Synthesis of 19-hydroxy-1β,19-cyclosteroids

John F. Templeton,*[a] Weiyang Lin,[a] Yangzhi Ling,[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*)-Substituted 1β,19-cyclo-5α-steroids have been synthesized by reductive cyclization of 3,17-dioxo-5α-androst-1-en-19-al with zinc in aqueous acetic acid or lithium in ammonia. The major product from the zinc reaction, the 19(*R*)-cyclopropanol, exists in equilibrium with the 3-hemiketal; the minor product, the 19(*S*)-alcohol, is isolated as the silyl ether and deprotected to give the 19(*S*)-cyclopropanol. The major product from the lithium–ammonia reaction is the 19(*S*)-cyclopropanol. Neither acid nor base treatment of the 19(*R*)- and 19(*S*)-alcohols gives evidence of their interconversion. Structures are established by NMR measurements.

Introduction

Various steroid cyclopropanols have been synthesized as potential steroid enzyme inhibitors.[1–3] The 19(*R/S*)-hydroxy-1β,19-cycloandrostane-3,17-diones were synthesized as potential aromatase inhibitors. While 1β,19-cycloandrostane derivatives have been synthesized previously, none with a C-19 substituent have been reported.[4] Recently we reported[3] the synthesis of 19(*R/S*)-hydroxy-5β,19-cycloandrostane derivatives by reductive cyclization of the 3-oxo-4-en-19-al with zinc in aqueous acetic acid or lithium in ammonia. We now report the synthesis and isomerization of 19(*R*)- and 19(*S*)-hydroxy-1β,19-cycloandrostane-3,17-dione derivatives by reductive cyclization of 3,17-dioxo-5α-androst-1-en-19-al with those reagents.

Results and discussion

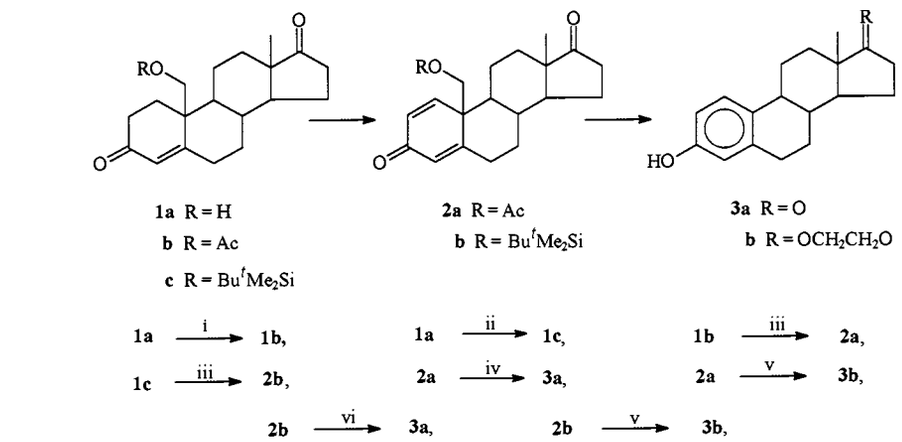
Weiland and Anner[4] prepared 1β,19-cycloandrostane derivatives by treating a steroid 19-mesylate 1-en-3-one with lithium and biphenyl in tetrahydrofuran. Earlier Weiland and Anner[5] attempted to synthesize both 1β,19-cycloandrostane and 5β,19-cycloandrostane derivatives in one reaction by treating a steroid 19-mesylate 1,4-dien-3-one with lithium and biphenyl but obtained only the 5β,19-cycloandrostane derivative. Initially we attempted to carry out a similar synthesis of 1β,19- and 5β,19-cycloandrostane 19(*R/S*)-alcohols from 3,17-dioxoandrosta-1,4-dien-19-al. However, preparation of the diene 19-alcohol for oxidation to the aldehyde was unsuccessful. 19-Acetoxyandrost-4-ene-3,17-dione **1b** or the 19-*tert*-butyldimethylsilyl ether **1c**, prepared from the 19-alcohol **1a**, on treatment with benzeneseleninic anhydride[6] gave the corresponding dienes, **2a** and **2b** (Scheme 1). However, removal of the acetate or silyl ether with NaOH or Bu_4NF, respectively, to obtain the dien-19-ol led to rapid ring A aromatization[7] to give estrone **3a**. Under the acidic conditions required for ketalization of the dienes **2a** and **2b**, aromatization also occurred to give the 17-ethylenedioxy ketal **3b**.

19-Hydroxyandrost-4-ene-3,17-dione **1a** on catalytic hydrogenation gives mainly the 5β-androstane derivative,[8,9] however, addition of a bulky 19-*tert*-butyldimethylsilyl group **1c** yielded the 5β-androstane **4** as the minor product and the 5α-androstane **5** as the major product after hydrogenation (Scheme 2). Introduction of a C-1 double bond through bromination of the ketone **5** followed by dehydrobromination with $LiBr–Li_2CO_3$ gave a low yield of the 1-en-3-one **6a** (14%) together with the 2β,19-oxide **7** (55%), and two minor products, the 4-en-3-one **1c** and diene **2b**. Treatment of the ketone **5** with benzeneseleninic anhydride[6] gave the desired 1-en-3-one **6a** (43%) as the major product and the unsaturated derivatives **1c** (19%) and **2b** (21%) as the minor products. Higher yields of the 1-en-3-one **6a** (70%) were obtained when the ketone **5** was refluxed with diphenyldiselenide, *m*-iodylbenzoic acid and camphorsulfonic acid in tetrahydrofuran[10] together with the 4-ene **1c** (12%) and the 1,4-diene **2b** (2%).

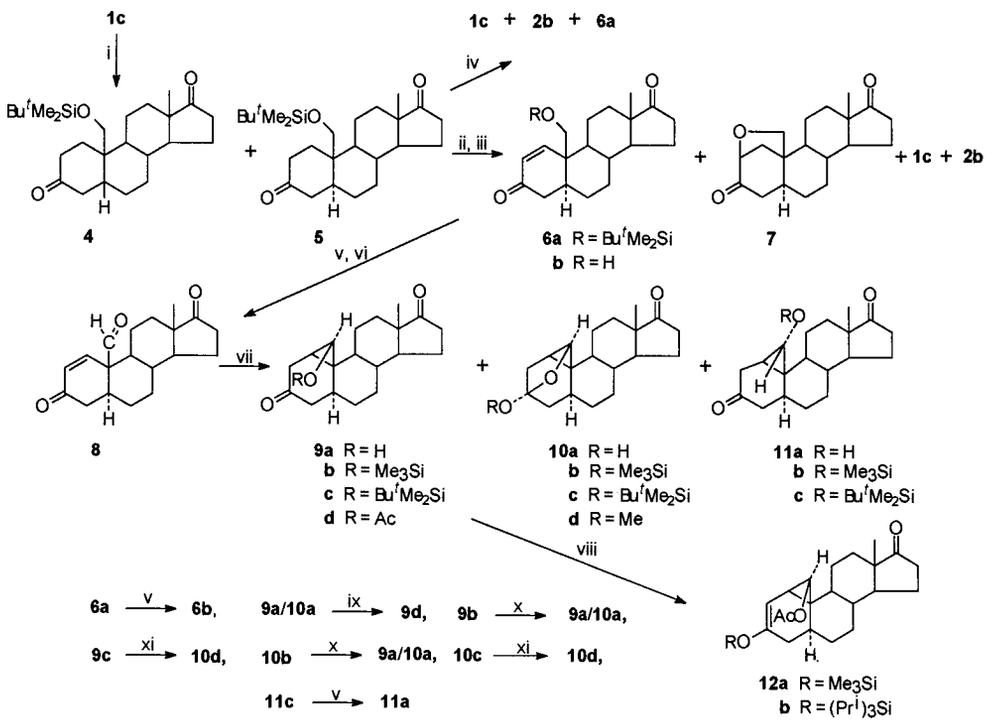
The 1-en-3-one **6a** was deprotected with fluoride ion to give the alcohol **6b** which was oxidized with pyridinium dichromate to the 19-aldehyde **8**. Treatment of the aldehyde **8** with zinc in aqueous acetic acid gave on crystallization 19(*R*)-hydroxy-1β,19-cyclo-5α-androstane-3,17-dione **9a** in equilibrium with the hemiketal tautomer, 3α-hydroxy-3β,19-epoxy-1β,19-cyclo-5α-androstan-17-one **10a** (51–68%) as the major product. A ^1H NMR spectrum of the mother liquor from the reaction, which was not further purified, showed signals at 3.58 ppm (d, $J = 2.5$ Hz) assigned to the 19(*S*)-isomer **11a** (5%).

Trimethylsilylation of the remaining mother liquor from zinc and acetic acid treatment of the aldehyde **8** after crystallization of the ketone–hemiketal **9a**/**10a** gave the 19(*R*)- and 19(*S*)-trimethylsilyl ethers, **9b** and **10b**, and the 3α-trimethylsilyl ketal **11b**. Removal of the silyl group from either the 19(*R*)-trimethylsilyl ether **9b** or the hemiketal silyl ether **10b** with K_2CO_3 in MeOH gave the ketone/hemiketal mixture **9a**/**10a**. A similar mixture from the zinc and acetic acid treatment of the aldehyde **8**, when treated with *tert*-butyldimethylsilylimidazole, gave the corresponding 19(*R*)- and 19(*S*)-*tert*-butyldimethylsilyl ethers **9c**, **10c** and the 3α-*tert*-butyldimethylsilyl ketal **11c**. Reaction of the 19(*R*)-alcohol **11a** with the more sterically hindered *tert*-butyldimethylsilyl reagent was considerably slower than with the trimethylsilyl reagent. Treatment of **9c** and **10c** with concentrated HCl in methanol gave the 3α-methoxyketal **10d** indicating an equilibrium in favour of that product. Deprotection of the 19(*S*)-*tert*-butyldimethylsilyl ether **11c** with Bu_4NF gave the 19(*S*)-cyclopropanol **11a**. Acetylation of the ketone–hemiketal mixture **9a**/**10a** with acetic anhydride and *N*,*N*-dimethylaminopyridine (DMAP) gave the 19(*R*)-acetate **9d**. Treatment of the 19(*R*)- or 19(*S*)-alcohols with either HCl or KOH under conditions which caused epimerization of the 19(*R/S*)-hydroxy-5β,19-cyclosteroids[3] failed to give evidence of epimerization in the ^1H NMR spectrum of the product.

By analogy with the formation of a 19(*R*)-hydroxy-5β,19-cyclosteroid reported earlier,[3] metal attack on the 3-carbonyl would produce a radical centre at C-1 in a position to form an anion which adds to the adjacent aldehyde group to give the



Scheme 1 *Reagents:* i, Ac_2O–DMAP; ii, Bu^tMe_2SiCl–imidazole; iii, $(PhSeO)_2O$; iv, NaOH; v, $HOCH_2CH_2OH$–*p*-TsOH; vi, Bu_4NF



Scheme 2 *Reagents:* i, H_2–10% Pd/C–EtOAc; ii, $PhCH_2Me_3NBr_3$; iii, LiBr–Li_2CO_3; iv, Ph_2Se_2-camphorsulfonic acid–iodylbenzoic acid; v, Bu_4NF; vi, PDC; vii, Zn–HOAc–H_2O; viii, TMSOTf or TIPSOTf; ix, Ac_2O–DMAP; x, K_2CO_3–MeOH; xi, HCl–MeOH

19(*S*)-alcohol **11a** (Scheme 3). Cyclization can then occur to give either the 19(*R*)- or 19(*S*)-alcohol; the 19(*R*)-alcohol is stabilized by hemiketal formation.

Treatment of the unsaturated aldehyde **8** with Li–NH_3–THF gave a mixture of 19(*S*) and 19(*R*) derivatives. *tert*-Butyldimethylsilylation of the product gave the disilylated 19(*R*) derivatives **13** (4%) and **14** (6%), the disilylated 19(*S*) derivative **15** (23%) and the trisilylated 19(*S*) derivative **16** (5%) (Scheme 4). The major product from reductive cyclization with Zn (*R*:*S*, 20:1) was the 19(*R*)-alcohol/hemiketal **9a**/**10a** whereas with Li the 19(*S*)-alcohol was the major product (*R*:*S*, 1:2.3) from ^{1}H NMR comparison of the 19-H proton. The different epimer ratio may be because of a difference in the preferred rotational conformation resulting from the temperature variance (90 °C) between the reactions. The heterogeneous nature of the Zn reaction may also be a factor in favouring formation of the 19(*R*)-epimer.

Preparation of the trimethylsilyl and triisopropylsilyl enol ethers of the diketone **9d** gave the non-crystalline C-2 enol derivatives **12a** and **12b**, respectively. Attempts to introduce a C-4 double bond either directly to the diketone **9d** using benzeneseleninic anhydride,[6] dichlorodicyanoquinone or through oxidation of the silyl enol ethers **12a** and **12b** with *N*-bromosuccinamide at 20 °C[11] or NBS–AIBN–CCl_4 under reflux[11] were unsuccessful probably because of the preferred C-2 enolization.

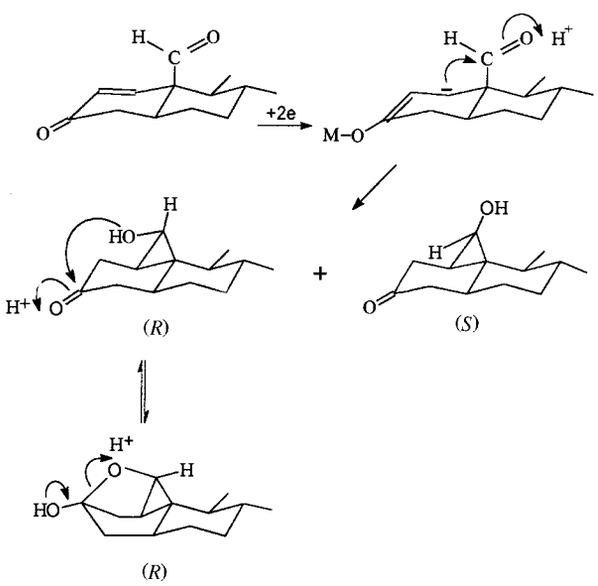
Nuclear magnetic resonance analysis

The structures of all products are in agreement with the NMR data described in Tables 1 and 2. The structures of the acetate **9d** and the silyl enol ether **12a** were confirmed by COSY[12] and HSQC[13] spectra which allowed complete NMR assignments. The ^{1}H NMR spectrum of the acetate showed a singlet at 2.03 ppm corresponding to the acetate group and a doublet at 4.31 ppm (*J* 7.5 Hz) assigned to the C-19 cyclopropyl proton. The observation of a strong NOE from H-19 to H-11β (10%) and H-8 (1.7%) confirms the location of the cyclopropyl ring on the β-face with the 19-H *exo*. The *cis* coupling (*J* 7.5 Hz) between the 19-H and the H-1α also agrees with the 19(*R*)-stereochemistry. The 19(*S*)-trimethylsilyl derivative **11b** showed the trimethylsilyl group as a singlet at 0.16 ppm and a doublet at 3.33 ppm (*J* 3.1 Hz) assigned to the C-19H. This *trans* coupling between the 19-H and the H-1α confirms the 19(*S*)-stereochemistry. The crude silyl enol ethers **12a** and **12b** showed

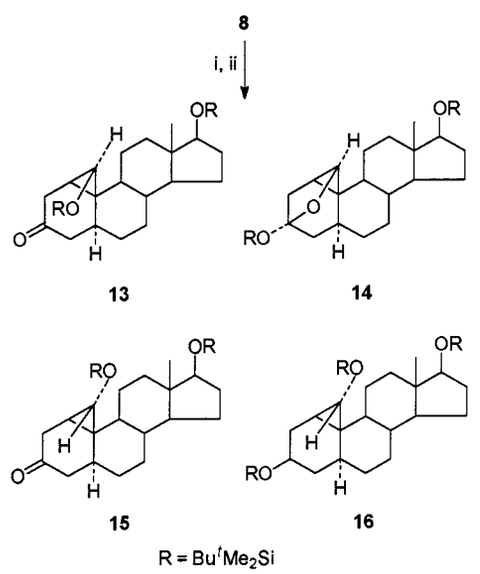
Table 1 ^{1}H NMR chemical shifts (J in Hz)[a]

Compd.	13-Me	19-H	$COCH_3$	Other
1a	0.92	3.94, 4.07 (d, J_{AB} 10.3)		5.96 (s, 4-H)
1b	0.92	4.19, 4.68 (d, J_{AB} 11.3)	2.02	5.93 (s, 4-H)
1c[b]	0.92	3.90 (dd, *J* 10.5, 12.5)		5.87 (s, 4-H)
2a	0.95	4.42, 4.64 (d, J_{AB} 10.9)	1.93	6.21 (s, 4-H), 6.36 (dd, *J* 1.9, 8.72, 2-H), 7.07 (d, *J* 10.2, 1-H)
2b[b]	0.95	3.86, 4.00 (d, J_{AB} 9.6)		6.15 (s, 4-H), 6.33 (dd, *J* 1.9, 10.2, 2-H), 7.09 (d, *J* 10.2, 1-H)
3a[c]	0.91			2.85 (m, 6-H), 4.80 (s, 3-OH), 6.58 (d, *J* 2.6, 4-H), 6.64 (dd, *J* 2.7, 8.4, 2-H), 7.15 (d, *J* 8.4, 1-H)
3b[c]	0.88			2.79 (m, 6-H), 3.91 (m, 17-OCH_2CH_2O), 4.86 (s, 3-OH), 6.55 (d, *J* 2.6, 4-H), 6.62 (dd, *J* 2.6, 8.3, 2-H), 7.15 (d, *J* 8.4, 1-H)
4[b–d]	0.90	3.60, 3.81 (d, J_{AB} 9.7)		2.26 (m, 5β-H), 2.63 (dd, *J* 14.6, 14.6, 4β-H)
5[b–d]	0.90	3.91, 3.97 (d, J_{AB} 10.8)		0.08, 0.10 (m, $SiMe_2$), 0.89 (s, CMe_3), 1.67 (m, 5α-H), 2.07 (m, 16α-H), 2.45 (m, 16β-H + 4β-H)
6a[b,c]	0.90	3.74, 3.98 (d, J_{AB} 10.6)		2.70 (dd, *J* 14.2, 17.8, 4β-H), 6.01 (d, *J* 10.3, 2-H), 6.98 (d, *J* 10.2, 1-H)
6b[c]	0.92	3.83, 4.11 (d, J_{AB} 11.5)		2.25 (dd, *J* 4.7, 17.8, 4α-H), 2.77 (dd, *J* 14.4, 18.0, 4β-H), 6.11 (d, *J* 10.2, 2-H), 7.01 (d, *J* 10.2, 1-H)
7[c,d]	0.83	3.89, 4.06 (d, J_{AB} 8.4)		2.08 (m, 16α-H), 2.18 (dd, *J* 5.8, 15.2, 4α-H), 2.40 (dd, *J* 11.8, 15.2, 4β-H), 2.53 (dd, *J* 7.4, 12.5, 1α-H), 4.14 (d, *J* 7.1, 2-H)
8[d]	0.96	9.93 (s)		6.23 (d, *J* 10.2, 2-H), 7.00 (d, *J* 10.2, 1-H)
9b[c,e]	0.87	3.49 (d, *J* 7.0)		2.54 (d, *J* 2.3, 2β-H), 2.59 (dd, *J* 4.9, 18.4, 2α-H)
9c[b,c]	0.86	3.53 (d, *J* 7.1)		
9d[c]	0.90	4.31 (d, *J* 7.5)	2.03	2.54 (d, *J* 17.5, 2β-H), 2.64 (dd, *J* 5.1, 17.5, 2α-H)
10b[c–e]	0.84	4.02 (d, *J* 5.6)		1.72 (dd, *J* 2.6, 4.4, 12β-H), 1.87 (d, *J* 11.7, 2β-H), 1.92 (t, *J* 11.0, 4α-H)
10c[b,c]	0.83	4.00 (d, *J* 5.3)		
10d[c]	0.84	4.02 (d, *J* 5.5)		3.32 (s, 3α-OMe)
11a[c]	0.88	3.58 (d, *J* 2.5)		
11b[c,e]	0.87	3.33 (d, *J* 3.1)		2.58 (d, *J* 5.2, 2β-H), 2.65 (dd, *J* 1.7, 19.4, 2α-H)
11c[b,c]	0.87	3.38 (d, *J* 3.1)		
12a[c,e]	0.87	4.10 (d, *J* 7.0)	2.03	4.90 (dd, *J* 1.7, 6.7, 2-H)
12b[c]	0.88	4.13 (d, *J* 7.0)	2.01	1.07 (d, *J* 5.9, $CHMe_2$), 4.87 (dd, *J* 1.7, 6.7, 2-H)
13[b]	0.69	3.55 (m)		3.55 (m, 17α-H)
14[b]	0.66	4.00 (d, *J* 5.5)		3.52 (t, *J* 8.2, 17α-H)
15[b,d]	0.69	3.35 (d, *J* 3.1)		3.55 (dd, *J* 7.9, 8.5, 17α-H)
16[b,d]	0.67	3.02 (d, *J* 2.9)		2.22 (m, 2β-H), 3.44 (m, 3α-H), 3.53 (t, *J* 8.2, 17α-H)

[a] For solution in $CDCl_3$ ($CHCl_3$ internal standard) on a Bruker AM300 instrument unless otherwise indicated. *J* Values are given in Hz. [b] Compounds **1c**, **2b**, **4**, **5**, **6a**, **9c**, **10c**, **11c**, **13**–**16** show Bu^{t}Me$_2$Si signals at 0.80–0.90 (s, CMe_3) and 0–0.13 (s, $SiMe_2$). [c] Compounds **3a**, **3b**, **4**, **5**, **6a**, **6b**, **7**, **9c**, **9b**, **10b**, **10c**, **10d**, **11a**, **11b**, **11c**, **12a**, **12b** show the 16β-H signal at *ca.* δ 2.5 (dd, *J* 9, 19). [d] Determined by 2D analysis on a Bruker AMX500 instrument. [e] Compounds **9b**, **10b**, **11b**, **12a** show the $SiMe_3$ signal at *ca.* δ 0.15 (s).



Scheme 3 Reductive cyclization of the steroid 3-oxo-1-en-19-al to 19(*R*/*S*)-hydroxy-1,19-cyclosteroids (M = Zn, Li); *R*:*S* (20:1, Zn), (1:2.3, Li)



Scheme 4 *Reagents:* i, Li–NH_3–THF; ii, Bu^{t}Me$_2$SiCl–Pr$^i_2$EtN–DMF

signals at 4.9 ppm (dd, *J* 1.7, 6.7 Hz) assigned to the 2-H based on 2D NMR analysis. The ^{1}H and ^{13}C NMR spectra of compounds **13**–**16** are consistent with their 17-oxo analogues **9c**, **10c** and **11c**, respectively, but show the presence of the 17β-alcohol. Compound **16** also shows a broad signal for the axial 3α-H and no NOE between the 3-H and the 19-H, showing the formation of the 3β-alcohol.

Aromatase inhibition

The 19(*R*)-ketone/hemiketal **9a**/**10a** and 19(*R*)-acetate **9d** showed 40–50% of the aromatase inhibitory activity of 4-hydroxyandrost-4-ene-3,17-dione used as a standard when tested on human placental aromatase microsomes.[14]

Experimental

Reactions were monitored by TLC which was carried out in

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

Carbon	Compound								
	1b[b,c]	**1c**[c]	**2a**[b]	**2b**[c]	**3b**[d]	**4**[c,e]	**5**[c,e]	**6a**[c]	**6b**
1	32.84	33.29[i]	151.05	152.45	126.48	31.16	33.96	130.27	131.13
2	34.51	34.69	130.46	129.99	112.62	36.91	38.64	153.46	152.54
3	198.99	199.65	185.89	186.40	153.29	212.84	211.91	200.17	200.16
4	126.87	126.02	126.73	126.03	115.23	42.06	44.86	41.68	41.70
5	164.82	167.25	163.49	165.54	138.28	36.38	46.23	44.35	44.31
6	33.49	33.58[i]	32.37[i]	32.23	29.62	24.49	28.32	27.37	27.25
7	31.53	30.79[j]	31.48	31.63	26.93	25.90	30.66[i]	30.36[i]	30.34[i]
8	35.67	35.93	35.66	35.71	39.54	35.21	35.51	35.77	35.60
9	54.02	54.07	52.86	52.27	43.60	41.59	54.33	52.05	51.85
10	41.82	43.60	47.56[j]	49.58[i]	132.73	39.22	39.54	43.37	43.68
11	20.78	20.96[k]	22.63	22.60	26.16	20.59	21.72[j]	21.16[j]	21.16[j]
12	30.85	31.73[j]	32.40[i]	32.81	30.75	32.04	31.93[i]	31.80[i]	31.71[i]
13	47.41	47.59	47.69[j]	47.70[i]	46.18	47.77	47.79	47.88	47.79
14	51.09	51.34	50.84	50.97	49.36	51.92	51.66	50.23	50.16
15	21.57	21.71[k]	21.83	21.87	22.37	21.71	21.78[j]	21.69[j]	21.67[j]
16	35.56	35.71	35.51	35.60	34.24	35.83	35.79	35.75	35.72
17	219.64	220.10	219.14	219.62	119.50	220.47	220.72	220.27	220.22
18	13.73	13.89	13.85	13.96	14.36	13.91	13.92	14.10	13.98
19	66.49	65.81	63.48	64.34		65.19	60.87	62.06	61.39

Carbon	Compound								
	7[e]	**8**[e]	**9b**[f]	**9c**[c]	**9d**[b]	**10b**[f,e]	**10c**[c]	**10d**[g]	**11a**
1	41.28	132.14	17.66	17.66	17.41	19.28	19.28	19.07	20.38
2	81.45	147.24	35.08	34.89	34.73	36.27	36.29[k]	30.02[i]	35.98
3	209.57	197.54	211.99	211.75	210.10	104.29	104.11	105.84	199.42
4	42.42	41.24	44.47	44.53	43.96	42.79	42.88	39.41	43.74
5	44.67	45.14	38.56	38.77	38.02	35.67	35.70[i]	35.35[j]	38.77
6	29.71	28.18	32.52	32.70	32.68	35.75[i]	35.80[i]	35.77[j]	33.02
7	30.08	31.59[i]	30.83[i]	30.92[i]	30.68	30.30	30.37	30.28[i]	31.35
8	37.75	36.09	39.48	39.74	39.10	39.14	39.19	39.16	39.77
9	46.04	51.43	46.52	46.60	46.22	44.69	42.87	44.69	46.55
10	47.41	55.40	26.05	26.17	26.93	25.17	25.20	25.47	30.66
11	20.65	21.30[j]	21.69[j]	21.75[j]	21.57	21.46[j]	21.50[j]	21.49[k]	21.82
12	31.19	30.03[i]	31.08[i]	31.11[i]	31.02	31.27	31.33	31.28	31.68
13	47.66	47.79	47.54	47.58	47.54	47.61	47.66	47.60	47.89
14	51.30	48.92	50.97	50.98	50.95	50.68	50.73	50.69	51.63
15	21.70	21.62[j]	21.81[j]	21.83[j]	21.63	21.62[j]	21.68[j]	21.63[k]	23.04
16	35.74	35.66	35.86	35.92	35.80	35.82[i]	36.29[k]	35.82[j]	37.00
17	220.12	219.89	220.57	220.63	220.28	220.79	220.86	220.71	221.23
18	13.59	13.92	13.59	13.56	13.68	13.62	13.66	13.66	13.76
19	67.43	201.27	54.74	55.54	56.93	60.47	60.47	60.40	55.87

Carbon	Compound							
	11b[f]	**11c**[c]	**12a**[b,f]	**12b**[b,h]	**13**[c]	**14**[c]	**15**[c,e]	**16**[c,e]
1	19.93	20.17	19.17	19.19	17.42	19.10	19.97	20.13
2	35.98	35.95	97.28	95.77	34.94	36.06	37.38[i]	33.68
3	209.98	209.99	150.28	150.74	212.20	104.05	210.50	69.20
4	43.80	43.80	35.92[i]	35.85[i]	44.64	49.94	43.93	37.53[i]
5	38.24	38.34	36.98	37.21	38.87	35.78	38.51	39.96
6	32.97	32.99	31.93	31.92	32.90	36.37	33.21	32.33
7	31.36[i]	31.34	30.95[j]	31.00[j]	31.66	30.98	32.13	32.74
8	39.01	39.13	39.29	39.26	40.40	39.79	39.76	42.11
9	46.49	46.71	46.28	46.32	46.65	44.82	46.95	48.36
10	29.12	29.51	28.76	28.69	26.22	29.73	29.70	31.64
11	21.82	21.81	21.76[k]	21.75[k]	22.16	21.88	23.32	23.51
12	31.71[i]	31.76	31.03[j]	31.05[j]	36.54	36.87	37.45[i]	37.47[i]
13	47.86	47.86	47.55	47.57	43.19	43.24	43.35	43.48
14	51.54	51.67	51.00	51.03	50.14	49.94	50.98	51.23
15	22.82	22.82	21.68[k]	21.69[k]	23.47	23.41	23.52	23.59
16	37.37	37.31	35.79[i]	35.85[i]	30.97	31.13	31.03	31.06
17	221.29	221.23	220.50	220.55	81.61	81.72	81.62	81.71
18	13.38	13.76	13.66	13.67	11.23	11.27	11.40	11.55
19	55.51	56.62	59.77	59.88	56.65	60.68	56.72	60.85

[a] For solutions in $CDCl_3$ ($CHCl_3$ internal standard) on a Bruker AM300 instrument unless otherwise indicated. [b] The acetyl group signals occur at *ca.* δ 21 ($COCH_3$) and 171 ($COCH_3$). [c] The Bu^{t}Me$_2$Si signals occur at δ −5 to 6 (Si*Me*$_2$), [**10c** −2.77, −2.83; **13** −4.44, −4.81, −5.16, −5.32; **14** −2.80, −2.85, −5.27, −5.32; **15** −4.47, −4.77, −4.77, −5.15], *ca.* δ 18 (CMe_3) and 25 to 26 (CMe_3). [d] δ 64.21 and 64.47 (OCH_2CH_2O). [e] Determined by 2D analysis on a Bruker AMX500 instrument. [f] **9b** δ −0.53; **10b** 1.73; **11b** −0.27; **12a** 0.21 (Me_3Si). [g] δ 50.13 (OCH_3). [h] δ 12.61 (*Me*$_2$CHSi), 17.98 (Me_2CHSi). [i–k] Numbers in columns are interchangeable or overlapping signals.

the following solvent systems on silica gel (Merck type 60H): acetone–light petroleum (bp 35–60 °C) (LP), Et_2O–LP, EtOAc–LP; compounds were visualized by dipping the plates in 5% sulfuric acid–ethanol followed by heating on a hot-plate at *ca.* 120 °C. Reaction mixtures were separated by flash column chromatography (FCC). Melting points were determined on either an Electrothermal 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 obtained 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 $CDCl_3$ in 5 mm sample tubes. The residual $CHCl_3$ peak in the solvent ($\delta_C = 77.0$ ppm, $\delta_H = 7.26$ ppm) was used as the internal reference for both proton and carbon spectra. *J* Values are given in Hz. Sample temperature was controlled at 300 K for all spectra. Multiplicity of peaks in the carbon spectra were classified with the DEPT technique.[15]

Homonuclear correlation (COSY), heteronuclear correlation (HSQC) and nuclear Overhauser effect (NOE) difference spectra were recorded as described previously.[16]

19-Acetoxyandrost-4-ene-3,17-dione 1b and 19-acetoxyandrosta-1,4-diene-3,17-dione 2a

DMAP (200 mg) and Ac_2O (5 cm^3) were added to the 19-alcohol **1a** (1.0 g, 3.3 mmol) in CH_2Cl_2 (30 cm^3) and the mixture was stirred at 20 °C for 2 h when TLC indicated that the reaction was complete. The mixture was poured into water and extracted with CH_2Cl_2 to give the 19-acetate **1b**[8,17] which was used for the next reaction. The acetate **1b**, with benzeneseleninic anhydride (1.0 g) and $NaHCO_3$ (1.0 g) in benzene (30 cm^3), was heated under reflux in an inert atmosphere for 18 h. The mixture was cooled, washed with aqueous 0.1 M sodium phosphate buffer (pH 7.1) and diluted with CH_2Cl_2 as described by Cole and Robinson.[6] The aqueous phase was further extracted with CH_2Cl_2 and the organic layer washed with water and evaporated to give a residue which was separated by FCC. Elution with 30% acetone–LP gave the diene **2a** (340 mg, 30%), mp 151–153 °C (from CH_2Cl_2–Et_2O) (Found: C, 73.5; H, 7.7. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.65%) and the acetate **1b** (300 mg, 26%).

19-*tert*-Butyldimethylsilyloxyandrost-4-ene-3,17-dione 1c

Imidazole (2.0 g) and Bu^tMe_2SiCl (4.0 g, 26.5 mmol) were added to a solution of the 19-alcohol **1a** (7.0 g, 23 mmol) in dimethylformamide (DMF) (50 cm^3). The mixture, after 2 h at 50 °C, was cooled, diluted with water and extracted with Et_2O. The Et_2O layer was washed with brine, dried and evaporated to give the silyl ether **1c** (5.6 g, 58%), mp 161–162 °C (from CH_2Cl_2–Et_2O) (Found: C, 71.9; H, 9.7. $C_{25}H_{40}O_3Si$ requires C, 72.1; H, 9.7%).

19-*tert*-Butyldimethylsilyloxyandrosta-1,4-diene-3,17-dione 2b

The 19-Bu^tMe_2Si ether **1c** (500 mg, 1.20 mmol) was refluxed with benzeneseleninic anhydride (500 mg, 1.39 mmol) and $NaHCO_3$ (500 mg) in benzene (20 cm^3) under an Ar atmosphere for 20 h. The mixture was cooled to 20 °C and washed with aqueous 0.1 M sodium phosphate buffer (pH 7.1) and diluted with CH_2Cl_2.[6] The aqueous phase was further extracted with CH_2Cl_2 and the combined organic phases were washed with water, dried (Na_2SO_4) and evaporated to give a residue which was separated by FCC and on elution with 10% acetone–LP gave the diene **2b** (131 mg, 26%), mp 160–163 °C (from CH_2Cl_2–Et_2O) (Found: C, 72.2; H, 9.3. $C_{25}H_{38}O_3Si$ requires C, 72.4; H, 9.2%) and starting material **1c** (150 mg, 30%), mp 154–157 °C (from CH_2Cl_2–Et_2O).

Estra-1,3,5(10)-trien-17-one-3-ol (estrone) 3a

With NaOH. 10% Aqueous NaOH (1 cm^3) was added to the 1,4-diene **2a** (30 mg, 0.09 mmol) in methanol (2 cm^3) and the mixture was stirred at 20 °C for 2 h. The mixture was poured into water and extracted with CH_2Cl_2; work-up gave the estrone **3a** (18 mg, 76%), mp 257–260 °C (from CH_2Cl_2–Et_2O) (lit.,[18] mp 258–260 °C).

With Bu^n_4NF. Bu^n_4NF (7 mg) was added to the 1,4-diene **2b** (10 mg, 0.02 mmol) in THF (2 cm^3) and the mixture was stirred at 20 °C for 1 h to give the estrone **3a**. It was identified by TLC and ^{1}H NMR comparison with an authentic sample.

17,17-Ethylenedioxyestra-1,3,5(10)-trien-3-ol 3b

From 2a. *p*-TsOH (5 mg) and ethylene glycol (1 cm^3) were added to the 1,4-diene **2a** (30 mg, 0.09 mmol) in benzene (4 cm^3) and the mixture was refluxed for 1 h. It was then poured into water and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and evaporated to give a crude product which was separated by FCC. Elution with 10% acetone–LP gave fractions of the non-crystalline ketal **3b** (20 mg, 70%), identified by TLC and NMR comparison with the sample from **2b** below.

From 2b. Toluene-*p*-sulfonic acid (*p*-TsOH) (5 mg) and ethylene glycol (1 cm^3) were added to the 1,4-diene **2b** (60 mg, 0.14 mmol) in benzene (4 cm^3) and the mixture was refluxed for 1 h. It was then poured into water and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and evaporated to give a crude product which was separated by FCC. Elution with 10% acetone–LP gave the ketal **3b** (40 mg, 88%), mp 164–167 °C (from Et_2O) (Found: C, 76.2; H, 8.1. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%).

19-*tert*-Butyldimethylsilyloxy-5α-androstane-3,17-dione 4 and 19-*tert*-butyldimethylsilyloxy-5β-androstane-3,17-dione 5

A solution of the 19-Bu^tMe_2Si ether **1c** (13.4 g, 32 mmol) in EtOAc (120 cm^3) was stirred with 10% Pd–C (1.34 g) under a hydrogen atmosphere for 18 h. It was then filtered and evaporated under reduced pressure to give on FCC (elution with 30–50% Et_2O–LP) fractions of the 5α-isomer **5** (9.9 g, 73%), mp 136–138 °C (from Et_2O–LP) (Found: C, 71.4; H, 10.2. $C_{25}H_{42}O_3Si$ requires C, 71.7; H, 10.1%) and the 5β-isomer **4** (3.36 g, 25%), mp 153–154 °C (from Et_2O–LP) (Found: C, 71.7; H, 10.3. $C_{25}H_{42}O_3Si$ requires C, 71.7; H, 10.1%).

19-*tert*-Butyldimethylsilyloxyandrost-4-ene-3,17-dione 1c; 19-*tert*- butyldimethylsilyloxyandrosta-1,4-diene-3,17-dione 2b and 19-*tert*-butyldimethylsilyloxy-5α-androst-1-ene-3,17-dione 6a

From $Ph(SeO)_2O$. The silyl ether **5** (2.0 g, 4.8 mmol), with benzeneseleninic anhydride[6] (1.6 g) and $NaHCO_3$ (1.5 g) in benzene (80 cm^3), was heated under reflux in an Ar atmosphere for 2 h. The mixture was cooled, washed with aqueous 0.1 M aqueous sodium phosphate buffer (pH 7.1) and diluted with CH_2Cl_2.[6] The aqueous phase was further extracted with CH_2Cl_2, and the combined organic layers were washed with water and evaporated to give a residue which was separated by FCC. Elution with 10% acetone–LP gave the 1-ene **6a** (860 mg, 43%), mp 143–145 °C (from CH_2Cl_2–Et_2O), the 4-ene **1c** (380 mg, 19%), mp 155–158 °C (from CH_2Cl_2–Et_2O) and the 1,4-diene **2b** (424 mg, 21%), mp 155–158 °C (from CH_2Cl_2–Et_2O).

From Ph_2Se_2. A mixture of diphenyl diselenide (817 mg, 2.26 mmol), camphorsulfonic acid (3.0 g, 12.9 mmol) and iodylbenzoic acid (7.5 g, 26.3 mmol) was heated under reflux in dry THF until the yellow colour of the diselenide disappeared (10 min). A solution of the 19-Bu^tMe_2Si ether **5** (11 g, 26 mmol) in THF (220 cm^3) was added to the mixture and reflux continued for a further 2 h when TLC showed the absence of starting material. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with water and worked up to give a crude product which on FCC (elution with 30–40% Et_2O–LP) gave fractions of the 1-en-3-one **6a** (7.64 g, 70%), mp 144–146 °C (from CH_2Cl_2–EtOAc), the 4-ene **1c** (1.35 g, 12%), mp 157–159 °C (from

Et_2O–LP) and the 1,4-diene **2b** (180 mg, 2%), mp 166.5–167.5 °C (from Et_2O–LP).

19-*tert*-Butyldimethylsilyloxy-5α-androst-1-ene-3,17-dione 6a and 2β,19-epoxy-5α-androstane-3,17-dione 7

To a stirred solution of the silyl ether **5** (1.0 g, 2.4 mmol) in HOAc (10 cm^3) containing 48% (w/w) HBr (0.05 cm^3) was added benzyl(trimethyl)ammonium tribromide (1.24 g) in portions until the bromine colour disappeared (~5 min). The mixture was poured into water and extracted with CH_2Cl_2 and the extract was washed with water and evaporated to give a residue. This was treated with LiBr (2.5 g) and Li_2CO_3 (2.5 g) in DMF (30 cm^3) for 5 h under reflux and then poured into water and extracted with CH_2Cl_2. The extract was washed with water and evaporated to give a crude product which was separated by FCC. Elution with 20% EtOAc–LP, gave the 1-ene **6a** (141 mg, 14%), mp 139–141 °C (from CH_2Cl_2–Et_2O) (Found: C, 72.3; H, 9.7. $C_{25}H_{40}O_3Si$ requires C, 72.1; H, 9.7%), and the cyclic ether **7** (400 mg, 55%), mp 143–146 °C (from Et_2O–LP) (Found: C, 75.3; H, 8.7. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%). The R_F of two minor products on TLC corresponded to **1c** and **2b**.

19-Hydroxy-5α-androst-1-ene-3,17-dione 6b

To the silyl ether **6a** (500 mg, 1.20 mmol) in THF (25 cm^3) was added Bu_4NF (530 mg) and the mixture stirred for 1 h. It was then poured into water and extracted with CH_2Cl_2. The extract was washed with water and evaporated to yield a product which was separated by FCC. Elution with 25% acetone–LP gave the 19-alcohol **6b** (300 mg, 83%), mp 200–202 °C (from CH_2Cl_2–Et_2O) (Found: C, 75.2; H, 8.95. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%).

3,17-Dioxo-5α-androst-1-en-19-al 8

The 1-ene **6b** (735 mg, 2.43 mmol) and pyridinium dichromate (1.0 g) were dissolved in CH_2Cl_2 (50 cm^3) and the mixture stirred for 2 h. It was then diluted with Et_2O (50 cm^3), filtered through Celite and evaporated to give a residue which was separated by FCC. Elution with 30% acetone–LP gave the aldehyde **8** (603 mg, 82%), mp 148–150 °C (from CH_2Cl_2–Et_2O) (Found: C, 75.75; H, 8.0. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05%).

(19*R*)-19-Hydroxy-1β,19-cyclo-5α-androstane-3,17-dione/3-hydroxy-3β,19-epoxy-1β,19-cyclo-5α-androstan-17-one 9a/10a

From 8. Zn powder (25 g) was added to a solution of the aldehyde **8** (3.17 g, 10.6 mmol) in 50% aqueous HOAc (80 cm^3) and the mixture was stirred at 20 °C for 2 h. It was then filtered, poured into water and extracted with CH_2Cl_2. The extract was washed with water and saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated to give a mixture of the ketone and hemiketal **9a** and **10a** (2.18 g, 68%), mp 190–193 °C (from CH_2Cl_2–Et_2O) as determined by ^1H NMR spectroscopy (Found: C, 75.3; H, 8.5. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%). The ^1H NMR spectrum of the mother-liquor showed a signal (δ 3.58, *J* 2.5 Hz) corresponding to the isomer **11a** (5%).

From 9b. The (19*R*)-19-trimethylsilyl ether **9b** (15 mg, 0.04 mmol) in methanol (1 cm^3) was stirred with K_2CO_3 (15 mg) for 30 min and then poured into water and extracted with CH_2Cl_2. The extract was filtered, dried and evaporated, to give **9a**/**10a** (7.6 mg, 63%), mp 187–190 °C (from CH_2Cl_2–Et_2O).

From 10b. A solution of the 3α-trimethylsilyl ether **10b** (74 mg, 0.20 mmol) in methanol (5 cm^3) was stirred with K_2CO_3 (74 mg) at 20 °C for 30 min after which it was poured into water and extracted with CH_2Cl_2. Evaporation of the extract gave **9a**/**10a** (32 mg, 54%), mp 187–190 °C (from CH_2Cl_2–Et_2O).

(19*R*)-19-Trimethylsilyloxy-1β,19-cyclo-5α-androstane-3,17-dione 9b; 3-trimethylsilyloxy-3β,19-epoxy-1β,19-cyclo-5α-androstan-17-one 10b and (19*S*)-19-trimethylsilyloxy-1β,19-cyclo-5α-androstane-3,17-dione 11b

The mother-liquor residue **9a**/**10a** and **11a** (254 mg, 0.84 mmol) from the above cyclization of **8** was dissolved in CH_2Cl_2 (5 cm^3) and stirred with *N*-trimethylsilylimidazole (1 cm^3) for 30 min. The mixture was then poured into water and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to give a crude product; this was separated by FCC. Elution with 5–10% acetone–LP gave (i) the ketal silyl ether **10b** (50 mg, 0.13 mmol, 15%), mp 115–118 °C (from CH_2Cl_2–Et_2O) (Found: C, 70.4; H, 9.0. $C_{22}H_{34}O_3Si$ requires C, 70.5; H, 9.15%); (ii) the (19*R*)-19-silyl ether **9b** (147 mg, 46%), mp 110–113 °C (from Et_2O–LP) (Found: C, 70.2; H, 9.4. $C_{22}H_{34}O_3Si$ requires C, 70.5; H, 9.15%); and (iii) the (19*S*)-19-silyl ether **11b** (15 mg, 5%), mp 140–142 °C (from CH_2Cl_2–Et_2O) (Found: C, 70.3; H, 9.1. $C_{22}H_{34}O_3Si$ requires C, 70.5; H, 9.15%).

(19*R*)-19-*tert*-Butyldimethylsilyloxy-1β,19-cyclo-5α-androstane-3,17-dione 9c; 3α-*tert*-butyldimethylsilyloxy-3β,19-epoxy-1β,19-cyclo-5α-androstane-3,17-dione 10c and (19*S*)-19-*tert*-butyldimethylsilyloxy-1β,19-cyclo-5α-androstane-3,17-dione 11c

The mother-liquor residue **9a**/**10a** and **11a** (600 mg, 2.0 mmol) from the above cyclization of **8** was dissolved in CH_2Cl_2 (10 cm^3) and stirred with *tert*-butyldimethylsilylimidazole (1.0 g, 5.5 mmol) for 3 weeks when TLC indicated the absence of starting material. An excess of MeOH followed by water was added to the mixture which was then extracted with CH_2Cl_2. The extract on work-up gave a residue which on FCC with 10–50% Et_2O–LP as eluent yielded fractions of (i) the (19*S*)-19-Bu^tMe_2Si ether **11c** (65 mg, 8%), mp 193–196 °C (from CH_2Cl_2–EtOAc) (Found: C, 72.0; H, 9.8. $C_{25}H_{40}O_3Si$ requires C, 72.1; H, 9.7%); (ii) the (19*R*)-19-Bu^tMe_2Si ether **9c** (175 mg, 21%), mp 154–156 °C (from CH_2Cl_2–EtOAc) (Found: C, 72.2; H, 9.8. $C_{25}H_{40}O_3Si$ requires C, 72.1; H, 9.7%); and (iii) the 3β-Bu^tMe_2Si ketal **10c** (300 mg, 36%), mp 150–152 °C (from CH_2Cl_2–EtOAc) (Found: C, 72.2; H, 9.9. $C_{25}H_{40}O_3Si$ requires C, 72.1; H, 9.7%).

(19*R*)-19-Acetoxy-1β,19-cyclo-5α-androstane-3,17-dione 9d

Ac_2O (6.2 cm^3, 66 mmol) and DMAP (80 mg, 0.65 mmol) were added to a solution of the ketone/hemiketal mixture **9a**/**10a** (1.91 g, 6.32 mmol) in CH_2Cl_2 (30 cm^3). The reaction mixture was stirred at 20 °C for 2 h, after which it was diluted with MeOH (10 cm^3), poured into water and extracted with CH_2Cl_2. The extract was washed with water and evaporated to give a crude product which was separated by FCC. Elution with 20% acetone–LP gave the acetate **9d** (1.42 g, 46%), mp 163–166 °C (from Et_2O–LP) (Found: C, 72.3; H, 8.2. $C_{21}H_{28}O_4 \cdot 0.5H_2O$ requires C, 72.3; H, 8.2%).

3α-Methoxy-3β,19-epoxy-1β,19-cyclo-5α-androstane-3,17-dione 10d

From the (19*R*)-19-Bu^tMe_2Si ether 9c. To a solution of **9c** (50 mg, 0.12 mmol) in THF (2 cm^3) was added 1.6% (v/v) conc. HCl in MeOH (10 cm^3) and the mixture stirred for 12 h to give, after dilution with water and CH_2Cl_2 extraction, the methoxy ketal **10d** (20 mg, 52%), mp 207–210 °C (from $CHCl_3$–MeOH).

From the 3α-Bu^tMe_2Si ketal 10c. Treatment of **10c** (150 mg, 0.36 mmol) in THF (3 cm^3) with 1.6% (v/v) conc. HCl in MeOH (15 cm^3) as described above for **9c** gave, after two crystallizations, the 3-methoxy ketal **10d** (74 mg, 65%), mp 207–210 °C (from CH_2Cl_2–MeOH) (Found: C, 76.0; H, 9.2. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%).

(19*S*)-19-Hydroxy-1β,19-cyclo-5α-androstane-3,17-dione 11a

To a stirred solution of the (19*S*)-19-Bu^tMe_2Si ether **11c** (21 mg, 0.05 mmol) in THF (1 cm^3) was added 1M *n*-Bu_4NF–THF (200 μl, 0.2 mmol) at 20 °C. After 1 h the mixture was diluted with water and extracted with EtOAc to give, after two crystallizations, the alcohol **11a** (10 mg, 66%), mp 194–198 °C (decomp.) (from CH_2Cl_2–EtOAc) (Found: C, 73.4; H, 8.9. $C_{19}H_{26}O_3 \cdot 0.5H_2O$ requires C, 73.3; H, 8.7%).

(19*R*)-19-Acetoxy-3-trimethylsilyloxy-1β,19-cyclo-5α-androst-2-en-17-one 12a

To a cooled (ice-bath) solution of the ketone **9d** (140 mg, 0.41 mmol) and Et_3N (300 μl, 2.1 mmol) in DMF (1 cm^3) was added TMSOTf (240 μl, 1.24 mmol). After 3 h the mixture was diluted with water and extracted with Et_2O to give on FCC (18% Et_2O–LP containing 0.15% Et_3N) the non-crystalline 2-enol silyl ether (50 mg, 30%) **12a**.

(19*R*)-19-Acetoxy-3-triisopropylsilyloxy-1β,19-cyclo-5α-androst-2-en-17-one 12b

A cooled (ice-bath) solution of the ketone **9d** (200 mg, 0.58 mmol) and Et_3N (250 μl, 1.7 mmol) in Et_2O (25 cm^3) was treated with TIPSOTf (450 μl, 1.3 mmol) under Ar. The mixture was refluxed for 2 h to give on FCC (20% Et_2O–LP) the non-crystalline 2-enol silyl ether **12b** (280 mg, 96%).

(19*R*)-17β,19-Bis(*tert*-butyldimethylsilyloxy)-1β,19-cyclo-5α-androstan-3-one 13; 3α,17β-bis(*tert*-butyldimethylsilyloxy)-3β,19-epoxy-1β,19-cyclo-5α-androstane 14; (19*S*)-17β,19-bis(*tert*-butyldimethylsilyloxy)-1β,19-cyclo-5α-androstan-3-one 15 and (19*S*)-3β,17β,19-tris(*tert*-butyldimethylsilyloxy)-1β,19-cyclo-5α-androstan-3-one 16

To a stirred mixture of NH_3 (100 cm^3) and THF (10 cm^3) containing Li metal (520 mg, 75 mmol) was added a solution of the unsaturated aldehyde **8** (440 mg, 1.47 mmol) in THF (20 cm^3) over 20 min. After 1.4 h solid NH_4Cl (8 g, 150 mmol) was added to the mixture followed by CH_2Cl_2 (150 cm^3). After removal of NH_3 from the mixture by evaporation, the organic layer was washed with water to give a residue which was treated with Bu^tMe_2SiCl (990 mg, 6.57 mmol) and Pr^i_2EtN (1.5 cm^3, 8.6 mmol) in dry DMF [19] (20 cm^3) for 2 h at 20 °C to give a residue. FCC of the residue, using (0.5–50%) Et_2O–LP as eluent, gave fractions of (i) the non-crystalline tris-Bu^tMe_2Si ether **16** (38 mg, 5%), (ii) the ketal **14** (48 mg, 6%), mp 166–170 °C (from Et_2O–MeOH) (Found: C, 70.0; H, 10.6. $C_{31}H_{56}O_3Si_2$ requires C, 69.9; H, 10.6%), (iii) **15** (180 mg, 23%), mp 125–127 °C (from Et_2O–MeOH) (Found: C, 69.7; H, 10.8. $C_{31}H_{56}O_3Si_2$ requires C, 69.9; H, 10.6%), and (iv) **13** (30 mg, 4%), mp 152–160 °C (from Et_2O–MeOH) (Found: C, 69.9; H, 10.75. $C_{31}H_{56}O_3Si_2$ requires C, 69.9; H, 10.6%).

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