The Solvolytic Ring Opening of a 4β,5β-Epoxy-3,6-dione Steroid: Preparation of Potential Aromatase Inhibitors

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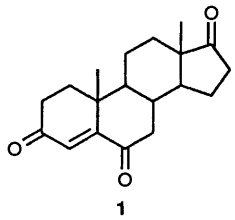
4β,5β-Epoxyandrostane-3,6,17-trione **2** undergoes cleavage of the epoxy ring as a result of nucleophilic attack by water to give both 2-hydroxy-1,4-diene-3,6-dione **3** and 7α-hydroxy-4-ene-3,6-dione **9** upon treatment with sulfuric acid in aqueous acetone. In the similar reaction in acetic acid, 2α-acetoxy-4-ene-3,6-dione **6** and its 2β-isomer **7** are produced along with the diosphenol **3**. Reaction of the epoxide **2** with sodium hydroxide in methanol affords 4-methoxy-4-ene-3,6-dione **12** the dealkylation of which with hydrochloric acid yields the 4-hydroxy derivative **14**.

As a part of a study of aromatase inhibitors, we have synthesized and carried out a biochemical evaluation of androst-4-ene-3,6,17-trione **1** derivatives.[1] An oxygen function (carbonyl or hydroxy) at the 3-position of a 4-en-6-one steroid is essential for it to induce inactivation of aromatase. In spite of this, 4-hydroxyandrost-4-ene-3,17-dione, which is a potent suicide substrate of the enzyme,[2] is now under clinical evaluation for treatment of breast cancer.[3] Thus, we were interested in the combination of the 4-ene-3,6-dione grouping with a 4-hydroxy substituent. As far as we know, however, the synthesis of 4-hydroxyandrost-4-ene-3,6,17-trione **14** has not been reported.

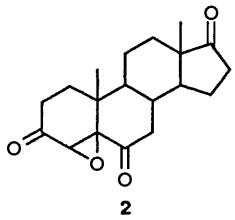
Although it has been reported that the acid-catalysed ring-opening of 4β,5β-epoxy steroids leads principally to products of normal epoxide fission, 4-hydroxy-4-en-3-one steroids,[2a,4] treatment of 4β,5β-epoxides with sulfuric acid in aqueous acetone or in refluxing acetic acid affords 2α-hydroxy- or 2α-acetoxy-4-en-3-one analogues, the abnormal products of epoxide fission.[4a,5] 4β,5β-Epoxyandrostane-3,17-dione, however, on treatment with methanolic sodium hydroxide produces the 4-methoxy-4-en-3-one derivative.[6] Since the acid- and alkaline-catalysed reactions of 4β,5β-epoxyandrostane-3,6,17-trione **2** have not been reported so far, and in order both to obtain the 4-hydroxy-4-ene-3,6-dione **14** and to explore the chemical aspects of the reactions, we treated the steroid **2** both with sulfuric acid under a variety of conditions and with strong bases in alcohol.

The substrate **2** was prepared by treatment of the 4-ene-3,6,17-trione **1** with alkaline hydrogen peroxide.[1d] The assignment of the stereochemistry to the epoxide followed from its ^{1}H NMR spectrum. Thus, there was no significant NOE enhancement of the 19-methyl proton (δ 1.05) when the 4α-proton (δ 3.81) was irradiated and the 6-deoxy analogue of compound **2** showed a similar NOE result. Reaction of the epoxide **2** with sulfuric acid in acetic acid was initially carried out at room temperature according to the method[5] reported earlier. Column chromatography followed by reversed-phase high performance liquid chromatography (HPLC) (C_{18} column, acetonitrile–water) gave 2-hydroxyandrosta-1,4-diene-3,6,17-trione **3** (15%), 2α-acetoxyandrost-4-ene-3,6,17-trione **6** (15%), and its 2β-isomer **7** (13%). The structural assignments for these compounds were confirmed by their spectral data. In compound **3**, the ^{1}H NMR spectrum showed two singlet signals for olefinic protons at C-1 (δ 6.51) and C-4 (δ 6.33) and a singlet signal for the 4-hydroxy proton (δ 6.29); its IR (ν_{max} 1689 cm^{-1}), UV (λ_{max} 256 and 310 nm), and mass (M^+ 314) spectra also supported the structure. The final proof for its structure was obtained from ^{13}C NMR spectroscopy; the ^{1}H-decoupled ^{13}C spectrum disclosed in the lower field region the presence of 7 sp^2 carbons (three carbonyl and four C=C double bond carbons). Acetylation of this compound with acetic anhydride in pyridine yielded 2,6-diacetoxyandrosta-1,4,6-triene-3,17-dione **5** [^{1}H NMR, two acetoxy groups (δ 2.25 and 2.27) and three olefinic protons (δ 5.84, 6.23 and 6.72); UV, λ_{max} 262 and 301 nm] along with the 2-acetoxy derivative **4** (^{1}H NMR, an acetoxy group at δ 2.17).

In compounds **6** and **7**, these ^{1}H NMR spectra revealed the presence of an acetoxy group (δ 2.18 for **6** and 2.14 for **7**), a C*H*(OAc) group [δ 5.44 (dd, *J* 13.9 and 5.1 Hz) for **6** and δ 5.33 (dd, *J* 8.9 and 5.0 Hz) for **7**], and an olefinic proton at C-4 (δ 6.21 for **6** and 6.14 for **7**). The C*H*(OAc) signal appears as a double doublet in each and irradiation of the signal produced 21% of NOE enhancement of the 19-methyl proton of compound **6** whereas the small NOE (2%) was observed with the other. The ^{1}H NMR experiments proved compound **6** to have a 2α-acetoxy group and the other to be its 2β-acetoxy isomer. Coupling constants ($J_{1,2}$) of their 2β- and 2α-protons are comparable with those reported for the corresponding 6-deoxy steroids, suggesting that A-ring conformations of the 2α-acetate **6** and its 2β-isomer **7** are, respectively, close to chair and inverted chair as reported previously in the androst-4-ene-3,17-



1



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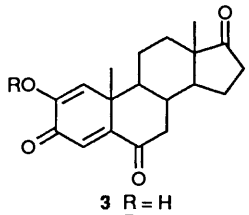
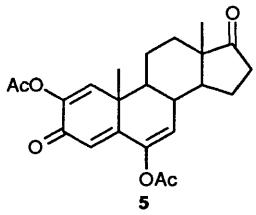


3 R = H
4 R = Ac



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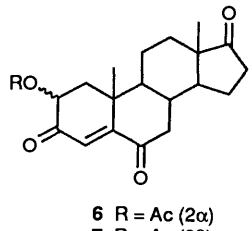
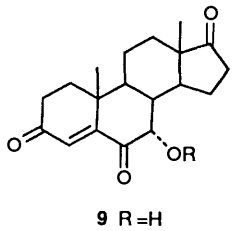


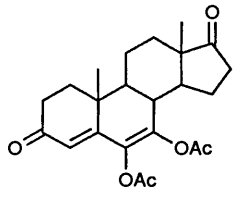
6 R = Ac (2α)
7 R = Ac (2β)
8 R = OH (2ξ)



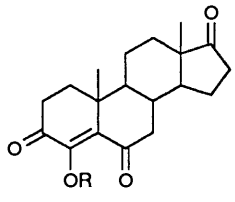
9 R = H
10 R = Ac

dione series.[4d,7] Treatment of the acetate **6** with potassium carbonate in aqueous methanol for 3 h produced the diosphenol **3** in high yield. It has previously been reported that a 2α-acetoxy-4-en-3-one steroid is converted into its 2-hydroxy-1,4-dien-3-one derivative *via* a 2α-ol under hydrolysis conditions similar to those employed in this study.[8] Thus, it is presumed that compound **3** would be produced through the oxidation of 2ξ-hydroxy-4-ene-3,6-dione **8** which is initially formed in the reaction. TLC analysis of the hydrolysis with a short reaction time (30 min) indeed indicated the production of the more polar steroid than the starting material, probably 2ξ-ol **8**, which, however, could not be isolated in a pure form because it is easily converted into the diosphenol **3** during isolation procedures (TLC and HPLC).

When the solvolysis of compound **2** catalysed by sulfuric acid was carried out in aqueous acetone, 7α-hydroxyandrost-4-ene-3,6,17-trione **9** (45%) along with the diosphenol **3** (16%) were obtained. The ^{1}H NMR spectrum of compound **9** revealed signals at δ 4.13 [1 H, d, *J* 2.6 Hz, 7-C*H*(OAc)] and 6.23 (1 H, d, *J* 1.1 Hz, 4-H). The configuration of the 7-hydroxy group was established on the basis that the small coupling constant of 7-H was a result of its *cis* orientation with respect to 8β-H; the dihedral angle between 7β-H and 8β-H for a Dreiding model is *ca.* 61°.[9] The structure was further characterized by ^{13}C NMR, IR and UV spectroscopy. Acetylation of the 7α-ol **9** with acetic anhydride in pyridine yielded its 7α-monoacetate **10** (35%) (^{1}H NMR, an acetoxy group at δ 2.09 and the C-7β proton at δ 5.15) and 6,7-diacetoxyandrosta-4,6-diene-3,17-dione **11** (40%) (^{1}H NMR, two acetoxy groups at δ 2.20 and 2.26 and an olefinic proton at δ 6.15; UV, λ_{max} 290 nm).



11



12 R = Me
13 R = Et
14 R = H

Treatment of compound **2** with formic acid according to the method[2a] previously reported for the synthesis of a 4-hydroxy-4-en-3-one steroid, afforded the diosphenol **3** (15%), together with many unidentified products.

The abnormal ring opening of a 4β,5β-epoxy ketone yielding a 2α-hydroxy-4-en-3-one or 2α-acetoxy-4-en-3-one steroid,[4a,5] as a sole product, formally involves S_N2' substitution at the sterically less hindered C-2α position of the enol tautomer of the starting material. Based upon *cine* substitution,[10] a possible mechanism for the solvolysis of the α,β-epoxy diketone **2** can be rationalized as follows. Acid-catalysed enolization of the C-3 carbonyl group followed by attack of an acetoxy anion from both the α- and β-sides leads to a mixture of the 2α- and 2β-substituted products (**6** and **7**). Alternatively, the nucleophile attacks the sterically less hindered C-2α position to yield the 2α-acetate **6** which then isomerizes to the 2β-isomer **7** under the same conditions. However, compound **7** having an axial orientated 2β-acetoxy group is thermodynamically less stable than the 2α-isomer. Considering this along with the fact that the yields of the isomers are almost identical, the former sequence rather than the latter seems principally to operate in the reaction. A similar S_N2' displacement by water is probably involved in the conversion of compound **2** into the 2-ol **8** which is instantaneously oxidized to give the diosphenol **3**.

On the other hand, when the sulfuric acid-catalysed enolization of the 6-carbonyl function occurs in aqueous acetone, water attacks at C-7 from the less sterically hindered α-side to give stereospecifically the 7α-ol **9** through an S_N2' process. Thus, formation of the normal epoxy-ring fission product of the 4β,5β-epoxy diketone **2** could not be detected in this study, indicating that the enolization of a carbonyl function at C-3 or C-6 rather than the epoxy ring cleavage occurs under acidic conditions.

We then focused our attention upon reaction of the epoxide **2** under basic conditions. Reaction of this with sodium hydroxide in methanol[6] or sodium ethoxide in ethanol produced 4-methoxyandrost-4-ene-3,6,17-trione **12** (70%) or its 4-ethoxy derivative **13** (30%). Spectral data are consistent with the assigned structures. Attempted demethylation of the 4-methoxide **12** with HBr in acetic acid or BBr_3 failed, producing a complex mixture of products. In contrast, treatment of compound **12** with 12 mol dm^{-3} HCl in dioxane[6] finally gave 4-hydroxy steroid **14** in fair yield.

In our preliminary studies, compounds **3**, **12** and **14** were evaluated as having good inhibitory activity against aromatase from human placental microsomes. The detailed biochemical results will be reported elsewhere.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer FT-IR 1725X spectrophotometer and UV spectra in ethanol solution on a Hitachi 150–20 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solution with JEOL GX 270 (270 MHz for ^{1}H and 67.9 MHz for ^{13}C) and GX 400 (400 MHz for ^{1}H and 100.5 MHz for ^{13}C) spectrometers using tetramethylsilane (δ 0.00) as an internal standard, and mass spectra (electron impact) were obtained with JEOL JMS-DX 303 spectrometer. Analytical TLC was performed with Merck precoated TLC plates (silica gel 60F–254, layer thick 0.25 mm). Column chromatography was conducted on silica gel 60, 70–230 mesh (Merck). HPLC was carried out using Waters Model 510 pump, YMCA D-ODS-5 column (250 mm × 20 i.d. mm), acetonitrile–water (55:45 v/v, flow rate 6 cm^3 min^{-1}) as the solvent, and UV detector (285 nm).

4β,5β-*Epoxyandrostane*-3,6,17-*trione* **2**.—This compound was prepared according to the method previously reported,[1d] m.p. 158–160 °C (lit.,[1d] 158–160.5 °C).

Reaction of the 4β,5β-*Epoxide* **2** *with Sulfuric Acid in Acetic Acid.*—Sulfuric acid (0.2 cm^3) was added to a solution of compound **2** (305 mg, 0.96 mmol) dissolved in acetic acid (3.5 cm^3) and the mixture was stirred at room temperature for 3 h. After this time, the mixture was diluted with ethyl acetate (200 cm^3), washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated under reduced pressure to give an oily residue. Column chromatography (hexane–ethyl acetate, 5:1) of the residue and a subsequent reversed-phase HPLC yielded the following three products. 2-Hydroxyandrosta-1,4-diene-3,6,17-trione **3** [37 mg, 12%; retention time of HPLC (t_R) 15.6 min] m.p. 199–202 °C (Found: C, 72.6; H, 6.8. $C_{19}H_{22}O_4$ requires C, 72.59; H, 7.06%); ν_{max}/cm^{-1} 3411 (OH), 1737 (17-ketone) and 1689 (3- and 6-ketones); λ_{max}/nm 221 (15 700), 256 (8200) and 310 (2600); δ_H(400 MHz) 0.97 (3 H, s, 18-Me), 1.26 (3 H, s, 19-Me), 6.29 (1 H, s, exchangeable with D_2O, 2-OH), 6.33 (1 H, s, 4-H) and 6.51 (1 H, s, 1-H); δ_C(100.5 MHz) 13.7, 19.4, 21.6, 22.6, 30.9, 34.0, 35.4, 45.3, 45.7, 47.8, 50.1, 51.1, 122.3, 122.6, 146.9, 163.7, 180.8, 200.5 and 218.7; *m*/*z* 314 (M^+, 100%), 296 (5), 286 (15) and 268 (12). 2α-Acetoxyandrost-4-ene-3,6,17-trione **6** (52 mg, 15%; t_R 21.4 min), m.p. 194–197 °C (Found: C, 70.4; H, 7.3. $C_{24}H_{26}O_5$ requires C, 70.37; H, 7.31%); ν_{max}/cm^{-1} 1741 (ester and 17-ketone) and 1698 (3- and

6-ketones); λ_{max}/nm 249 (13 000); δ_H(400 MHz) 0.94 (3 H, s, 18-Me), 1.33 (3 H, s, 19-Me), 2.18 (3 H, s, 2α-OCOMe), 5.44 (1 H, dd, *J* 13.9 and 5.1, 2β-H) and 6.21 (1 H, s, 4-H); *m/z* 356 (M^+, 20%), 330 (5), 316 (100), 298 (49) and 288 (17). 2β-Acetoxyandrost-4-ene-3,6,17-trione **7** (42 mg, 13%); t_R 22.2 min, m.p. 195–197 °C (Found: C, 70.3; H, 7.35. $C_{21}H_{26}O_5$ requires C, 70.37; H, 7.31%); ν_{max}/cm^{-1} 1750 (ester and 17-ketone) and 1693 (3- and 6-ketones); λ_{max}/nm 245 (12 100); δ_H 0.94 (3 H, s, 18-Me), 1.24 (3 H, s, 19-Me), 2.14 (3 H, s, 2β-Ac), 5.33 (1 H, dd, *J* 8.9 and 5.0, 2α-H) and 6.14 (1 H, s, 4-H); *m/z* 358 (M^+, 13%), 330 (19), 316 (100), 298 (29) and 288 (78).

Reaction of Compound **2** *with Sulfuric Acid in Aqueous Acetone.*—A mixture of compound **2** (790 mg, 2.5 mmol), sulfuric acid (0.4 cm^3), water (1.2 cm^3), and acetone (31 cm^3) was stirred at room temperature for 46 h and then concentrated to about 15 cm^3 under reduced pressure at < 40 °C, diluted with ethyl acetate (300 cm^3), washed with aqueous $NaHCO_3$ and water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a solid which was suspended in ethyl acetate (20 cm^3). The solid material was collected by filtration and washed well with the solvent. The combined organic layers were subjected to column chromatography (hexane–ethyl acetate, 5:1) to yield the diosphenol **3** (130 mg, 17%), m.p. 199–202 °C (from MeOH), identified by comparison (^1H NMR, TLC, and mixed melting point) with an authentic sample obtained by the reaction in acetic acid described above. The solid product, poorly soluble in ethyl acetate, was recrystallized from methanol–chloroform to give 7α-hydroxyandrost-4-ene-3,6,17-trione **9** (352 mg, 45%), m.p. 192–196 °C (Found: C, 72.2; H, 7.6. $C_{19}H_{24}O_4$ requires C, 72.13; H, 7.65%); ν_{max}/cm^{-1} 3382 (OH), 1739 (17-ketone) and 1678 (3- and 6-ketones); λ_{max}/nm 249 (11 400); δ_H(400 MHz) 0.93 (3 H, s, 18-Me), 1.20 (3 H, s, 19-Me), 4.13 (1 H, d, *J* 2.6, 7β-H) and 6.23 (1 H, d, *J* 1.1, 4-H); δ_C(100.5 MHz) 13.2, 17.5, 20.0, 20.9, 30.5, 33.7, 35.3, 35.5, 38.7, 40.2, 42.7, 44.2, 47.2, 72.6, 126.9, 162.1, 199.4, 202.0 and 220.6; *m/z* 316 (M^+, 100%), 301 (14), 288 (61) and 272 (38).

Reaction of Compound **2** *with Formic Acid.*—A solution of compound **2** (350 mg, 1.11 mmol) in formic acid (6 cm^3) was heated at 60 °C for 45 min and then poured into water (100 cm^3). The mixture was further stirred at room temperature for 30 min and then extracted with ethyl acetate (2 × 100 cm^3). The combined extracts were washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated under reduced pressure to afford an oil. The oily product was purified by column chromatography (hexane–ethyl acetate, 6:1) to give the diosphenol **3** (50 mg, 16%), m.p. 199–202 °C, along with a complex mixture of other products. Compound **3** was identical with an authentic sample (TLC, ^1H NMR, and mixed melting point).

Reaction of Compound **2** *with Sodium Hydroxide in Methanol.*—Aqueous sodium hydroxide (4 mol dm^{-3}; 3 cm^3) was added to a solution of compound **2** (310 mg, 0.98 mmol) in methanol (38 cm^3) and the mixture was heated under reflux for 40 min. After cooling, the mixture was neutralized with 3 mol dm^{-3} HCl and then evaporated under reduced pressure. The residue was treated with water (100 cm^3) and the product was extracted with ethyl acetate (2 × 100 cm^3). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to yield a solid which was recrystallized from methanol to afford 4-methoxyandrost-4-ene-3,6,17-trione **12** (210 mg, 65%), m.p. 221–225 °C (Found: C, 72.7; H, 7.9. $C_{20}H_{26}O_4$ requires C, 72.70; H, 7.93%; ν_{max}/cm^{-1} 1737 (17-ketone) and 1699 (3- and 6-ketones); λ_{max}/nm 270 (10 300); δ_H(270 MHz) 0.93 (3 H, s, 18-Me), 1.26 (3 H, s, 19-Me) and 3.70 (3 H, s, 4-OMe); δ_C(67.9 MHz) 13.6, 17.0, 20.2, 21.6, 30.9, 34.4, 34.8, 35.5, 36.0, 42.2, 47.4, 47.7, 51.4, 53.4, 61.3, 145.3, 146.9, 194.9, 201.9 and 219.1; *m/z* 330 (M^+, 100%) and 315 (10) and 302 (7).

Reaction of Compound **2** *with Sodium Ethoxide in Ethanol.*—Compound **2** (200 mg, 0.63 mmol) was dissolved in a solution of sodium metal (210 mg, 9.1 mmol) in absolute ethanol (25 cm^3) and the mixture was heated under reflux under N_2 for 90 min. After cooling, the reaction mixture was adjusted to pH 4 with 3 mol dm^{-3} HCl and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (200 cm^3) and the solution washed with aqueous $NaHCO_3$ and water and dried (Na_2SO_4), and evaporated to give an oil. This was purified by column chromatography (hexane–ethyl acetate, 6:1) to afford 4-ethoxyandrost-4-ene-3,6,17-trione **13** (65 mg, 30%), m.p. 166–168 °C (from MeOH) (Found: C, 73.3; H, 8.1. $C_{21}H_{28}O_4$ requires C, 73.23; H, 8.19%); ν_{max}/cm^{-1} 1736 (17-ketone) and 1693 (3- and 6-ketones); λ_{max}/nm 270 (9100); δ_H(270 MHz) 0.91 (3 H, s, 18-Me), 1.18 (3 H, s, 19-Me), 2.26 (3 H, t, *J* 7.1, 4-OCH$_2$*Me*), 3.76 and 4.05 (1 H each, m, 4-OCH_2Me); *m/z* 344 (M^+, 100%), 328 (15) and 315 (5).

Acetylation of the Hydroxy Steroids **3** *and* **9**.—Acetic anhydride (0.35 cm^3) was added separately to a solution of the hydroxy steroid **3** or **9** (70 mg, 0.22 mmol) in pyridine (0.7 cm^3) and the mixture was allowed to stand at room temperature overnight. Excess of acetic anhydride was decomposed by addition of methanol after which the mixture was evaporated under reduced pressure to give an oil. This was purified by column chromatography (hexane–ethyl acetate, 7:1).

2-*Acetoxyandrosta*-1,4-*diene*-3,6,17-*trione* **4**.—The more polar acetate obtained from compound **3** was recrystallized from acetone to yield the *title compound* **4** (13 mg, 16%), m.p. 218–221 °C (Found: C, 70.6; H, 6.8. $C_{21}H_{24}O_5$ requires C, 70.77; H, 6.79%); ν_{max}/cm^{-1} 1773 (ester), 1734 (17-ketone), and 1703 and 1666 (3- and 6-ketones); λ_{max}/nm 252 (12 900); δ_H(400 MHz) 0.96 (3 H, s, 18-Me), 1.30 (3 H, s, 19-Me), 2.17 (3 H, s, 2-OAc), 6.46 (1 H, s, 4-H) and 6.74 (1 H, s, 1-H); *m/z* 356 (M^+, 5%), 314 (100) and 296 (14).

2,6-*Diacetoxyandrosta*-1,4,6-*triene*-3,17-*dione* **5**.—Recrystallization of the less polar acetate produced from compound **3** afforded the *title compound* **5** (67 mg, 74%), m.p. 103–106 °C (Found: C, 69.0; H, 6.4. $C_{23}H_{26}O_6$ requires C, 69.33; H, 6.58%); ν_{max}/cm^{-1} 1767 (esters), 1741 (17-ketone) and 1668 (3-ketone); λ_{max}/nm 262 (10 600) and 301 (8 800); δ_H(400 MHz) 0.93 (3 H, s, 18-Me), 1.40 (3 H, s, 19-Me), 2.25 and 2.27 (3 H each, s, 2- and 6-OAc), 5.84 (1 H, d, *J* 2.2, 7-H), 6.23 (1 H, s, 4-H) and 6.72 (1 H, s, 1-H); *m/z* 398 (M^+, 6%), 356 (100) and 314 (97).

7α-*Acetoxyandrost*-4-*ene*-3,6,17-*trione* **10**.—Recrystallization of the more polar product obtained by acetylation of compound **9** gave the *title compound* **10** (20 mg, 25%), m.p. 190–193 °C (Found: C, 70.1; H, 7.5. $C_{21}H_{26}O_5$ requires C, 70.37; H, 7.31%); ν_{max}/cm^{-1} 1749 (ester), 1729 (17-ketone) and 1658 (3- and 6-ketones); λ_{max}/nm 236 (10 400); δ_H(400 MHz) 0.93 (3 H, s, 18-Me), 1.22 (3 H, s, 19-Me), 2.09 (3 H, s, 7-OAc), 5.15 (1 H, d, *J* 2.2, 7β-H) and 6.07 (1 H, d, *J* 1.1, 4-H); δ_C(100.5 MHz) 13.3, 17.9, 20.3, 20.7, 21.3, 30.6, 33.8, 35.4, 35.7, 38.9, 40.1, 44.5, 44.9, 47.5, 75.2, 126.6, 161.1, 169.4, 197.6, 198.2 and 218.7; *m/z* 358 (M^+, 25%), 330 (11), 316 (44), 298 (10) and 288 (100).

6,7-*Diacetoxyandrosta*-4,6-*diene*-3,17-*dione* **11**.—The less polar acetate produced from compound **9** was recrystallized from methanol to afford the *title compound* **11** (27 mg, 30%), m.p. 201–205 °C (Found: C, 69.0; H, 7.1. $C_{23}H_{28}O_6$ requires C, 68.98; H, 7.05%); ν_{max}/cm^{-1} 1763 (esters), 1737 (17-ketone) and 1677 (3-ketone); λ_{max}/nm 290 (21 800); δ_H(400 MHz) 0.93 (3 H,

s, 18-Me), 1.26 (3 H, s, 19-Me), 2.20 and 2.26 (3 H each, s, 6- and 7-OAc) and 6.15 (1 H, d, *J* 2.2, 4-H); δ_C(100.5 MHz) 13.8, 17.1, 20.3, 20.8, 21.1, 24.0, 25.9, 30.6, 33.1, 35.9, 36.2, 44.4, 46.3, 48.2, 48.4, 109.2, 138.1, 147.2, 157.0, 168.3, 168.5, 192.0 and 220.0; *m/z* 400 (M^+, 5%) and 358 (100).

Hydrolysis of the 2α-Acetoxy Steroid **6** *with Potassium Carbonate.*—A mixture of the 2α-acetate **6** (23 mg, 64 μmol), potassium carbonate (9 mg, 64 μmol), methanol (3 cm^3), and water (5 cm^3) was stirred at room temperature for 3 h. After being adjusted to pH 4 with acetic acid, the mixture was concentrated under a N_2 stream, diluted with ethyl acetate (10 cm^3), washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated to give a solid. This was recrystallized from ethyl acetate to yield the diosphenol **3** (14 mg, 70%), m.p. 199–202 °C. This was identical with an authentic sample.

Demethylation of the 4-*Methoxide* **12**.—Hydrochloric acid (12 mol dm^{-3}; 0.85 cm^3) was added to a solution of the methoxide **12** (81 mg, 0.25 mmol) in dioxane (10 cm^3) and the mixture was heated under reflux for 5 h. After being cooled, the solution was poured into water (100 cm^3) and extracted with ethyl acetate (2 × 100 cm^3). The combined extracts were washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated to afford a solid which was recrystallized from acetone to give 4-hydroxyandrost-4-ene-3,6,17-trione **14** (50 mg, 65%), m.p. 211–215 °C (Found C, 71.9; H, 7.4. $C_{19}H_{24}O_4$ requires C, 72.13; H, 7.65%); ν_{max}/cm^{-1} 3443 (OH), 1737 (17-ketone) and 1702 (3- and 6-ketones); λ_{max}/nm 319 (3 500); δ_H(400 MHz) 0.94 (3 H, s, 18-Me), 1.28 (3 H, s, 19-Me) and 3.49 (1 H, s, exchangeable with D_2O, 4-H); *m/z* 316 (M^+, 40%), 301 (100), 288 (33) and 273 (96).

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