase attack but may not be suitably located in either isomer.

### Experimental

Reactions were monitored by TLC which was carried out in the following solvent systems on silica gel (Merck type 60H): acetone–light petroleum (bp 35–60 °C) (LP), diethyl ether–LP, ethyl acetate–LP; compounds were visualized by dipping the plates in 5% sulfuric acid–ethanol followed by heating on a hot-plate at ~120 °C. Flash column chromatography (FCC) was carried out on silica gel (Merck type 60). Anhydrous Na<sub>2</sub>SO<sub>4</sub>

was used as a drying agent for solvents during work-up of a reaction mixture. Melting points were determined on either an Electro-thermal or Kofler type hot-stage apparatus and are uncorrected. Elemental analyses were performed by Mr W. Baldeo, School of Pharmacy, University of London, England.

<sup>1</sup>H and <sup>13</sup>C NMR spectra are reported in Tables 1 and 2. Survey spectra were recorded on a Bruker AM300 instrument while two-dimensional and NOE spectra were recorded on a Bruker AMX500 spectrometer. Samples were measured as ~50 mmol dm<sup>-3</sup> solutions in 5-mm sample tubes in CDCl<sub>3</sub>, CD<sub>3</sub>OD, CDCl<sub>3</sub>-CD<sub>3</sub>OD (1:1), or CD<sub>3</sub>COCD<sub>3</sub> as indicated in the Tables. For samples in CDCl<sub>3</sub> the residual CHCl<sub>3</sub> peak in the solvent ( $\delta_{\rm C}$  77.0 ppm,  $\delta_{\rm H}$  7.26 ppm) was used as the internal reference for both proton and carbon spectra. For the remaining solvents SiMe<sub>4</sub> was used as an internal reference. Sample temperature was controlled at 300 K for all spectra. Carbon spectra were classified as to multiplicity with the DEPT technique.<sup>24</sup>

Homonuclear correlation (COSY), heteronuclear correlation (HSQC) and nuclear Overhauser effect (NOE) difference spectra were recorded as described previously.<sup>1</sup>

#### 19-Formylandrost-4-ene-3,17-dione 1

19-Hydroxyandrost-4-ene-3,17-dione (5.0 g, 16.4 mmol) and pyridinium dichromate (10.0 g, 26.6 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 cm<sup>3</sup>) and the mixture stirred at 20 °C for 18 h. After dilution with diethyl ether (100 cm<sup>3</sup>), the mixture was filtered through Celite to give, after work-up, a residue which on FCC on elution with 30% acetone–LP, gave the aldehyde **1** (3.0 g, 60%), mp 132–134 °C (from CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O) (lit., <sup>25</sup> 129–133 °C).

# $(19\it{R})$ -19-Hydroxy-5 $\beta$ ,19-cycloandrostane-3,17-dione 2a, (19.5)-19-hydroxy-5 $\beta$ ,19-cycloandrostane-3,17-dione 3a/(19.5)-3-hydroxy-3 $\beta$ ,19-oxido-5 $\beta$ ,19-cycloandrostan-17-one 4 and estra-5(10)-ene-3,17-dione 5a

Zn powder (40 g) was added to a solution of the aldehyde 1 (8.00 g, 26.5 mmol) in 50% acetic acid (160 cm<sup>3</sup>) and the mixture stirred for 1.5 h, after which it was diluted with CH<sub>2</sub>Cl<sub>2</sub> (500 cm<sup>3</sup>) and filtered. The filtrate was washed with water and aqueous NaHCO<sub>3</sub>, dried, concentrated (~15 cm<sup>3</sup>) and diluted with Et<sub>2</sub>O to give the 19(R)-alcohol 2a (5.00 g, 62.5%), mp 160-167 °C which on recrystallization gave an analytically pure sample, mp 169-179 °C (decomp.) (from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O) (Found: C, 75.4; H, 8.8. C<sub>19</sub>H<sub>26</sub>O<sub>3</sub> requires C, 75.5; H, 8.7%). A portion of the mother liquor (1 g) on FCC gave, on elution with 80% Et<sub>2</sub>O–LP, estra-5(10)-3,17-dione **5a** (240 mg, 3.3%), mp 144–148 °C (from Et<sub>2</sub>O–LP) (lit.,<sup>26</sup> 144–146 °C), the 19(*R*)-alcohol **2a** (130 mg), mp 160–167 °C (from CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O) and the 19(S)-alcohol/hemiketal mixture 3a/4 (45 mg, 0.56%), mp 160-165 °C (from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O-LP) (Found: C, 75.4; H, 8.7. C<sub>19</sub>H<sub>26</sub>O<sub>3</sub> required: C, 75.5; H, 8.7%). The wide mp range observed results from the thermal instability of the cyclopropanols.

# (19*R*)-19-Hydroxy-5β,19-cycloandrostane-3,17-dione acetate 2b To the 19(*R*)-alcohol 2a (200 mg, 0.66 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 cm<sup>3</sup>) was added 4-dimethylaminopyridine (DMAP) (50 mg) and Ac<sub>2</sub>O (1 cm<sup>3</sup>) after which the mixture was stirred at 20 °C for 1 h. After dilution with water (10 cm<sup>3</sup>), the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the extract washed with saturated aqueous NaHCO<sub>3</sub> and water to give, on work-up, the 19(*R*)-acetate 2b (100 mg, 44%), mp 180–183 °C (from CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O)

#### (19R)-19-Trimethylsiloxy-5ß,19-cycloandrostane-3,17-dione 2c

(Found: C, 73.0; H, 8.5. C<sub>21</sub>H<sub>28</sub>O<sub>4</sub> requires C, 73.2; H, 8.2%).

To a solution of the 19(*R*)-alcohol **2a** (150 mg, 0.50 mmol) in  $CH_2Cl_2$  (2 cm<sup>3</sup>) was added 1.0 M 1-(trimethylsilyl)imidazole in  $CH_2Cl_2$  (0.5 cm<sup>3</sup>) and the mixture stirred at 20 °C for 2 h. It was then poured into water and extracted with  $CH_2Cl_2$ . The extract was washed with water to give, on work-up, the trimethylsilyl

ether **2c** (74 mg, 40%), mp 96–98 °C (from Et<sub>2</sub>O–LP) (Found: C, 70.6; H, 9.2. C<sub>22</sub>H<sub>34</sub>O<sub>3</sub>Si requires C, 70.5; H, 9.15%).

#### (19.5)-19-Hydroxy-5 $\beta$ ,19-cycloandrostane-3,17-dione 3a/ hemiketal 4 from the dione 2a

**Epimerization in KOH–MeOH.** The 19(*R*)-alcohol **2a** (150 mg, 0.50 mmol) was dissolved by stirring in 0.5 M metanolic KOH (10 cm<sup>3</sup>) at 20 °C for 1 h. After dilution with  $CH_2Cl_2$  (80 cm<sup>3</sup>) the mixture was washed with water and worked up to give the 19(*S*)-alcohol/hemiketal mixture **3a/4** (105 mg, 70%), mp 160–165 °C (decomp.) (from  $CH_2Cl_2$ –Et<sub>2</sub>O).

**Epimerization in HCl-THF.** The 19(*R*)-alcohol **2a** (150 mg, 0.50 mmol) was stirred in THF (15 cm<sup>3</sup>) containing 12 M aqueous HCl (0.5 cm<sup>3</sup>) at 20 °C for 4 h. Work-up as above gave, after FCC, on elution with 20% acetone–LP the 19(*S*)-alcohol/hemiketal mixture **3a** and **4** (64 mg, 42%), mp 147–166 °C (decomp.) (from CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O).

## (19.5)-19-Hydroxy-5 $\beta$ ,19-cycloandrostane-3,17-dione acetate 3b To the 19(*S*)-alcohol/hemiketal mixture 3a/4 mixture (100 mg, 0.20 mmol) in pyridine (1 cm<sup>3</sup>) was added DMAP (25 mg) and

Ac<sub>2</sub>O (1 cm<sup>3</sup>) and the mixture stirred at 20 °C for 1 h. After this, the mixture was poured into water and extracted with  $CH_2Cl_2$ . The extract was washed with water to give on FCC on elution with 25% acetone–LP the non-crystalline cyclopropanol acetate **3b** (80 mg, 70%).

### $(19.5) \hbox{-} 19 \hbox{-} Trimethylsiloxy \hbox{-} 5\beta, 19 \hbox{-} cycloandrostane \hbox{-} 3, 17 \hbox{-} dione \ 3c$

To the 19(*S*)-alcohol/hemiketal mixture **3a**/**4** (75 mg, 0.25 mmol) in dimethylformamide (DMF) (0.5 cm<sup>3</sup>) was added 1.0 M 1-(trimethylsilyl)imidazole in  $CH_2Cl_2$  (0.2 cm<sup>3</sup>) and the mixture stirred at 20 °C for 3 h. After dilution with Et<sub>2</sub>O the mixture was washed with water to give, on work-up, the silyl ether **3c** (32 mg, 35%), mp 122–125 °C (from Et<sub>2</sub>O–LP) (Found: C, 70.55; H, 9.3.  $C_{22}H_{34}O_3$ Si required: C, 70.5; H, 9.15%).

## (19*R*)-19-Hydroxy-5 $\beta$ ,19-cycloandrostane-3,17-dione 2a, estr-5(10)-ene-3,17-dione 5a, 17 $\beta$ -hydroxyestr-5(10)-en-3-one 5b and (19*R*)-17 $\beta$ ,19-dihydroxy-5 $\beta$ ,19-cycloandrostan-3-one 6a

A solution of the aldehyde **1** (500 mg, 1.66 mmol) in tetrahydrofuran (25 cm<sup>3</sup>) was added over a period of 1 h to a stirred mixture of liquid ammonia (100 cm<sup>3</sup>) and THF (10 cm<sup>3</sup>) containing lithium metal (681 mg, 98 mmol). Stirring was continued for a further 30 min at which time NH<sub>4</sub>Cl (7.0 g, 130 mmol) was added to the mixture followed by Et<sub>2</sub>O (100 cm<sup>3</sup>). Following evaporation of the ammonia the residue was washed with water and evaporated to provide a residue. This on FCC with 10–40% acetone–LP as eluent gave fractions which yielded the ketone **5a** (50 mg, 11%), mp 147–149 °C (from acetone–LP) (lit.,<sup>26</sup> 144–146 °C), the 17β-alcohol **5b** (53 mg, 12%), mp 192– 196 °C (from acetone–EtOAc) (lit.,<sup>27</sup> 193–196 °C), the 19(*R*)alcohol **2a** (55 mg, 11%), mp 166–168 °C (from CH<sub>2</sub>Cl<sub>2</sub>), and the 17β,19(*R*)-diol **6a** (173 mg, 34%), mp 168–170 °C (from acetone–EtOAc).

### (19R)-17 $\beta$ ,19-Dihydroxy-5 $\beta$ ,19-cycloandrostan-3-one diacetate 6b

The 19(*R*)-diol **6a** (153 mg, 0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 cm<sup>3</sup>) was treated with Et<sub>3</sub>N (0.20 cm<sup>3</sup>) and Ac<sub>2</sub>O (0.5 cm<sup>3</sup>), at 20 °C for 1 h after which it was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 cm<sup>3</sup>). The organic layer was separated, washed with 3% aqueous HCl, water and aqueous NaHCO<sub>3</sub> and worked up to give a residue which on FCC with 10% acetone–LP as eluent gave the 19(*R*)-diacetate **6b** (130 mg, 67%), mp 139.5–142 °C (from EtOAc–LP) (Found: C, 70.9; H, 8.3. C<sub>23</sub>H<sub>32</sub>O<sub>5</sub> requires C, 71.1; H, 8.3%).

# $\begin{array}{l} (19\it{R})\mbox{-}19\mbox{-}Methoxy\mbox{-}5\beta\mbox{,}19\mbox{-}cycloandrostane\mbox{-}3\mbox{,}17\mbox{-}dione\mbox{ 7, (19.S)\mbox{-}19\mbox{-}methoxy\mbox{-}5\beta\mbox{,}19\mbox{-}cycloandrostane\mbox{-}3\mbox{,}17\mbox{-}dione\mbox{ 8 (19.S)\mbox{-}3\mbox{-}methoxy\mbox{-}3\beta\mbox{,}19\mbox{-}epoxy\mbox{-}5\beta\mbox{,}19\mbox{-}cycloandrostan\mbox{-}3\mbox{-}17\mbox{-}one\mbox{ 9, 3,}19\mbox{-}19\mbox{-}trimethoxy\mbox{-}3\beta\mbox{,}5\beta\mbox{-}cycloandrostan\mbox{-}17\mbox{-}one\mbox{ 9, 3,}19\mbox{-}19\mbox{-}10\mbox{-}trimethoxy\mbox{-}3\beta\mbox{,}5\beta\mbox{-}cycloandrostan\mbox{-}17\mbox{-}one\mbox{ 10}\mbox{-}10\mbox{-}1$

To a solution of the 19(R)-alcohol 2a (360 mg, 1.19 mmol) in

MeOH (30 cm<sup>3</sup>) cooled in an ice–water bath was added 12 M aqueous HCl (0.5 cm<sup>3</sup>). After the mixture had been allowed to come to 20 °C, it was stirred for 3 h, diluted with Et<sub>2</sub>O (150 cm<sup>3</sup>) and washed with water. Work-up gave a residue which on FCC with 30% Et<sub>2</sub>O–LP as eluent gave fractions (56 mg) which after two crystallizations from Et<sub>2</sub>O–LP yielded the 3 $\beta$ ,5 $\beta$ -cyclopropanol **10** (14 mg, 3%), mp 104–106 °C (from Et<sub>2</sub>O–LP) (Found: C, 73.0; H, 9.6. C<sub>22</sub>H<sub>34</sub>O<sub>4</sub> requires C, 72.9; H, 9.45%), the 3-methoxy ketal **9** (107 mg, 28%), mp 220–223 °C (from CH<sub>2</sub>Cl<sub>2</sub>–acetone–LP), the 19(*R*)-methyl ether **7** (66 mg, 18%), mp 115–118 °C (from acetone–LP) or mp 199–203 °C (from Et<sub>2</sub>O) (Found: C, 75.85; H, 8.9. C<sub>20</sub>H<sub>28</sub>O<sub>3</sub> requires C, 75.9; H, 8.9%), and the 19(*S*)-methyl ether **8** (104 mg, 28%), mp 147–149 °C (from acetone–LP).

### $(19.5)-19-Methoxy-5\beta, 19-cycloandrostane-3, 17-dione~8~and (19.5)-3-methoxy-3\beta, 19-epoxy-5\beta, 19-cycloandrostan-17-one~9$

The 19(*S*)-alcohol/hemiketal mixture **3a**/4 (480 mg, 1.6 mmol) was added to NaH (50% oil suspension; 96 mg, 2 mmol) in benzene (5 cm<sup>3</sup>) and DMF (2.5 cm<sup>3</sup>) and the mixture stirred for 5 min at 20 °C. Iodomethane (1.12 g, 8.0 mmol) was then added to the mixture and stirring continued at 20 °C for 1 h. The mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water and worked up to give a residue which on FCC with 12% acetone–LP as eluent gave the 3-methoxyketal **9** (223 mg, 44%), mp 224–226 °C (from CH<sub>2</sub>Cl<sub>2</sub>–acetone–LP) (Found: C, 75.7; H, 9.0. C<sub>20</sub>H<sub>28</sub>O<sub>3</sub> requires C, 75.9; H, 8.9%), the 19(*S*)-methyl ether **8** (90 mg, 18%), mp 150–151 °C (from acetone–LP) (Found: C, 75.7; H, 8.9. C<sub>20</sub>H<sub>28</sub>O<sub>3</sub> requires C, 75.9; H, 8.9%); and starting material **3a**/4 (65 mg, 13.5%), mp 156–172 °C (from CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O).

# (19.5)-3-Methoxy-3 $\beta$ ,19-epoxy-5 $\beta$ ,19-cycloandrostan-17-one 9 and (19.5)-19-methoxy-4 $\alpha$ -methyl-5 $\beta$ ,19-cycloandrostane-3,17-dione 11

To a stirred solution of the 19(R)-alcohol **2a** (300 mg, 0.99 mmol) in benzene (5 cm<sup>3</sup>) and DMF (5 cm<sup>3</sup>) was added iodomethane (700 mg, 5.0 mmol) followed by NaH (50% oil suspension; 250 mg, 5.2 mmol) over 15 min. Stirring was continued at 20 °C for 2 h, after which the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water to give, on work-up, a residue. This, on elution with 5–8% acetone–LP gave the 3-methoxy ketal **9** (105 mg, 33%), mp 220–224 °C (from CH<sub>2</sub>Cl<sub>2</sub>–LP) and the 4 $\alpha$ -methyl derivative **11** (67 mg, 20%), mp 133–135 °C (from Et<sub>2</sub>O–LP) (Found: C, 76.1; H, 9.4. C<sub>21</sub>H<sub>30</sub>O<sub>3</sub> requires C, 76.3; H, 9.15%).

### 19-Formyl-5 $\beta$ -androstane-3,17-dione 12 and 19-formyl-5 $\beta$ -methyl-A-nor-5 $\beta$ -androstane-3,17-dione 13

The 19(*R*)-alcohol **2a** (300 mg, 0.99 mmol) was heated to reflux with toluene-*p*-sulfonic acid monohydrate (90 mg, 0.47 mmol) in benzene (10 cm<sup>3</sup>) for 2 h after which it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water. Work-up gave a residue which on FCC with 60% Et<sub>2</sub>O–LP as eluent gave the A-norsteroid **13** (48 mg, 16%), mp 145–150 °C (from CH<sub>2</sub>Cl<sub>2</sub>–LP) which was free of extraneous <sup>1</sup>H and <sup>13</sup>C NMR signals but proved to be too unstable for further purification, and the 19-formyl 5β-androstane-3,17-dione **12** (153 mg, 51%), mp 139–142 °C (from CH<sub>2</sub>Cl<sub>2</sub>–LP) (Found: C, 75.6; H, 8.85. C<sub>19</sub>H<sub>26</sub>O<sub>3</sub> requires C, 75.5; H, 8.7%).

### $19\mbox{-}Formyl-5\beta\mbox{-}methyl-A\mbox{-}nor-5\beta\mbox{-}androstane-3,17\mbox{-}dione\mbox{-}13\mbox{ and }5\beta\mbox{-}methyl-17\beta,19\mbox{-}dihydroxy-A\mbox{-}nor-5\beta\mbox{-}androstan-3\mbox{-}one\mbox{-}14$

The 19(*R*)-alcohol **2a** (250 mg, 0.83 mmol) was heated to reflux in 0.5  $\mbox{M}$  methanolic KOH (20 cm<sup>3</sup>) under argon for 3 h after which it was cooled to 20 °C, and treated with NaBH<sub>4</sub> (600 mg, 16 mmol). The mixture was stirred for 30 min after which it was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 3% aqueous HCl and water. Work-up gave a residue which on FCC with 30% acetone–LP as eluent gave the diol **14** (143 mg, 56%), mp 195– 197 °C (from acetone–LP) (Found: C, 74.3; H, 9.7.  $C_{19}H_{30}O_3$  requires C, 74.5; H, 9.9%). In a separate reaction the Anorsteroid **13** (57 mg from 150 mg, 37%), mp 147–153 °C (from acetone–LP) was separated by FCC with 15% acetone–LP as eluent but was not further purified.

### $(19\it{R})$ -17<br/>β,19-Dihydroxy-5β,19-cycloandrostan-3-one 6a and $(19\it{R})$ -5<br/>β,19-cycloandrostane-3β,17β,19-triol 15

LTBAH (168 mg, 0.66 mmol) was added to a solution of the 19(R)-alcohol 2a (200 mg, 0.66 mmol) in THF (20 cm<sup>3</sup>) and the mixture stirred at 20 °C for 14 h when TLC showed the presence of starting material and two products. A second portion of LTBAH (168 mg, 0.66 mmol) was added to the mixture and stirring continued for a further 4 h when TLC showed the absence of starting material. The mixture was then diluted with EtOAc (100 cm<sup>3</sup>) and the organic layer separated, washed with 5% aqueous HCl and water, dried and evaporated to give a residue. This on FCC with 2.5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> as eluent gave the diolone 6a (89 mg, 44%), mp 165-168 °C (from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O) (Found: C, 72.9; H, 9.3. C<sub>19</sub>H<sub>28</sub>O<sub>3</sub>·0.5H<sub>2</sub>O requires C, 72.9; H, 9.65%) and the 19(R)triol 15 (71 mg, 35%), mp 147-152 °C (from acetone-LP) (Found: C, 70.1; H, 9.9. C<sub>19</sub>H<sub>30</sub>O<sub>3</sub>·H<sub>2</sub>O requires C, 70.3; H, 9.9%).

### (19*R*)-Cycloandrostane- $3\beta$ ,17 $\beta$ ,19-triol 15

The 19(*R*)-alcohol **2a** (450 mg, 1.49 mmol) in methanol (25 cm<sup>3</sup>) was treated with NaBH<sub>4</sub> (125 mg, 3.3 mmol) at 20 °C for 30 min after which the mixture was diluted with EtOAc (80 cm<sup>3</sup>), washed with water and concentrated at <40 °C to *ca.* 10 cm<sup>3</sup> to give a residue. This afforded the 19(*R*)-triol **15** (307 mg, 68%), mp 147–152 °C (from acetone–LP).

### (19.5)-17,19-Dihydroxy-5 $\beta$ ,19-cycloandrostan-3-one 16a/(19.5)-3-hydroxy-3 $\beta$ ,19-epoxy-5 $\beta$ ,19-cycloandrostan-17-one 17

LTBAH (340 mg, 1.34 mmol) was added to a solution of the 19(*S*)-alcohol/hemiketal **3a**/4 (200 mg, 0.66 mmol) in THF (20 cm<sup>3</sup>) and the mixture stirred at 20 °C for 14 h when TLC showed the presence of one new component. Work-up was as described for compound **6a**. The EtOAc extract was concentrated under reduced pressure at <40 °C and diluted with Et<sub>2</sub>O to give the 19(*S*)-alcohol/hemiketal **16a**/17 (170 mg, 42%), mp 138–141 °C (from acetone–LP) (Found: C, 72.7; H, 9.4.  $C_{19}H_{28}O_3 \cdot 0.5H_2O$  requires C, 72.9; H, 9.65%).

### (195)-17 $\beta$ ,19-Dihydroxy-5 $\beta$ ,19-cycloandrostan-3-one diacetate 16b

The 19(*S*)-alcohol/hemiketal **16a**/**17** (70 mg, 0.23 mmol) was dissolved in pyridine (0.5 cm<sup>3</sup>) and treated with acetic anhydride (0.5 cm<sup>3</sup>) for 18 h to give, after FCC with 8% acetone–LP as eluent, the diacetate **16b** (44 mg, 49%), mp 110–112 °C (from acetone–LP) (Found: C, 71.0; H, 8.3.  $C_{23}H_{32}O_5$  requires C, 71.1; H, 8.3%).

### (19.5)-Cycloandrostane-3 $\beta$ ,17 $\beta$ ,19-triol 18 and (19.5)-cycloandrostane-3 $\alpha$ ,17 $\beta$ ,19-triol 19

The 19(*S*)-alcohol/hemiketal **3a**/**4** (270 mg, 0.89 mmol) in methanol (15 cm<sup>3</sup>) was treated with NaBH<sub>4</sub> (75 mg, 2.0 mmol) at 20 °C for 30 min after which the mixture was diluted with EtOAc (80 cm<sup>3</sup>) and washed with water. Work-up gave a residue which, in FCC with 30% acetone–LP as eluent, gave the 3β-alcohol **18** (172 mg, 62%), mp 165–169 °C (from MeOH-acetone–LP) (Found: C, 72.5; H, 9.9. C<sub>19</sub>H<sub>30</sub>O<sub>3</sub>·0.5H<sub>2</sub>O requires C, 72.4; H, 9.9%) and the non-crystalline  $3\alpha$ -alcohol **19** (34 mg, 12%) which proved too unstable for further purification.

### 3 $\beta$ ,17 $\beta$ -Dihydroxy-5 $\alpha$ -androstan-19-al 20 and 5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ ,19-triol 21

The 19(R)-triol **15** (150 mg, 0.50 mmol) was heated to reflux in 0.5 M methanolic KOH (10 cm<sup>3</sup>) under argon for 24 h. After

cooling to 20 °C the mixture was treated with NaBH<sub>4</sub> (200 mg, 5.3 mmol) and stirred for 30 min. It was then diluted with ethyl acetate and washed with water to give, after FCC with 7.5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> as eluent, the triol 21 (73 mg, 48%), mp 227-232 °C (from MeOH-acetone-LP) (lit.,10 233-234 °C from acetone). In a separate reaction as above the aldehyde 20 (40 mg from 100 mg, 40%), mp 163-167 °C (from acetone-LP) was isolated by FCC with 30% acetone-LP as eluent but proved to be too unstable for further purification.

#### 36,176-Dihydroxy-56-androstan-19-al 22 and 56-androstane-36,176,19-triol 23

The 19(R)-triol 15 (100 mg, 0.33 mmol) was stirred with THF (15 cm<sup>3</sup>) containing 12 м aqueous HCl (0.5 cm<sup>3</sup>) at 25 °C for 24 h after which the mixture was diluted with EtOAc (100 cm<sup>3</sup>), washed with water, and evaporated under reduced pressure at 40 °C. The residue was taken up in MeOH (10 cm<sup>3</sup>) and treated with NaBH<sub>4</sub> (200 mg, 5.29 mmol) at 25 °C for 30 min. EtOAc (100 cm<sup>3</sup>) was added to the mixture which was then washed with water. Work-up provided a residue which on FCC with 7.5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> as eluent, gave the triol **23** (26 mg, 25%), mp 220-221 °C from (MeOH-acetone-LP) or mp 220-221.5 °C (from EtOAc) [lit.,<sup>11</sup> 230-232 °C (from EtOAc)]. Because of the mp difference elemental analysis was carried out (Found: C, 73.7; H, 10.3. C<sub>19</sub>H<sub>32</sub>O<sub>3</sub> requires C, 74.0; H, 10.5%). In a separate reaction the aldehyde 22 (39 mg from 100 mg, 39%), mp 170-174 °C (from acetone-LP) was obtained by FCC with 20% acetone-LP as eluent, but proved to be too unstable for further purification.

### 56-Androstane-36,176,19-triol 23

The 19(S)-triol 18 (150 mg, 0.49 mmol) in THF (15 cm<sup>3</sup>) containing 12 M aqueous HCl (0.5 cm<sup>3</sup>) was set aside at 20 °C for 49 h after which it was worked up as described for the preparation of compound 23 from the triol 15, to give a residue which was taken up in MeOH and treated with NaBH<sub>4</sub> (200 mg, 5.29) mmol). The mixture was stirred for 30 min and worked up to give the triol 23 (69 mg, 45%), mp 220-221 °C (from MeOHacetone-LP).

### 5α-Androstane-3β,17β,19-triol 21 and 5β-hydroxymethyl-10βestrane-3β,17β-diol 25

The 19(S)-triol 18 (150 mg, 0.49 mmol) was dissolved in 0.5 M methanolic KOH (10 cm<sup>3</sup>) and the solution heated to reflux for 72 h; it was then cooled to 20 °C and treated with NaBH<sub>4</sub> (200 mg, 5.3 mmol), the mixture being stirred for 30 min before dilution with EtOAc. After this, the mixture was washed with water to give on FCC with 7.5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> as eluent the triol 25 (22 mg, 15%), mp 194-195 °C (from acetone-LP) (Found: C, 73.9; H, 10.6. C<sub>19</sub>H<sub>32</sub>O<sub>3</sub> requires C, 74.0; H, 10.5%) and the triol 21 (45 mg, 30%), mp 227-231 °C (from MeOHacetone-LP).

### (19R)-19-Hydroxy-5β,19-cycloandrost-1-ene-3,17-dione 27a

The saturated dione 2b (500 mg, 1.45 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 cm<sup>3</sup>) was added in portions over 5 min, to a stirred and cooled (acetone-solid CO<sub>2</sub> bath) mixture of Pr<sup>i</sup><sub>2</sub>EtN (230 μl, 1.9 mmol) and trimethylsilyl trifluoromethanesulfonate (340 µl, 0.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 cm<sup>3</sup>), under Ar. After the mixture had been stirred for a further 1.5 h it was treated with MeOH (0.5 cm<sup>3</sup>) to destroy the excess of reagent and diluted with further ether. It was then washed with brine, dried and evaporated to give a residue which on FCC (18% Et<sub>2</sub>O-0.2% Et<sub>3</sub>N in LP) gave fractions of the 2- and 3-enol silyl ethers 26a (464 mg) (HC-2/4, 6:1:1);  $\delta$ (CDCl<sub>3</sub>) 4.66 (ddd, J 6.1, 2.4, 2.4) and 5.30 (d, J 2, allylic coupling). Pd(OAc)<sub>2</sub> (263 mg, 1.17 mmol) in MeCN (5 cm<sup>3</sup>) was added to the enol mixture dissolved in MeCN (30 cm<sup>3</sup>) at 20 °C and the solution stirred at 50 °C for 5.5 h.<sup>28</sup> It was then evaporated under reduced pressure, diluted with Et<sub>2</sub>O and treated with activated carbon. After the mixture had been

heated under reflux for 5 min, it was filtered through Celite and evaporated to give a residue which on FCC (5% acetone-LP) gave the unsaturated dione 27a (120 mg, 24%), mp 146-149 °C (from Et<sub>2</sub>O-LP) (Found: C, 73.4; H, 7.8. C<sub>21</sub>H<sub>26</sub>O<sub>4</sub> requires C, 73.6; H, 7.65%).

### (19S)-19-Hydroxy-56,19-cycloandrost-1-ene-3,17-dione 27b

Trimethylsilyl trifluoromethanesulfonate (3.5 cm<sup>3</sup>, 0.018 mmol) was added to a stirred solution of the saturated dione 3b (748 mg, 2.17 mmol) and Et<sub>3</sub>N (6 cm<sup>3</sup>, 42 mmol) in dry DMF cooled in an ice-bath. After 2 h the mixture was poured into Et<sub>2</sub>O and the organic layer separated and washed with brine to give after FCC (8% EtOAc-LP) fractions (462 mg, 0.99 mmol) of the 2- and 3-enol silvl ethers **26b** (H-2/4, 2.3:1);  $\delta$ (CDCl<sub>3</sub>) 3.70 (s, 19-H in 3-enol) and 3.79 (s, 19-H in 2-enol). These fractions were dissolved in MeCN (30 cm<sup>3</sup>) and treated with Pd(OAc)<sub>2</sub> (228 mg, 1.02 mmol) at 40 °C for 30 min and worked up as described for 27a to give the unsaturated dione 27b (238 mg, 32%), mp 203-205 °C (from CH<sub>2</sub>Cl<sub>2</sub>-EtOAc) (Found: C, 73.65; H, 7.9. C<sub>21</sub>H<sub>26</sub>O<sub>4</sub> requires C, 73.6; H, 7.65%).

#### 5β,19-Cycloandrost-1-ene-3,17-dione 28

Treatment of 19-hydroxyandrost-4-ene-3,17-dione (500 mg, 1.65 mmol) with diethyl(2-chloro-1,1,2-trifluoroethyl)amine as described by Knox et al.14 gave the 1-ene, mp 184-186 °C (120 mg, 25%) (lit.,<sup>14</sup> mp 185–187 °C).

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