OBSERVATIONS ON THE PREPARATION OF 2β-HYDROXY-19-OXOANDROST-4-ENE-3,7-DIONE; SYNTHESIS OF A 2β,19-OXAANDROST-4-ENE-3,17-DIONE#

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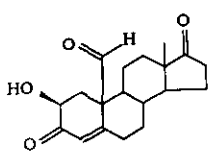
Dedicated to Professor Derek H.R. Barton's 70th birthday.

Abstract - Several modifications of the synthesis of the title compounds were explored and are reported.

For studies of estrogen biosynthesis[1,2], we required 2β-hydroxy-19-oxoandrost-4-ene-3,17-dione (1). The compound is rather difficult to prepare and the reported synthesis proceeded in ca. 0.09% yield[3]. We have explored several modifications of the synthesis which are described therein. Previously, we noted that acetoxylation of (2a) with lead tetraacetate[4,5] gave a complex mixture of products from which 2α-(3a) and 2β-acetoxy-(4a) were isolated in a (2:1) ratio in poor yield[6]. Consequently, the route through acetolysis of 6β-bromide[3] was investigated. The reported syntheses[1-6] of (1) proceed via: (a) 2β-acetoxylation of an appropriate intermediate, and (b) the selective silylation of 2β-hydroxyl of 2β,19-dihydroxyandrost-4-ene-3,17-dione (4d) to yield the 2β-silyl ether (4f). Oxidation of (4f), followed by the removal of the silyl moiety of the resulting (9c), yields (1). Since our plan was to introduce the 2β-acetoxy group via the acetolysis of 6β-bromide, we thought that it might be advantageous to protect the 19-hydroxyl of the starting material (2b) as t-butyldimethylsilyl ether[7] rather than as an acetate. We reasoned that the presence of the acid sensitive ether at C-19 and the base sensitive ester at C-2 will facilitate selective deprotection and manipulation of the two hydroxyls. While considering the subsequent transformations, it was preferable to have the 2β-hydroxyl protected as silyl ether; however, the projected scheme of C-2 oxygenation (via acetolysis) excluded this option.

The commercially available starting material (2b) was converted[7] to 19-silyl ether (2c) and brominated (NBS;2,2'-azobisisobutyronitrile in CCl_4). The recovered 6β-bromide (5), on treatment with potassium acetate in acetic acid, gave a residue which was fractionated by column chromatography on silica gel to yield the 4,6-diene (6) (24%), 2α-acetoxy (3b) (36.6%) and an unresolved mixture of two compounds. Preparative layer chromatography (plc) of the unresolved residue yielded 2β-acetoxy (4b) (8.5%) and 6β-acetoxy(7) (6%). In view of the poor yield of the required (4b) (8.5%), several synthetic modifications and the feasibility of salvaging the 2α-acetoxy (3b) were explored.



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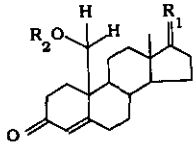
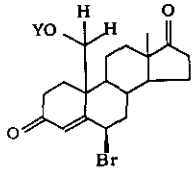
Y = t - But.Me_2 Si



2a. R_1 = 17 β— OAc. ; R_2 = Ac.

b. R_1 = O ; R_2 = Y

c. R_1 = O ; R_2 = Y



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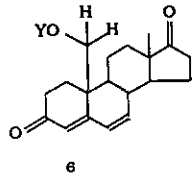

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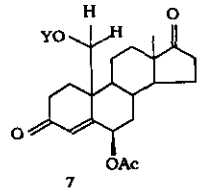

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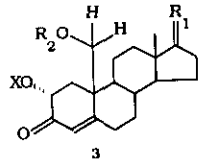

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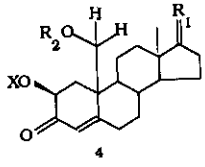


4

a. R_1 = 17 β—OAc.; R_2 = Ac. ;X = Ac.

b R_1 = O; R_2 = Y ; X = Ac.

c R_1 = O; R_2 = H ;X = Ac.

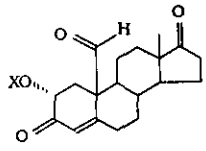
d. R_1 = O; R_2 = H ;X = H

e. R_1 = O; R_2 = Y ;X = H

f. R_1 = O; R_2 = H ;X = Y

g. R_1 = O ; R_2 = X = Y

Y = t-But.Me_2 Si



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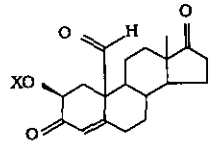
a. X = Ac.

b. X = H

c. X = Y



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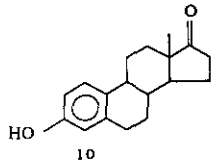

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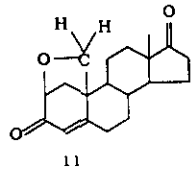

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Although we were aware that conversion of 2β-acetoxy-19-aldehyde (9a) to 2β-hydroxy (1) may pose problems, the seeming simplicity of the sequence (4b) --> (4c) --> (9a) --> (1) encouraged us to evaluate this route. The silyl ethers (3b) and (4b) were hydrolyzed [aqueous HF (48%) in acetonitrile (1:10)] to give the 19-hydroxy-2α-acetoxy (3c) and 19-hydroxy-2β-acetoxy (4c), respectively. The 2α- and 2β-acetoxy-19-hydroxy products were oxidized with pyridinium chlorochromate (PCC)[8] to the corresponding 19-aldehydes [(8a) and (9a)] (70% yield from 19-OH). The deprotection of the C-2 hydroxyl was tested on the more abundant 2α-acetoxy (8a). Unfortunately, when a methanolic solution of (8a) was treated with either aqueous $KHCO_3$, aq. K_2CO_3, or an ethanolic solution with KCN[9], estrone (10) and not alcohol (8b) was obtained. Similarly, estrone (10) was formed when a dioxane solution of (8a) was treated with dilute aq. H_2SO_4. Analogous results were obtained for the 2β-acetoxy (9a).

Since attempts of deprotecting the 2α- and 2β-hydroxyls by conventional procedures failed, enzymatic transesterification[10,11] was explored. Indeed, incubation of (8a) with Candida cylindracea and 1-octanol gave 2α-hydroxyaldehyde (8b) in 61% yield. In contrast, the analogous transesterification of 2β-acetoxy (9a) failed, and the starting material (80%), accompanied by small amounts of 2α-hydroxy (8b) (5-10%) was recovered.

The formation of 2α-hydroxy (8b) from the 2β-acetoxy (9a) under the mild conditions of the C. cylindracea catalyzed transesterification is noteworthy. The results could be rationalized as follows. Previously, we reported that the yeast lipase catalyzed transesterification of steroid esters is largely stereo- and regio-selective[11]. In the present case, the reaction was stereoselective for the 2α-acetoxy rather than the 2β-acetoxy group. However, it could be speculated that a small amount of the 2β-acetoxy (9a) was isomerized via 2(3)-enol to give 2α-acetoxy (8a). The resulting (8a) was then transesterified to the 2α-hydroxy (8b).

In view of scarcity of the 2β-acetoxy-19-oxo compound, we abandoned further exploration of this route. However, based on the above results, we inferred that removal of the 2-acetate should precede the elaboration of the 19-aldehyde.

As indicated earlier, the major product of the acetolysis of 6β-bromide was 2α-acetoxy (3b). In an attempt to salvage the 2α-acetoxy (3b), we explored the feasibility of inversion[12,13] of the 2α-hydroxyl of the 2α,19-diol (3d). Saponification of 2α-acetoxy-19-hydroxy (3c) with aq. methanolic K_2CO_3 gave the diol (3d) (60%). Treatment of a THF solution of (3d) with diethyl azodicarboxylate, triphenylphosphine and formic acid for 17 h at ambient temperature[13] gave the 2β,19-oxaandrost-4-ene-3,17-dione (11) (70%) rather than the 2β-formate. The ms of (11) showed ions at m/z 300 (M^+; 100%) and 270 (M^+-CH_2O; 20%) and the nmr and uv spectra were in accord with the proposed structure (see experimental). When the inversion reaction was carried out in

the presence of CF_3COOH, followed by addition of sodium benzoate[14], the yield of the 2,19-ether (11) was lower (25%). Apparently electrons of the C-19 oxygen atom are better positioned for an intramolecular attack at the 2β-site of the hypothetical 2α-alkoxyphosphonium salt than the external anion[13,14]. Intramolecular formation of cyclic ethers under the employed reaction conditions was observed[13,15]. The inversion was also tried on the 2α-hydroxy-19-silyloxy (3e), but only starting material was recovered.

To complete the synthesis, the diol (4d) was treated with t-butyldimethylsilyl chloride in imidazole[7] to yield 2β-silyl ether (4f) (50%) and 2β,19-disilyl ether (4g). The disilyl ether (4g) was recycled by treatment with aqueous HF (48%) in acetonitrile (1:19) and the resulting diol (4d) was then silylated as above to give (4f) (48%) and (4g). It is of interest that the 2- and 19-monosilyl ethers required a higher concentration of aqueous HF (48%) in acetonitrile for cleavage than the 2,19-disilyl ether. The overall yield of (4f) from diol-(4d) (with recycling) was ca. 75%.

The 2β-silyloxy (4f) was oxidized (PCC) to give the 19-oxo (9c) (67%), which in turn was treated with aqueous HF in acetonitrile. The recovered product was purified by HPLC to yield 19-oxo-2β-hydroxyandrost-4-ene-3,17-dione (1) (ca.1% from 2b). While we marginally improved (from 0.09% to 1%) the yield of (1), the described route is not satisfactory and we are exploring alternative synthetic approaches .

EXPERIMENTAL

^1H Nmr spectra were recorded on a Varian EM-390 or Bruker WM-250 instrument for solutions in [^2H]chloroform and are reported in δ values relative to internal Me_4Si. Mass spectra were recorded on a Varian-MAT model 312 instrument. The Merck A.G. Silica gel 60 (70-230 mesh) was used for column chromatography. Analytical and preparative TLC were carried out using precoated silica gel 60 (HF 254 + 366) plates (Analtech Inc., Newark, DE). Candida cylindracea (cat. No. 1754) was purchased from Sigma Chemical Co. A Micromeritics HPLC instrument equipped with Model 750 solvent delivery system and Model 788 dual variable detector was used. Melting points (mp) were taken on a hot stage and are corrected. Conventional workup refers to recovering the products with a solvent, washing the extract and then drying it over anhydrous sodium sulfate.

6β-Bromo-19-[(t-butyldimethylsilyl)oxy]androst-4-ene-3,17-dione (5).

A solution of 19-[(t-butyldimethylsilyl)oxy]androst-4-ene-3,17-dione (2c) (3.25 g, 7.81 mmol) in dry CCl_4 (70 ml) was refluxed with N-bromosuccinimide (2.98 g, 16.74 mmol) and 2,2'-azobisisobutyronitrile (17 mg) for 1.5 h. Cooling, filtration and evaporation of the solvent gave 3.7 g (96%) of 5 [95% pure by TLC, (silica gel, cyclohexane-EtOAc (2:1))]. A homogeneous sample was obtained by preparative TLC [silica gel, cyclohexane-EtOAc (2:1)],

mp 95-97°C, ^{1}H nmr: 0.02 (3H, s, one of $Si(CH_3)_2$), 0.05 (3H, s, one of $Si(CH_3)_2$), 0.83 (12H, s, $SiC(CH_3)_3$), 0.93 (3H, s, 18-H), 3.86, 3.97 (1H, B-part of an AB-system, J = 10 Hz, one of 19-CH_2-OSi-): 4.18, 4.29 (1H, A-part of an AB-system, J = 10 Hz, one of 19-CH_2-OSi-), 5.01 (1H, dd, J_1 = 1Hz, J_2 = 2Hz, 6α-H), 5.96 (1H, s, 4-H). Mass spectrum, m/z 496, 494 (M^+, 2%), 437 (M^+ - $C(CH_3)_3$; 44%), 357 (M^+-(HBr + $C(CH_3)_3$); 50%).

2α-Acetoxy-19-[(t-butyldimethylsilyl)oxy]androst-4-ene-3,17-dione (3b);

2β-Acetoxy-19-[(t-butyldimethylsilyl)oxy]androst-4-ene-3,17-dione(4b);

19-[(t-butyldimethylsilyl)oxy]androst-4,6-diene-3,17-diene (6);

6β-Acetoxy-19-[(t-butyldimethylsilyl)oxy]androst-4-ene-3,17-diene (7)

To a solution of the 6β-bromide (5) (3.6 g, 7.27 mmol) in glacial acetic acid (50 ml) dry potassium acetate (10 g) was added, and the mixture was refluxed for 15 min. The mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with 1N NaOH, water, dried and the solvent evaporated. The residue (3.2 g) was fractionated by column chromatography on silica gel and the products were eluted with mixtures of hexane–ethyl acetate. Elution of the column with hexane–ethyl acetate (9:1) gave:(3b), 1.3 g (36.6%); (6), 0.74 g (24%), and 0.6 g of a mixture of (4b) and (7). The mixture was fractionated by preparative layer chromatography (plc) [silica gel; cyclohexane–EtOAc (2:1) X 2] to give 0.3 g (8.5%) of (4b) and 0.2 g (5.6%) of (7).

For 3b: mp 65-67°C. ^{1}H Nmr: 0.02 (6H, s, $Si(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.92 (3H, s, 18-H), 2.14 (3H, s, 2α-$OCOCH_3$), 4.00 (2H, s, 19-CH_2-OSi-), 5.86 (1H, dd, J_1 = 7 Hz, J_2 = 14 Hz, 2β-H), 5.95 (1H, s, 4-H). Mass spectrum, m/z 474 (M^+; 1%), 459 (M^+-CH_3; 2%), 417 (M^+ - $C(CH_3)_3$; 100%), 357 (M^+ - $C(CH_3)_3$ - CH_3COOH; 24%).

For 4b: mp 80-82°C. ^{1}H Nmr: 0.02 (6H, s, $Si(CH_3)_2$), 0.84 (9H, s, $SiC(CH_3)_3$), 0.9 (3H, s, 18-H), 2.16 (3H, s, 2β-$OCOCH_3$), 3.53, 3.66 (1H, B-part of an AB-system, J = 10 Hz, one of 19-CH_2-OSi-), 3.96, 4.07 (1H, A-part of an AB-sytstem, J = 10 Hz, one of 19-CH_2-OSi-), 5.37 (1H, dd, J_1 = 1.5 Hz, J_2 = 9 Hz; 2α-H), 5.88 (1H, s, 4-H). Mass spectrum, m/z 474 (M^+;1%); 417 (M^+-$C(CH_3)_3$; 38%); 375 (417-C_2H_2O; 78%); 357 (417-CH_3COOH; 62%); 387 (417-CH_2O; 16%); 345 (387-C_2H_2O; 36%); 327 (357-CH_2O).

For 6: mp 110-112°C. ^{1}H Nmr: 0.03 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, s, 18-H), 3.60, 3.78 (1H, B-part of an AB-system, J = 11 Hz, one of 19-CH_2-OSi-), 3.78, 3.94 (1H, A-part of an AB-system, J = 11 Hz, one of 19-CH_2-OSi-), 5.8 (1H, s, 4-H), 6.21 (2H, s, 6 and 7-H). Mass spectrum, m/z 414 (M^+; 8%); 384 (M^+-CH_2O; 8%); 357 (M^+-$C(CH_3)_3$; 100%).

For 7: mp 58-60°C. ^{1}H nmr: 0.02 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.95 (3H, s, 18-H), 2.05 (3H, s, 6β-$OCOCH_3$), 3.92 (2H, s, 19-CH_2-OSi-), 5.52 (1H, t, $J \approx 3$Hz, 6α-H), 6.08 (1H, s, 4-H). Mass spectrum, m/z 474 (M^+; 2%); 417 (M^+-$C(CH_3)_3$; 62%); 444 (M-CH_2O; 7%); 384 (444-CH_3COOH; 50%); 357 (417-CH_3COOH; 100%).

2β-Acetoxy-19-hydroxyandrost-4-ene-3,17-dione (4c).

To a solution of 4b (100 mg) in acetonitrile (5 ml), HF (48% in H_2O) (0.5 ml) was added and the mixture was stirred at room temperature for 1.5 hr. Water was added and the product was extracted ($CHCl_3$) to give after workup 4c (74 mg, 96%) as a white solid. mp 90-92°C. ^{1}H Nmr: 0.88 (3H, s, 18-H), 2.12 (3H, s, 2β-$OCOCH_3$), 3.86 (2H, m, 19-CH_2 OH), 5.34 (1H, dd, J_1 = 4.5 Hz, J_2 = 12 Hz, 2α-H), 5.93 (1H, s, 4-H). Mass spectrum, m/z 360 (M^+; 2%); 330 (M^+-CH_2O; 14%); 288 (330-C_2H_2O; 34%); 270 (330-CH_3COOH;100%).

2α-Acetoxy-19-hydroxyandrost-4-ene-3,17-dione (3c).

Treatment of 3b (300 mg) with HF as described above gave 3c (220 mg 95%). mp 120-122°C. ^{1}H Nmr: 0.9 (3H, s, 18-H), 2.1 (3H, s, 2α-$OCOCH_3$), 3.9 (2H, m, 19-CH_2OH), 5.8 (1H, dd, J_1 = 7Hz, J_2 = 15Hz, 2β-H), 5.95 (1H, s, 4-H). Mass spectrum, m/z 360 (M^+; 6%); 330 (M^+-CH_2O; 38%); 288 (330-C_2H_2O; 60%); 270 (330-CH_3COOH;100%).

2β-Acetoxy-19-oxoandrost-4-ene-3,17-dione (9a).

A solution of 4c (60 mg, 0.167 mmol) in dry CH_2Cl_2 (5 ml) was stirred with pyridinium chlorochromate (72 mg, 0.334 mmol) for 2.5 h. The dark red mixture was stirred with brine for 10 min and extracted with CH_2Cl_2 (3x). The combined organic layer was dried and concentrated, and the residue was purified by tlc [silica gel; cyclohexane-EtOAc (1:1)] to give 9a (42 mg, 70%), mp 105-106°C. ^{1}H nmr: 0.9 (3H, s, 18-H), 2.06 (3H, s, 2β-$OCOCH_3$), 5.27 (1H, dd, J_1 = 4 Hz, J_2 = 9 Hz, 2α-H), 6.07 (1H, s, 4-H), 9.83 (1H, s, 19-CHO).

2α-Acetoxy-19-oxoandrost-4-ene-3,17-dione (8a)

Oxidation of 3c (150 mg, 0.417 mmol) with pyridinum chlorochromate (180 mg, 0.83 mmol) as described above gave 8a (108 mg, 72%). mp 150-153°C. ^{1}H Nmr: 0.88 (3H, s, 18-H), 2.16 (3H, s, 2α-$OCOCH_3$), 5.36 (1H, dd, J_1 = 6 Hz, J_2 = 14 Hz, 2β-H), 6.02 (1H, s, 4-H), 10.13 (1H, s, 19-CHO). Mass spectrum, m/z 358 (M^+; 16%), 329 (M^+-CHO; 10%), 298 (M^+ - CH_3COOH; 26%), 272 (M^+ - H_2C = CHOAc; 77%), 244 (272-CO; 36%).

Attempted saponification of 2α-acetoxy-19-oxoandrost-4-ene-3,17-dione (8a)

1. To a solution of 8a (10 mg) in methanol (0.4 ml) a solution of $KHCO_3$ (8 mg) in water (0.2 ml) was added and the mixture was stirred at room temperature for 2 h under N_2. The solution was concentrated, extracted (EtOAc) and processed in the conventional manner to give

after purification by tlc [silica gel; cyclohexane–EtOAc, (2:1)], estrone (10) (6 mg, 80%). mp 260-262°C. ^{1}H Nmr: 0.9 (3H, s, 18-H), 6.97-7.20 (3H, aromatic protons). The alcohol 8b could not be detected.

2. Treatment of 8a (5 mg) with K_2CO_3 (5 mg) as described above also gave estrone (10).

3. Treatment of 8a (5 mg) in 95% ethanol (0.2 ml) with KCN (4 mg) at room temperature for 18 h gave estrone (10).

4. To a solution of 8a (2 mg) in dioxane (0.5 ml) 5% aq. H_2SO_4 (0.1 ml) was added and the mixture was stirred at 80°C for 1.5 h. The reaction was processed in the conventional manner to give estrone (10).

Attempted saponification of 2β-acetoxy-19-oxoandrost-4-ene-3,17-dione (9a)

Treatment of 9a as described above for 8a gave estrone (10).

2α, 19-Dihydroxyandrost-4-ene-3-17-dione (3d).

A solution of 3c (100 mg) in methanol (0.5 ml) was treated with methanolic K_2CO_3 (5 ml) (prepared by dissolving 1 g anhydrous K_2CO_3 in 30 ml of water and diluting with 115 ml of methanol) and stirred at room temperature for 3 h under N_2. The solution was concentrated and extracted with $CHCl_3$. The extract was washed, dried, concentrated and the residue was purified by preparative tlc [silica gel; $CHCl_3$ - MeOH (9:1)] to give 3d (53 mg, 60%) mp 202-204°C. ^{1}H Nmr: 0.9 (3H, s, 18-H), 4.0 (2H, s, 19-CH_2-OH), 4.66 (1H, dd, J_1 = 6Hz, J_2 = 13Hz, 2β-H), 5.93 (1H, s, 4-H).

2α-Hydroxy-19-[(t-butyldimethylsilyl)oxy]androst-4-ene-3,17-dione (3e).

Treatment of 3b (120 mg) with methanolic K_2CO_3 as described above gave 3e (71 mg, 65%) mp 165-167°C. ^{1}H Nmr: 0.05 (6H, s, $Si(CH_3)_2$), 0.84 (9H, s, $SiC(CH_3)_3$), 0.92 (3H, s, 18-H), 3.77, 3.91 (1H, B-part of an AB-system, J = 12 Hz, one of 19-CH_2-OSi-), 3.99, 4.13 (1H, A-part of an AB-system, J = 12 Hz, one of 19-CH_2-OSi-), 4.62 (1H, dd, J_1 = 6Hz, J_2 = 13 Hz, 2β-H), 5.92 (1H, s, 4-H). Mass spectrum, m/z 432 (M^+; 23%), 375 ($M^+ - C(CH_3)_3$; 26%), 345 (375-CH_2O; 98%), 300 ($M^+ - C(CH_3)_3Si(CH_3)_2OH$; 78%).

2α-Hydroxy-19-oxoandrost-4-ene-3,17-dione (8b).

To a solution of 8a (100 mg) in acetonitrile containing 5% water (5.5 ml) and 1-octanol (181.5 mg, 5 mole equiv.), yeast lipase Candida cylindracea (500 mg) was added and the suspension was shaken on an orbit shaker, 300 rpm at 37°C for 7 days. The enzyme was removed by filtration and the filtrate was concentrated to a residue which was purified by plc [silica gel; cyclohexane–EtOAc (1:2)] to give starting material (20 mg) and 8b (53.8 mg, 61%), mp 205-208°C. ^{1}H Nmr: 0.88 (3H, s, 18-H), 4.17 (1H, dd, J_1 = 6 Hz, J_2 = 14 Hz, 2β-H),

6.04 (1H, s, 4-H), 10.09 (1H, s, 19-CHO). Mass spectrum, m/z 316 (M^+; 64%), 298 (M^+-H_2O; 40%), 287 (M^+ - CHO; 92%), 272 (M^+-CH_2=CHOH;100%) 244 (272-CO; 72%).

Treatment of 2β-acetoxy-19-oxo (9a) (15 mg) in acetonitrile-5% water (1 ml) and octanol (30 µl) with lipase (100 mg) for 10 days gave (8b) (ca. 10%) and starting material (80-90%).

2β,19-Dihydroxyandrost-4-ene-3,17-dione (4d).

Treatment of 4c (85 mg) with methanolic K_2CO_3 as described above for 3d afforded 4d (45 mg, 60%), mp 140-142°C. ^{1}H Nmr: 0.9 (3H, s, 18-H), 3.65 (1H, d, J = 10.5 Hz, one of the 19-CH_2-OH), 4.1 (2H, 2α-H and one of 19-CH_2-OH), 5.97 (1H, s, 4-H).

2β-[(t-Butyldimethylsilyl)oxy]-19-hydroxyandrost-4-ene-3,17-dione (4f).

To a solution of 4d (40 mg) in DMF (2 ml) were added t-butyldimethylsilyl chloride (60 mg) and imidazole (95 mg) and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with ethyl acetate (5 ml), washed with H_2O, dried and concentrated. The residue was purified by plc [silica gel; cyclohexane-EtOAc (1:1)] to give 4f (27.5 mg, 50%) and the 2β,19-disilyl ether 4g (32 mg).

The 2β-monosilyl ether (4f) showed: mp 131-133°C. ^{1}H Nmr: 0.08 (3H, s, one of $Si(CH_3)_2$), 0.15 (3H, s, one of $Si(CH_3)_2$), 0.85 (12H, s, 18-CH_3 and $SiC(CH_3)_3$), 3.45 - 4.16 (3H, 2α-H and 19-CH_2-OH), 5.93 (1H, s, 4-H).

The disilyl ether 4g: ^{1}H Nmr: 0.00 (6H, s, one set of $Si(CH_3)_2$), 0.06 (3H, s, one of $Si(CH_3)_2$), 0.08 (3H, s, one of $Si(CH_3)_2$), 0.83 (9H, s one set of $SiC(CH_3)_3$), 0.86 (9H, s, set of $SiC(CH_3)_3$), 3.84 (2H, d, J = 3 Hz, 19-CH_2-OSi-), 4.1 (1H, m, 2α-H), 5.78 (1H, s, 4-H).

Recycling of 4g (to 4f): A mixture of (4g) (30 mg), acetonitrile (0.2 ml) and aq. HF (48%) (0.01 ml) was stirred at room temperature for 1.5 h. The recovered diol (4d) (17 mg) was silylated as described above to give 4f (11.6 mg). The overall yield of (4f) from the diol (4d) was ca. 75%.

2β-[(t-Butyldimethylsilyl)oxy]-19-oxoandrost-4-ene-3,17-dione (9c).

A solution of 4f (20 mg) in dry CH_2Cl_2 (2 ml) was oxidized with pyridinium chlorochromate (20 mg) and processed as described for 9a. Following plc [silica gel; cyclohexane-EtOAc, (2:1)], 9c (13.5 mg, 67%), mp 186-188°C,was obtained. ^{1}H Nmr: 0.00 (3H, s, one of $Si(CH_3)_2$), 0.06 (3H, s, one of $Si(CH_3)_3$), 0.81 (9H, s, $SiC(CH_3)_3$), 0.85 (3H, s, 18-H), 4.00 (1H, broad s, 2α-H), 5.89 (1H, s, 4-H), 9.87 (1H, s, 19-CHO).

2β-Hydroxy-19-oxoandrost-4-ene-3,17-dione (1).

A solution of 9c (9 mg) in acetonitrile (0.5 ml) was treated with aqueous HF (48%)(0.1 ml) and the mixture was stirred at room temperature for 1 h. $CHCl_3$ (2 ml) and H_2O (1 ml) were added

and the organic phase separated. The aqueous phase was extracted with $CHCl_3$ (x 3); the combined organic phase was washed with H_2O (X 2), dried and evaporated at room temperature to give a white solid residue (7.6 mg). The residue was fractionated by HPLC [Alltech Co. column;silica 10μ; 25 cm X 4.6 mm (i.d.); 20% isopropanol in isooctane; flow rate 1 ml/min, uv detector 242 nm] to give 1 (3 mg, 45%), mp 166-168°C. ^{1}H Nmr: 0.95 (3H, s, 18-H), 4.21 (1H, dd, J_1 = 6 Hz, J_2 = 10 Hz, 2α-H), 6.07 (1H, s, 4-H), 9.69 (1H, s, 19-CHO).

2β,19-Oxaandrost-4-ene-3,17-dione (11)

(a) A solution of diethyl azodicarboxylate (55 mg, 0.31 mmol) in dry THF (0.3 ml) was added dropwise over a period of 5 min to a stirred mixture of 2α,19-dihydroxyandrost-4-ene-3,17-dione (3d) (50 mg, 0.6 mmol), triphenylphosphine (165 mg, 0.63 mmol) and formic acid (15.4 mg, 0.31 mmol) in dry THF (2 ml) at room temperature. Stirring at room temperature was continued for 17 h, then the solvent was removed under reduced pressure. The residue was fractionated by plc [silica gel; cyclohexane-EtOAc (2:1) X 2] to give (11) (31 mg, 70%), mp 100-102°C. ^{1}H Nmr: 0.91 (3H, s, 18-H), 3.46, 3.50 (1H, B-part of an AB-system, J = 7.5 Hz, one of 19-CH_2-OSi-), 4.02, 4.10 (1H, A-part of an AB-system, J = 7.5 Hz, one of 19-CH_2-OSi-), 4.3 (1H, dd, J_1 = 1.5 Hz, J_2 = 6 Hz, 2α-H), 5.82 (1H, s, 4-H). Mass spectrum m/e 300 (M^+, 100%), 270 (M^+-19-CH_2O; 20%). Uv (ethanol) 241 nm (log ε 4.0);

(b) To a stirred solution of diethyl azodicarboxylate (62 mg; 0.36 mmol) and 2α,19-dihydroxyandrost-4-ene-3,17-dione (3d) (50 mg; 0.18 mmol) in dry THF (2 ml) was added trifluoroacetic acid (40 mg; 0.36 mmol) followed by addition of solid triphenylphosphine (94 mg; 0.36 mmol). After 5 min, sodium benzoate (52 mg; 0.36 mmol) was added and the mixture was stirred 16 h at ambient temperature. The solvent was evaporated, the residue was taken up in $CHCl_3$ and processed in the usual manner. The resulting yellow oil was fractionated by plc [silica;cyclohexane-EtOAc (1:1)] to yield (11) (12 mg; 25%) and starting material (3d) (20 mg).

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