19-Hydroxy-5β,19-cyclosteroids: synthesis, isomerization and ring opening

John F. Templeton,*[a] Yangzhi Ling,[a] Weiyang Lin,[a] Helena Majgier-Baranowska[a] and Kirk Marat[b]

[a] *Faculty of Pharmacy, University of Manitoba, Winnipeg, Manitoba, Canada R3T 2N2*
[b] *Department of Chemistry, University of Manitoba, Winnipeg, Manitoba, Canada R3T 2N2*

19(*R*/*S*)-Hydroxy-5β,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-5β,19-cyclosteroid together with the 17β-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 3α-methoxy-3β,5β-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 5β-methyl-A-norsteroid. Metal hydride reduction of the 3-ketone in the 19(*R*)-alcohol gave only the 3β-alcohol whereas the 19(*S*)-alcohol gave both the 3α- and 3β-alcohols. Acid treatment of the 3β-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 5β,19-cyclosteroids, namely, 19(*R*/*S*)-chloro-5β,19-cycloandrostane[1] and 19(*R*/*S*)-hydroxy-5β,19-cycloandrostane.[2] In this report details of the synthesis, isomerization, metal hydride reduction, and acid and base catalysed cyclopropanol ring transformations of the 19(*R*/*S*)-hydroxy-5β,19-cycloandrostanes are presented.

19(*R*/*S*)-Hydroxy-5β,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.[3] Aromatase inhibition or inactivation is of therapeutic importance because malignant cell growth in many female breast cancers is dependent on endogenous estrogen levels.[4]

The synthesis of unsubstituted 5β,19-cyclosteroids has been reported by addition of the Simmons–Smith reagent to the steroid 5(10)-double bond,[5] reduction of the 19,19-dibromo-5β,19-cyclosteroid,[6] elimination of a 19-methanesulfonate 4-ene with hydride ion[7] or a 5-ene with pyridine[8] or acetate ion,[9] reductive elimination of a C-19 sulfonate or halogen in the steroid 4-en-3-one with Li– or Na–NH_3,[9–11] or zinc in aqueous acetic acid.[7,12,13] A unique rearrangement of the steroid 19-diethyl-[2-chloro-1,1,2-difluoroethyl]-amine derivative gave the C-1 unsaturated 5β,19-cyclosteroid.[14] Treatment of the 19-methanesulfonate 1,4-dien-3-one with biphenyl in tetrahydrofuran (THF) also gave the C-1 unsaturated 5β,19-cyclosteroid.[15]

Results and discussion

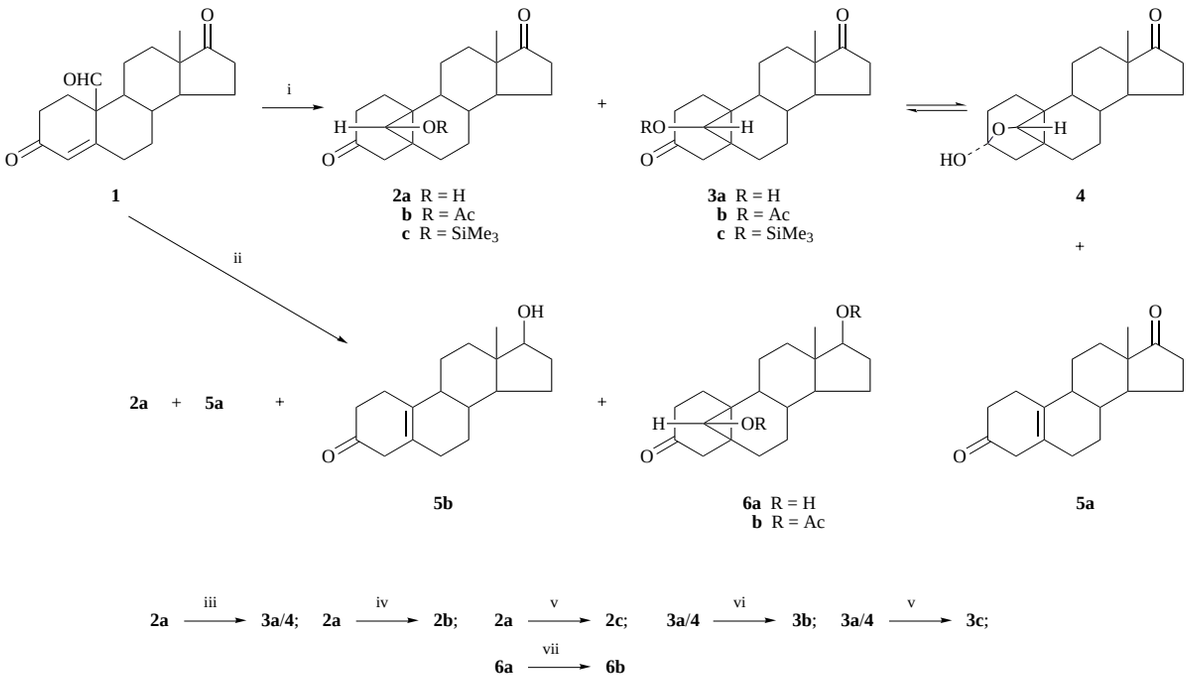
19-Formylandrost-4-ene-3,17-dione **1**, prepared by pyridinium dichromate oxidation of 19-hydroxyandrost-4-ene-3,17-dione, on treatment with zinc in aqueous acetic acid gave a mixture of the 19(*R*/*S*)-hydroxy-5β,19-cycloandrostane derivatives (Scheme 1). The major product was the 19(*R*)-alcohol **2a** (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-3,17-dione **5a** (3.3%) was probably initiated by H_2O attack on the 19-aldehyde. Bond formation between carbons 5 and 19 occurs readily as shown by the facile reductive cyclizations to the 19-unsubstituted 5β,19-cyclosteroids.[7–15] 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 π-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 17β-alcohol analogue **6a** (34%), and the 5(10)-olefin **5a** (11%) together with its 17β-alcohol analogue **5b** (12%). The 17β-alcohol **6a** was further characterized as the diacetate **6b**.

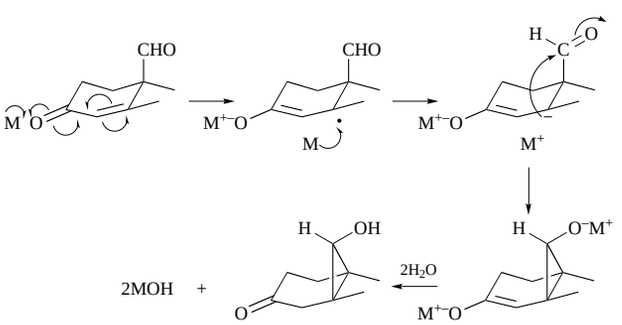
A detailed NMR analysis has determined the conformation of ring A in the 19(*R*)- and 19(*S*)-substituted derivatives.[16] Ring A in the 19(*R*)-isomers, in which a hydrogen is located over ring A, takes up a boat conformation. The 19(*S*)-isomers, with a larger substituent over ring A, adopt an inverted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

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

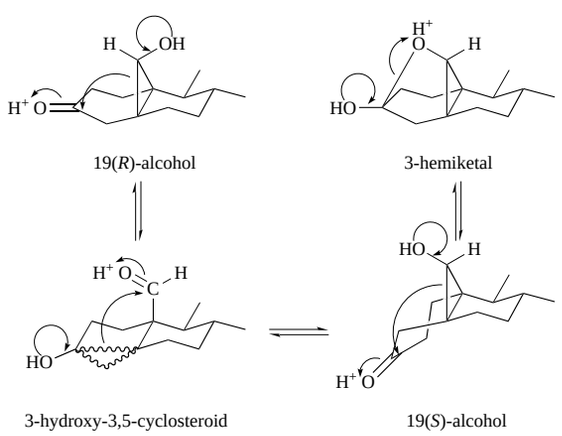
Treatment of the 19(*R*)-alcohol **2a** with dilute solutions of either concentrated HCl–THF or KOH–MeOH at 20 °C for 1–4 h caused isomerization to the thermodynamically more stable 19(*S*)-alcohol **3a**/**4**. In this homoenolic system[19] isomerization can occur through an initial 19(*R*)-cyclopropanol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



Scheme 1 *Reagents:* i, Zn–HOAc–H_2O; ii, Li–NH_3; iii, KOH–MeOH or HCl–THF; iv, Ac_2O–DMAP–CH_2Cl_2; v, Me_3Si–imidazole–CH_2Cl_2; vi, Ac_2O–pyridine; vii, Ac_2O–DMAP–Et_3N–CH_2Cl_2



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



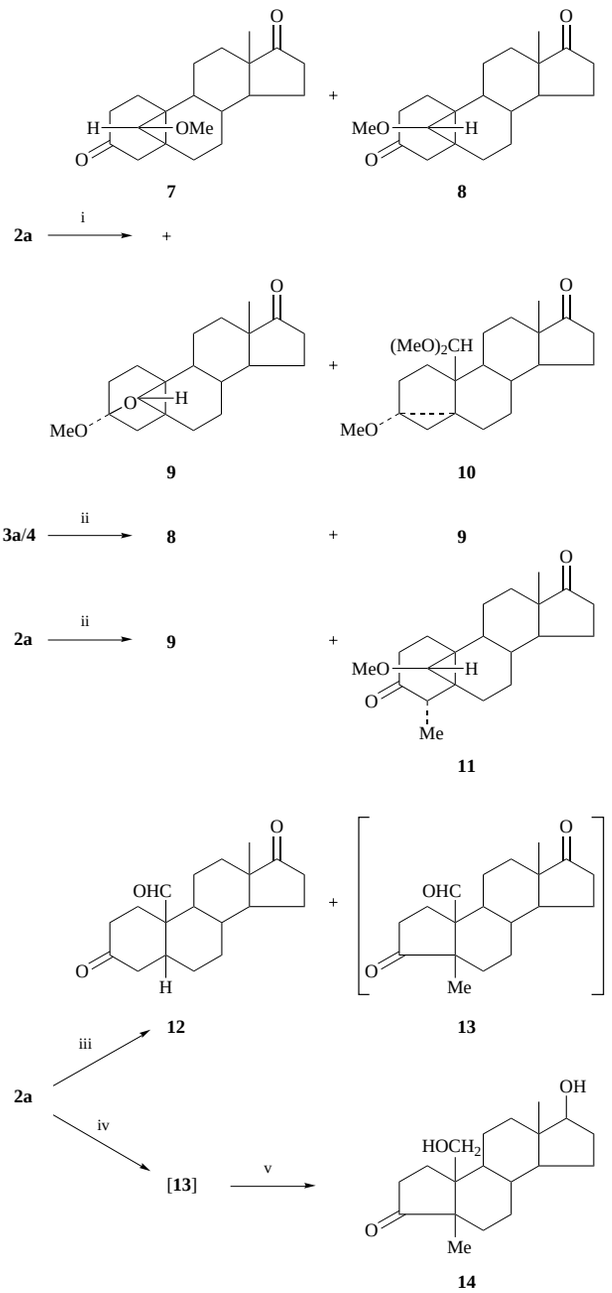
Scheme 3 Isomerization of 19(*R*)- and 19(*S*)-hydroxy-5,19-cyclosteroids

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 3α-methoxy-3β,5β-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 3α-methoxy-3β,5β-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 19-aldehyde **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 4α-methyl compound **11**, derivable from the product **8** above, was obtained together with the 3-methoxy ketal **9**. Isomerization of the 19(*R*)-alcohol **2a** to the 19(*S*)-alcohol **3a**/**4** occurs rapidly under the reaction conditions as only derivatives of the 19(*S*)-isomer were isolated. Formation of 4α-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 α-face, more readily than at C-2.

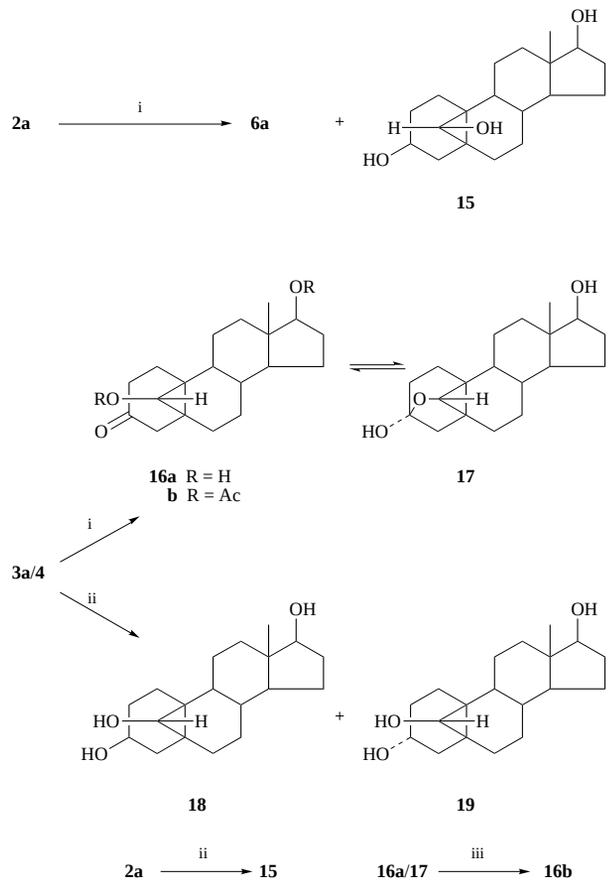
More vigorous acidic or basic treatment of the 19(*R*)-alcohol **2a** led to further rearrangement products (Scheme 4). When the 19(*R*)-alcohol **2a** was heated under reflux with toluene-*p*-sulfonic acid in benzene the major product was the 5β-androstan-19-al **12** together with the unstable 5β-methyl-A-norsteroid 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 β-face protonation of the 3,4-bond in the intermediate 3-hydroxy-3,5-cyclosteroid (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, $NaBH_4$

then employed to examine the course of the cyclopropanol ring opening in the absence of the carbonyl group. Lithium tri-*tert*-butoxyaluminium 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 β-face attack by the reagent, probably because of steric hindrance from the 19-H. Furthermore α-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 3β-hydroxy group in the 19(*S*)-triol **18** is formed by α-face attack of the reagent on the less sterically hindered face of the molecule the 3α-hydroxy group in the 19(*S*)-triol **19** requires attack on the more sterically hindered β-face. β-Face attack may occur either directly on the



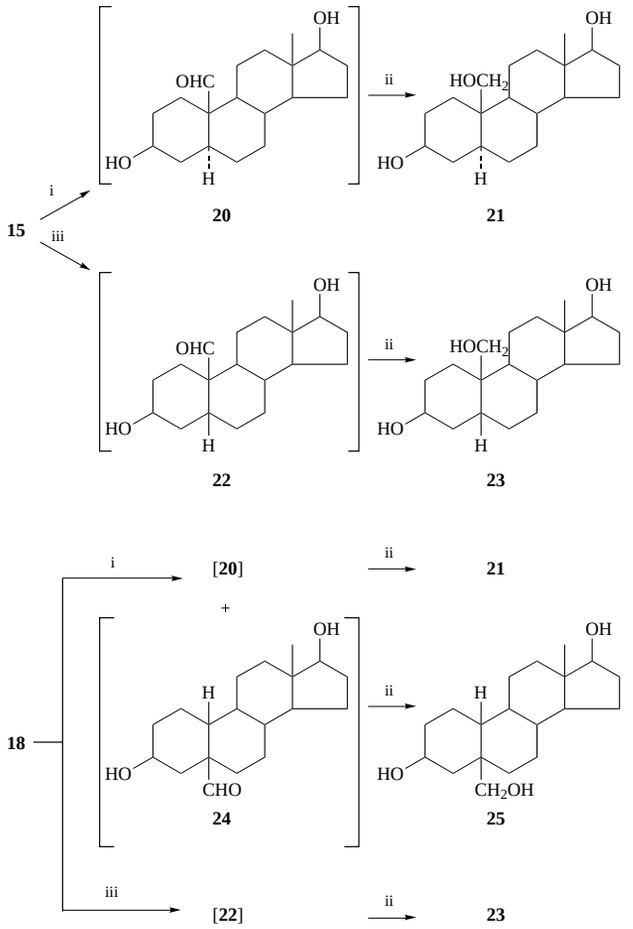
Scheme 5 *Reagents:* i, LTBAH–THF; ii, $NaBH_4$MeOH; iii, Ac_2O–pyridine

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-3,5-cyclosteroid. Treatment of the 19(*R*)-triol **15** with KOH–MeOH under reflux for 24 h gave the 5α,19β-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 5β,19β-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** (10β-CH_2OH/5α-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 10β-H/5β-CH_2OH product **24**/**25** isolated in 15% yield.

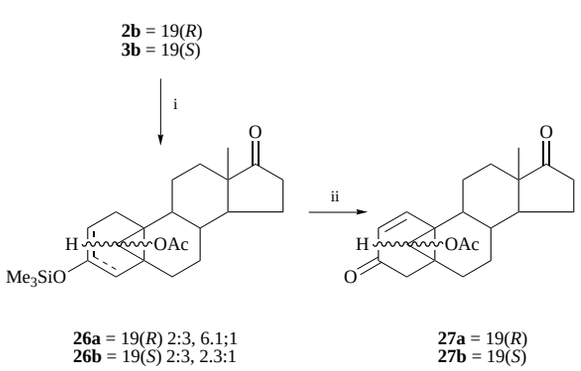
Gibson and De Puy[21] have reviewed the ring opening of cyclopropanols under both acidic and basic conditions. Generally under acidic conditions cyclopropanol ring opening proceeds with retention of configuration while under basic conditions ring opening results in inversion. In agreement with their 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, $NaBH_4$–MeOH; iii, HCl–THF, 24 h

the 5β 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 5β 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 $Pd(OAc)_2$ (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 $Pd(OAc)_2$ gave the unsaturated ketone **27b**. 5β,19-



Scheme 7 *Reagents:* i, TMSOTf-Pr^i_2EtN or Et_3N; ii, $Pd(OAc)_2$–MeCN

Cycloandrost-1-ene-3,17-dione **28** was prepared as previously reported for NMR comparison.[14] 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.[22]

Irradiation of the cyclopropyl proton (19-H) in the 19(*R*)-alcohol **2a** resulted in NOEs to the 1β-H (3.2%), 2β-H (2.4%) and 4β-H (4.1%). In the 19(*R*)-acetate **2b** irradiation gave NOEs with the 1β-H (3.0%), 2β-H (4.5%) and 4β-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 β hydrogens in ring A.

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

The ^1H NMR spectrum of the ketone/hemiketal mixture **3a**/**4** in [$^2H_6$]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 ^{13}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 ^1H and ^{13}C NMR assignments obtained from the 2D measurements.

Examination of rows extracted from the HSQC spectrum of compound **10** showed that both the 6α-H and 6β-H lacked the expected coupling to the 5-H and that the 2α-H and 2β-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-4α), 0.32 ppm, (J = 1.5, 5.4 Hz) coupled to a doublet at 0.84 ppm (4β-H) and to the 2α-H was also observed. These data strongly suggest a 3,5-cyclosteroid structure. Irradiation of the 19-H resulted in NOEs to the 1β-H (1.3%) and to the lowfield cyclopropyl proton (3.5%). The latter NOE identifies this as the *endo* cyclopropyl proton (4β-H). Irradiation of the *exo* cyclopropyl proton (4α-H) resulted in NOEs to, the 6α-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 4α-methyl derivative **11** showed NOE with the 7β-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 4α-methyl stereochemistry.

Examination of the 4α-H, 4β-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 5β stereochemistry. Irradiation of the aldehyde peak (19-H) resulted in an NOE to both the 5-H (4.1%) and the 1β-H (1.5%). Irradiation of the 4α-H resulted in an NOE to the 7α-H (5.6%) an the 9-H (5.7%). These results are in agreement with the 5β 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 6β-H (3.2%) and the 1β-H (4.9%). Irradiation of the highfield 19-

Table 1 ^{1}H NMR chemical shift (J in Hz)[a]

Compd.	13-Me	19-H	Other
2a[b,c]	0.90	3.30	0.80 (m, 7α-H), 2.31d (4β-H), 2.49d (4α-H), J_{AB} 17.3
2b[b,c]	0.91	4.03	2.14 (s, OAc), 2.50d[d] (4α-H), 2.55d[d] (4β-H) J_{AB} 17.7
2c	0.87	3.12	0.16 (s, $SiMe_3$), 2.31d (4β-H), 2.50d (4α-H) J_{AB} 16.7
3b[b,c]	0.92	3.88	2.09 (m, 16α-H), 2.08 (s, OAc), 2.25d (4β-H), 2.38d (4α-H), J_{AB} 16.5
3c[c]	0.92	3.15	0.17 (s, $SiMe_3$), 0.73 (m, 7α-H), 2.09d (4β-H), 2.53d (4α-H) J_{AB} 16.3
6a[b,e,f]	0.77	3.21	2.22 (m, 2β-H), 2.34d (4β-H), 2.49d (4α-H) J_{AB} 17.0
6b	0.82	4.00	2.04 (s, 17-OAc), 2.14 (s, 19-OAc), 3.48d[d] (4α-H), 2.55d[d] (4β-H) J_{AB} 17.9, 4.63 (dd, J 7.8, 9.0) (17α-H)
7[c]	0.90	2.86	0.81 (m, 7α-H), 2.38d (4β-H), 2.53d (4α-H) J_{AB} 17.1, 3.38 (s, 19-MeO)
8[c]	0.92	2.93	0.72 (m, 7α-H), 2.25d (4β-H), 2.53d (4α-H) J_{AB} 16.3, 3.34 (s, 19-MeO)
9[b,c]	0.86	3.61	3.33 (s, 3-MeO)
10[b,g]	0.89	4.11	0.32 (dd, J 1.7, 5.4, 4β-H), 0.84 (d, J 5.4, 4α-H), 3.27 (s, 3-MeO), 3.45, 3.48 [s, 19-$(MeO)_2CH$]
11[b,c]	0.91	2.97	0.66 (m, 7α-H), 1.12 (d, J 6.6, 4α-Me), 2.27d, 2.29d, 2-H_2), 2.61 (q, J 6.7, 4β-H), 3.37 (s, 19-MeO)
12[b,c]	0.98	9.63	2.65 (dd, J 13.7, 14.6, 4α-H)
13	0.88[d]	9.94	0.90[d] (s, 5-Me)
14[b,e,f]	0.80	3.73d, 3.81d, J_{AB} 11.5	1.02 (s, 5β-Me), 2.27 (m, 2-H_2)
15[b,f,h]	0.73	3.11	2.15 (m, 1β-H), 3.50 (m, 3α-H)
16b[e]	0.83	3.87	2.04, 2.07 (s, 17-OAc, 19-OAc), 2.25d (4β-H), 2.40d, (4α-H), J_{AB} 16.4, 4.62 (t, J 8.3, 17α-H)
18[b,f,h]	0.73	3.11	3.69 (m, 3α-H)[j]
19[b,f,h]	0.73	2.97	1.30 (dd, J 8.1, 13.0, 4-axial-H), 1.95 (m, 16α-H), 2.20 (dd, J 5.0, 13.2, 4-equatorial-H), 3.57 (m, 3β-H)[j]
20[f,h]	0.65	10.0	2.38 (dt, J 3.4, 13.4, 1β-H), 3.55 (m, 3β)[j]
21[b,f,h]	0.77	3.74d, 3.86d, J_{AB} 11.7	2.30 (dt, J 3.4, 13.4, 1β-H), 3.54 (m, 3β-H)[j]
22[f,h]	0.79	9.58	2.31 (m, 5β-H), 4.05 (br s, 3β-H)
23[b,f,h]	0.71	3.45d, 3.85d, J_{AB} 11.1	2.19 (m, 5β-H), 4.01 (br s, 3β-H)
25[b,f,h]	0.73	3.40d, 3.91d, J_{AB} 11.2[i]	4.03 (br s, 3β-H)
27a	0.87	3.64	2.19 (s, 19-COMe), 2.45 (d, J 18.6, 4β-H), 2.83 (d, J 18.6, 4α-H), 5.80 (d, J 10.2, 1-H), 7.14 (d, 10.2, 2-H)
27b	0.95	3.94	1.90 (s, 19-COMe), 2.34 (d, J 18.4, 4β-H), 2.77 (d, J 18.4, 4α-H), 5.97 (d, J 10.2, 1-H), 6.77 (d, J 10.2, 2-H)
28[b]	0.90	0.35d, 1.16d, J_{AB} 4.3	2.50d (4α-H), 2.87d (4β-H), J_{AB} 18.4, 5.76 (d, J 10.2, 1-H), 7.28 (d, J 10.2, 2-H)

[a] For solutions in $CDCl_3$ (residual C*H*Cl_3 peak δ 7.26 as internal standard) on a Bruker AM300 instrument unless otherwise indicated. J Values are given in Hz. [b] Determined by 2-D analysis on a Bruker AMX500 instrument. [c] ~2.45 (dd, J ~8.4, 19.3, 16β-H). [d] Interchangeable. [e] $CDCl_3$–CD_3OD (1:1). [f] ~3.57 (t, J ~8.5, 17α-H). [g] CD_3COCD_3. [h] CD_3OD. [i] 5β-CH_2OH. [j] Overlapping with the 17α-H.

proton showed NOEs to the 1β-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 11β-H (6.3%). These NOE effects are consistent with a β orientation for both the 19-CH_2OH 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.[22]

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

The ^{1}H and ^{13}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 6β-H (2.3%), the 7β-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 3α-alcohol configuration to compound **19** (see below), obtained from the same reaction mixture, the triol **18** is assigned to the 3β-alcohol. Furthermore, on acid treatment compound **18** gave the same ring-opened product **23** obtained from the triol **15** hence confirming the 3β-OH configuration.

The stereochemistry at C-19 in compound **19** was determined from NOEs observed from the 19-H to the 6β-H (3.2%), the 7β-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 4α-H must be axial. Further NOEs were obtained from the 3-H to the 4β-H (4.8%) and the axial 1-proton (3.8%) and from the 4β-H to the 3-H (5.1%) and the equatorial 2-proton (3.0%). These data are consistent only with a 2α,3α-half chair conformation with the 1β-H, 2α-H and 4α-H (J 8.0 Hz) to the 3-H and it follows that the 3-H is β and therefore the 3-hydroxy group is α.

In compound **21** the 5-H was observed to have axial couplings to both the 6β-H and the 4β-H, consistent only with α 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 2β-H (5.2%), 4β-H (7.8%). These data imply β stereochemistry at C-10. Consistent with a normal chair conformation for ring A in a 5α-steroid,[22] both the 2β-H and the 4β-H are observed to be axial. Because the 3-proton is also axial with couplings of 11.2 and 12.2 Hz to the 2β-H and 4β-H, respectively, the 3-hydroxy group is β.

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 19-proton (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 ^{13}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.[22]

In compound **25**, from examination of the 1α-H, 1β-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 1β-H (1.3%), the 6α-H (3.9%), the 10-H (0.8%). Irradiation of the lowfield 5-hydroxymethyl proton resulted in NOEs to the 1β-H (3.4%) and the 10-H (3.0%). These data establish

Table 2 ^{13}C NMR chemical shifts[a]

	Compound													
Carbon	**2a**[b]	**2b**[b]	**2c**[c]	**3b**[b,d]	**3c**[c]	**6a**[b,e]	**6b**[f]	**7**	**8**	**9**[b]	**10**[b,g]	**11**[b]	**12**[b]	**13**
1	27.61	22.47	27.31	23.12	20.88	28.05	27.49[l]	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	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[l]
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[l]	21.01	20.86[l]	23.97	24.66	37.68[l]	27.89	37.62	53.05[m]
6	25.71	26.60[l]	26.31	31.68	31.59	25.95	26.52[l]	26.05	31.49	25.38	27.21	24.83	27.38	30.21
7	26.23	25.87[l]	26.40	25.70	26.08	27.33	27.52[l]	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[l]	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[l]	24.79	25.56[l]	29.31	25.97	52.26	30.72	50.36	58.82[m]
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[l]	35.82	35.67	35.69	36.10	35.72	35.78	35.68
17	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[l]
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						58.66	58.66	58.20		58.27	58.41		
	58.98													
4-Me												10.18		
5-Me														21.22

	Compound												
Carbon	**14**[b,e]	**15**[b,h]	**16b**[i]	**18**[b,h]	**19**[b,h]	**20**[h]	**21**[b,h]	**22**[h]	**23**[b,h]	**25**[b,h]	**27a**[j]	**27b**[k]	**28**[b]
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[l]	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[l]	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[l]	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[l]	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	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
3-OMe													
19-OMe													
4-Me													
5-Me	21.32												

[a] For solution in $CDCl_3$ (residual $CHCl_3$ peak at δ_C 77.0 internal standard) unless otherwise indicated on a Bruker AM300 instrument. [b] Determined by 2-D analysis on a Bruker AMX500 instrument. [c] −0.35 (s, $SiMe_3$). [d] 20.53 (19-OCO*C*H$_3$), 171.14 (19-O*C*OCH$_3$). [e] $CDCl_3$:CD_3OD (1:1). [f] 20.92 (19-OCO*C*H$_3$), 170.74 (19-O*C*OCH$_3$), 21.14 (OCO*C*H$_3$), 171.05 (17-O*C*OCH$_3$). [g] CD_3COCD_3. [h] CD_3OD. [i] 20.25 (19-OCO*C*H$_3$), 171.13 (19-O*C*OCH$_3$), 21.14 (17-OCO*C*H$_3$), 171.08 (17-O*C*OCH$_3$). [j] 20.76 (19-CO*Me*), 169.93 (19-*C*OMe). [k] 20.32 (19-CO*Me*), 170.70 (19-*C*OMe). [l,m] Numbers 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 β.

The ^{1}H and ^{13}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.[23] 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.[16] 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_2SO_4

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.

^{1}H and ^{13}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^{-3} solutions in 5-mm sample tubes in $CDCl_3$, CD_3OD, $CDCl_3$–CD_3OD (1:1), or CD_3COCD_3 as indicated in the Tables. For samples in $CDCl_3$ the residual $CHCl_3$ peak in the solvent (δ_C 77.0 ppm, δ_H 7.26 ppm) was used as the internal reference for both proton and carbon spectra. For the remaining solvents $SiMe_4$ 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.[24]

Homonuclear correlation (COSY), heteronuclear correlation (HSQC) and nuclear Overhauser effect (NOE) difference spectra were recorded as described previously.[1]

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_2Cl_2 (30 cm^3) and the mixture stirred at 20 °C for 18 h. After dilution with diethyl ether (100 cm^3), 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_2Cl_2–Et_2O) (lit.,[25] 129–133 °C).

(19*R*)-19-Hydroxy-5β,19-cycloandrostane-3,17-dione 2a, (19*S*)-19-hydroxy-5β,19-cycloandrostane-3,17-dione 3a/(19*S*)-3-hydroxy-3β,19-oxido-5β,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^3) and the mixture stirred for 1.5 h, after which it was diluted with CH_2Cl_2 (500 cm^3) and filtered. The filtrate was washed with water and aqueous $NaHCO_3$, dried, concentrated (~15 cm^3) and diluted with Et_2O 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_2Cl_2–Et_2O) (Found: C, 75.4; H, 8.8. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%). A portion of the mother liquor (1 g) on FCC gave, on elution with 80% Et_2O–LP, estra-5(10)-3,17-dione **5a** (240 mg, 3.3%), mp 144–148 °C (from Et_2O–LP) (lit.,[26] 144–146 °C), the 19(*R*)-alcohol **2a** (130 mg), mp 160–167 °C (from CH_2Cl_2–Et_2O) and the 19(*S*)-alcohol/hemiketal mixture **3a**/**4** (45 mg, 0.56%), mp 160–165 °C (from CH_2Cl_2–Et_2O–LP) (Found: C, 75.4; H, 8.7. $C_{19}H_{26}O_3$ 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_2Cl_2 (10 cm^3) was added 4-dimethylaminopyridine (DMAP) (50 mg) and Ac_2O (1 cm^3) after which the mixture was stirred at 20 °C for 1 h. After dilution with water (10 cm^3), the mixture was extracted with CH_2Cl_2 and the extract washed with saturated aqueous $NaHCO_3$ and water to give, on work-up, the 19(*R*)-acetate **2b** (100 mg, 44%), mp 180–183 °C (from CH_2Cl_2–Et_2O) (Found: C, 73.0; H, 8.5. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%).

(19*R*)-19-Trimethylsiloxy-5β,19-cycloandrostane-3,17-dione 2c

To a solution of the 19(*R*)-alcohol **2a** (150 mg, 0.50 mmol) in CH_2Cl_2 (2 cm^3) was added 1.0 M 1-(trimethylsilyl)imidazole in CH_2Cl_2 (0.5 cm^3) 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_2O–LP) (Found: C, 70.6; H, 9.2. $C_{22}H_{34}O_3Si$ requires C, 70.5; H, 9.15%).

(19*S*)-19-Hydroxy-5β,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^3) at 20 °C for 1 h. After dilution with CH_2Cl_2 (80 cm^3) 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_2O).

Epimerization in HCl–THF. The 19(*R*)-alcohol **2a** (150 mg, 0.50 mmol) was stirred in THF (15 cm^3) containing 12 M aqueous HCl (0.5 cm^3) 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_2Cl_2–Et_2O).

(19*S*)-19-Hydroxy-5β,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^3) was added DMAP (25 mg) and Ac_2O (1 cm^3) 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*S*)-19-Trimethylsiloxy-5β,19-cycloandrostane-3,17-dione 3c

To the 19(*S*)-alcohol/hemiketal mixture **3a**/**4** (75 mg, 0.25 mmol) in dimethylformamide (DMF) (0.5 cm^3) was added 1.0 M 1-(trimethylsilyl)imidazole in CH_2Cl_2 (0.2 cm^3) and the mixture stirred at 20 °C for 3 h. After dilution with Et_2O the mixture was washed with water to give, on work-up, the silyl ether **3c** (32 mg, 35%), mp 122–125 °C (from Et_2O–LP) (Found: C, 70.55; H, 9.3. $C_{22}H_{34}O_3Si$ required: C, 70.5; H, 9.15%).

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

A solution of the aldehyde **1** (500 mg, 1.66 mmol) in tetrahydrofuran (25 cm^3) was added over a period of 1 h to a stirred mixture of liquid ammonia (100 cm^3) and THF (10 cm^3) containing lithium metal (681 mg, 98 mmol). Stirring was continued for a further 30 min at which time NH_4Cl (7.0 g, 130 mmol) was added to the mixture followed by Et_2O (100 cm^3). 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.,[26] 144–146 °C), the 17β-alcohol **5b** (53 mg, 12%), mp 192–196 °C (from acetone–EtOAc) (lit.,[27] 193–196 °C), the 19(*R*)-alcohol **2a** (55 mg, 11%), mp 166–168 °C (from CH_2Cl_2), and the 17β,19(*R*)-diol **6a** (173 mg, 34%), mp 168–170 °C (from acetone–EtOAc).

(19*R*)-17β,19-Dihydroxy-5β,19-cycloandrostan-3-one diacetate 6b

The 19(*R*)-diol **6a** (153 mg, 0.50 mmol) in CH_2Cl_2 (5 cm^3) was treated with Et_3N (0.20 cm^3) and Ac_2O (0.5 cm^3), at 20 °C for 1 h after which it was diluted with CH_2Cl_2 (20 cm^3). The organic layer was separated, washed with 3% aqueous HCl, water and aqueous $NaHCO_3$ 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. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%).

(19*R*)-19-Methoxy-5β,19-cycloandrostane-3,17-dione 7, (19*S*)-19-methoxy-5β,19-cycloandrostane-3,17-dione 8 (19*S*)-3-methoxy-3β,19-epoxy-5β,19-cycloandrostan-3-one 9, 3,19,19-trimethoxy-3β,5β-cycloandrostan-17-one 10

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

MeOH (30 cm^3) cooled in an ice–water bath was added 12 M aqueous HCl (0.5 cm^3). After the mixture had been allowed to come to 20 °C, it was stirred for 3 h, diluted with Et_2O (150 cm^3) and washed with water. Work-up gave a residue which on FCC with 30% Et_2O–LP as eluent gave fractions (56 mg) which after two crystallizations from Et_2O–LP yielded the 3β,5β-cyclopropanol **10** (14 mg, 3%), mp 104–106 °C (from Et_2O–LP) (Found: C, 73.0; H, 9.6. $C_{22}H_{34}O_4$ requires C, 72.9; H, 9.45%), the 3-methoxy ketal **9** (107 mg, 28%), mp 220–223 °C (from CH_2Cl_2–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_2O) (Found: C, 75.85; H, 8.9. $C_{20}H_{28}O_3$ 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*S*)-19-Methoxy-5β,19-cycloandrostane-3,17-dione 8 and (19*S*)-3-methoxy-3β,19-epoxy-5β,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^3) and DMF (2.5 cm^3) 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_2Cl_2, 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_2Cl_2–acetone–LP) (Found: C, 75.7; H, 9.0. $C_{20}H_{28}O_3$ 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. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%); and starting material **3a**/**4** (65 mg, 13.5%), mp 156–172 °C (from CH_2Cl_2–Et_2O).

(19*S*)-3-Methoxy-3β,19-epoxy-5β,19-cycloandrostan-17-one 9 and (19*S*)-19-methoxy-4α-methyl-5β,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^3) and DMF (5 cm^3) 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_2Cl_2 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_2Cl_2–LP) and the 4α-methyl derivative **11** (67 mg, 20%), mp 133–135 °C (from Et_2O–LP) (Found: C, 76.1; H, 9.4. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.15%).

19-Formyl-5β-androstane-3,17-dione 12 and 19-formyl-5β-methyl-A-nor-5β-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^3) for 2 h after which it was diluted with CH_2Cl_2 and washed with water. Work-up gave a residue which on FCC with 60% Et_2O–LP as eluent gave the A-norsteroid **13** (48 mg, 16%), mp 145–150 °C (from CH_2Cl_2–LP) which was free of extraneous ^1H and ^{13}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_2Cl_2–LP) (Found: C, 75.6; H, 8.85. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%).

19-Formyl-5β-methyl-A-nor-5β-androstane-3,17-dione 13 and 5β-methyl-17β,19-dihydroxy-A-nor-5β-androstan-3-one 14

The 19(*R*)-alcohol **2a** (250 mg, 0.83 mmol) was heated to reflux in 0.5 M methanolic KOH (20 cm^3) under argon for 3 h after which it was cooled to 20 °C, and treated with $NaBH_4$ (600 mg, 16 mmol). The mixture was stirred for 30 min after which it was diluted with CH_2Cl_2 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 A-norsteroid **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*R*)-17β,19-Dihydroxy-5β,19-cycloandrostan-3-one 6a and (19*R*)-5β,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^3) 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^3) 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_2Cl_2 as eluent gave the diolone **6a** (89 mg, 44%), mp 165–168 °C (from CH_2Cl_2–Et_2O) (Found: C, 72.9; H, 9.3. $C_{19}H_{28}O_3 \cdot 0.5H_2O$ 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. $C_{19}H_{30}O_3 \cdot H_2O$ requires C, 70.3; H, 9.9%).

(19*R*)-Cycloandrostane-3β,17β,19-triol 15

The 19(*R*)-alcohol **2a** (450 mg, 1.49 mmol) in methanol (25 cm^3) was treated with $NaBH_4$ (125 mg, 3.3 mmol) at 20 °C for 30 min after which the mixture was diluted with EtOAc (80 cm^3), washed with water and concentrated at <40 °C to *ca*. 10 cm^3 to give a residue. This afforded the 19(*R*)-triol **15** (307 mg, 68%), mp 147–152 °C (from acetone–LP).

(19*S*)-17,19-Dihydroxy-5β,19-cycloandrostan-3-one 16a/(19*S*)-3-hydroxy-3β,19-epoxy-5β,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^3) 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_2O 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%).

(19*S*)-17β,19-Dihydroxy-5β,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^3) and treated with acetic anhydride (0.5 cm^3) 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*S*)-Cycloandrostane-3β,17β,19-triol 18 and (19*S*)-cycloandrostane-3α,17β,19-triol 19

The 19(*S*)-alcohol/hemiketal **3a**/**4** (270 mg, 0.89 mmol) in methanol (15 cm^3) was treated with $NaBH_4$ (75 mg, 2.0 mmol) at 20 °C for 30 min after which the mixture was diluted with EtOAc (80 cm^3) 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. $C_{19}H_{30}O_3 \cdot 0.5H_2O$ requires C, 72.4; H, 9.9%) and the non-crystalline 3α-alcohol **19** (34 mg, 12%) which proved too unstable for further purification.

3β,17β-Dihydroxy-5α-androstan-19-al 20 and 5α-androstane-3β,17β,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^3) under argon for 24 h. After

cooling to 20 °C the mixture was treated with $NaBH_4$ (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_2Cl_2 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.

3β,17β-Dihydroxy-5β-androstan-19-al 22 and 5β-androstane-3β,17β,19-triol 23

The 19(*R*)-triol **15** (100 mg, 0.33 mmol) was stirred with THF (15 cm^3) containing 12 M aqueous HCl (0.5 cm^3) at 25 °C for 24 h after which the mixture was diluted with EtOAc (100 cm^3), washed with water, and evaporated under reduced pressure at 40 °C. The residue was taken up in MeOH (10 cm^3) and treated with $NaBH_4$ (200 mg, 5.29 mmol) at 25 °C for 30 min. EtOAc (100 cm^3) was added to the mixture which was then washed with water. Work-up provided a residue which on FCC with 7.5% MeOH–CH_2Cl_2 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.,[11] 230–232 °C (from EtOAc)]. Because of the mp difference elemental analysis was carried out (Found: C, 73.7; H, 10.3. $C_{19}H_{32}O_3$ 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.

5β-Androstane-3β,17β,19-triol 23

The 19(*S*)-triol **18** (150 mg, 0.49 mmol) in THF (15 cm^3) containing 12 M aqueous HCl (0.5 cm^3) 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 $NaBH_4$ (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 MeOH–acetone–LP).

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

The 19(*S*)-triol **18** (150 mg, 0.49 mmol) was dissolved in 0.5 M methanolic KOH (10 cm^3) and the solution heated to reflux for 72 h; it was then cooled to 20 °C and treated with $NaBH_4$ (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_2Cl_2 as eluent the triol **25** (22 mg, 15%), mp 194–195 °C (from acetone–LP) (Found: C, 73.9; H, 10.6. $C_{19}H_{32}O_3$ requires C, 74.0; H, 10.5%) and the triol **21** (45 mg, 30%), mp 227–231 °C (from MeOH–acetone–LP).

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

The saturated dione **2b** (500 mg, 1.45 mmol) in CH_2Cl_2 (2.5 cm^3) was added in portions over 5 min, to a stirred and cooled (acetone–solid CO_2 bath) mixture of Pr^i_2EtN (230 μl, 1.9 mmol) and trimethylsilyl trifluoromethanesulfonate (340 μl, 0.39 mmol) in CH_2Cl_2 (10 cm^3), under Ar. After the mixture had been stirred for a further 1.5 h it was treated with MeOH (0.5 cm^3) 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_2O–0.2% Et_3N in LP) gave fractions of the 2- and 3-enol silyl ethers **26a** (464 mg) (HC-2/4, 6:1:1); $\delta(CDCl_3)$ 4.66 (ddd, *J* 6.1, 2.4, 2.4) and 5.30 (d, *J* 2, allylic coupling). $Pd(OAc)_2$ (263 mg, 1.17 mmol) in MeCN (5 cm^3) was added to the enol mixture dissolved in MeCN (30 cm^3) at 20 °C and the solution stirred at 50 °C for 5.5 h.[28] It was then evaporated under reduced pressure, diluted with Et_2O 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_2O–LP) (Found: C, 73.4; H, 7.8. $C_{21}H_{26}O_4$ requires C, 73.6; H, 7.65%).

(19*S*)-19-Hydroxy-5β,19-cycloandrost-1-ene-3,17-dione 27b

Trimethylsilyl trifluoromethanesulfonate (3.5 cm^3, 0.018 mmol) was added to a stirred solution of the saturated dione **3b** (748 mg, 2.17 mmol) and Et_3N (6 cm^3, 42 mmol) in dry DMF cooled in an ice-bath. After 2 h the mixture was poured into Et_2O 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 silyl ethers **26b** (H-2/4, 2.3:1); $\delta(CDCl_3)$ 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^3) and treated with $Pd(OAc)_2$ (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_2Cl_2–EtOAc) (Found: C, 73.65; H, 7.9. $C_{21}H_{26}O_4$ 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.,[14] mp 185–187 °C).

Acknowledgements

We thank the Medical Research Council of Canada for financial support. H. Majgier-Baranowska has been a recipient for a Leslie F. Buggey Graduate Scholarship.

References

1 J. F. Templeton, Y. Ling, W. Lin, R. J. Pitura and K. Marat, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1149.
2 J. F. Templeton, W. Lin, Y. Ling and K. Marat, *Tetrahedron Lett.*, 1994, **35**, 5755.
3 J. C. Orr, J. F. Templeton, H. Majgier-Baranowska and K. Marat, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2667.
4 L. Tin in *Frontiers in Biotransformation*, ed. K. Ruckpaul and H. Rein, Akademia Verlag, Berlin, 1992, vol. 6, pp. 1001–101.
5 H. Laurent and R. Weichert in *Organic Reactions in Steroid Chemistry*, ed. J. Fried and J. A. Edwards, Van Nostrand Reinhold Co., New York, 1972, vol. 2, pp. 110–113.
6 A. J. Birch and G. S. R. Subba Rao, *J. Chem. Soc.*, 1965, 5139.
7 S. Rakhit and M. Gut, *J. Am. Chem. Soc.*, 1964, **86**, 1432.
8 J. J. Bonet, H. Werhli and K. Schaffner, *Helv. Chim. Acta*, 1962, **45**, 2615.
9 J. Tadanier and W. Cole, *Tetrahedron Lett.*, 1964, 1345.
10 L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbe, E. Velarde and J. A. Edwards, *J. Org. Chem.*, 1965, **30**, 2198.
11 E. Santaniello and E. Caspi, *J. Steroid Biochem.*, 1976, **7**, 223.
12 R. L. Dyer and T. A. Harrow, *Steroids*, 1979, **33**, 617.
13 H. L. Holland and G. J. Taylor, *Can. J. Chem.*, 1978, **56**, 3121.
14 L. H. Knox, E. Velarde and A. D. Cross, *J. Am. Chem. Soc.*, 1963, **85**, 2533; L. H. Knox, E. Velarde, S. Berger, D. Cuadriello and A. D. Cross, *Tetrahedron Lett.*, 1962, 1213.
15 P. Wieland and G. Anner, *Helv. Chim. Acta*, 1968, **51**, 1932; P. Wieland and G. Anner, *Helv. Chim. Acta*, 1970, **53**, 116.
16 K. Marat, J. F. Templeton, Y. Ling, W. Lin and R. K. Gupta, *Magn. Res. Chem.*, 1995, **33**, 529.
17 E. Wenkert and E. Kariv, *Chem. Commun.*, 1965, 570; E. Kariv and E. Wenkert, *Israel J. Chem.*, 1967, **5**, 68.
18 W. Reusch, K. Grimm, J. E. Karoglan, J. Martin, K. P. Subrahamanian, Y. C. Toong, P. S. Venkataramani, J. D. Yordy and P. Zoutendam, *J. Am. Chem. Soc.*, 1977, **99**, 1953 and references therein.
19 N. H. Werstiuk, *Tetrahedron*, 1983, **39**, 205.
20 W. Reusch, K. Grimm, J. E. Karoglan, J. Martin, K. P. Subrahamanian, P. S. Venkataramani and J. D. Yordy, *J. Am. Chem. Soc.*, 1977, **99**, 1958.
21 D. H. Gibson and C. H. DePuy, *Chem. Rev.*, 1974, **74**, 605.
22 J. W. Blunt and J. B. Stothers, *Org. Magn. Res.*, 1977, **9**, 439.

23 A. M. H. Brodie, W. C. Schwarzel, A. A. Shaikh and H. J. Brodie, *Endocrinology*, 1977, **100**, 1684; J. F. Templeton, Y. Ling, W. Lin, R. J. Pitura, H. Majgier-Baranowska and A. M. H. Brodie, The IV International Aromatase Conference, June 7–11, 1996 Tahoe City, Tahoe, California, USA.
24 D. M. Doddrell, D. P. Pegg and M. T. Bendall, *J. Magn. Reson.*, 1982, **48**, 323.
25 H. Hagiwara, S. Noguchi and M. Nishikawa, *Chem. Pharm. Bull.*, 1960, **8**, 84.
26 H. Ueberwasser, K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta*, 1963, **34**, 343.
27 A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, 1953, **75**, 5366.
28 Y. Ito, T. Hirao and T. Saeguse, *J. Org. Chem.*, 1978, **43**, 1011.

Paper 6/04405K
Received 25*th June* 1996
Accepted 5*th March* 1997