METHANOLYSIS OF 3β-SUBSTITUTED 4,5-EPOXYANDROSTANES CATALYSED BY TETRACYANOETHYLENE

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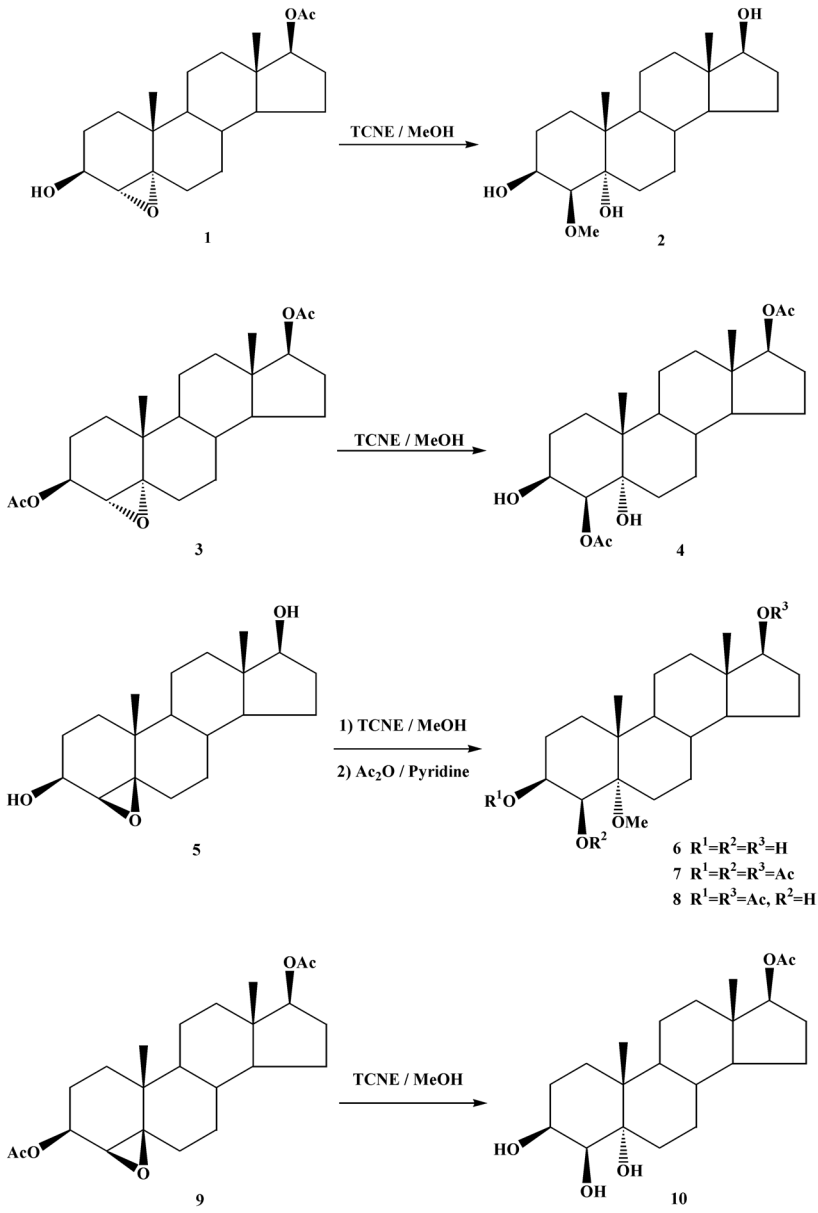
Received October 14, 2009
Accepted January 6, 2010
Published online April 15, 2010

The presence of a 3β-acetoxyl and 3β-hydroxyl group has been shown to modify the structures of the products arising from the tetracyanoethylene catalysed methanolysis of the epimeric 4,5-epoxyandrostanes when compared to the unsubstituted epoxyandrostanes.
Keywords: Steroids; Androstanes; Methanolysis; Epoxides; X-ray crystallography.

Tetracyanoethylene (TCNE) is a mild π-acid catalyst which has been used for the methanolysis of epoxides[1]. The stereochemistry of the reaction of simple polycyclic epoxides including those of the steroids follows a normal epoxide hydrolysis pathway in which there is a trans-anti-periplanar relationship between, in this case, the resultant methoxy and hydroxy groups[2]. Thus methanolysis of 4α,5-epoxy-5α-androstan-17β-yl acetate gave 5-hydroxy-4β-methoxy-5α-androstan-17β-yl acetate whilst 4β,5-epoxy-5β-androstan-17β-yl acetate gave a mixture (4:3) of 5-hydroxy-4α-methoxy-5β-androstan-17β-yl acetate and 4β-hydroxy-5-methoxy-5α-androstan-17β-yl acetate. In all three products there was a diaxial relationship between C-4 and C-5 substituents. However an adjacent *cis*-5-hydroxyl group has been shown to modify the regiochemistry of the TCNE catalysed methanolysis of 3,4-epoxyandrostanes from trans diaxial to diequatorial cleavage[3].

In this paper, we report the effect of 3β-acetoxyl and 3β-hydroxyl group on the cleavage of the epimeric 4,5-epoxides in which the 3-substituent modifies the reaction (Scheme 1). Adjacent substituents have been shown

doi:10.1135/cccc2009527


OAc
HO
O
1
TCNE / MeOH
OH
HO
OH
OMe
2
OAc
AcO
O
3
TCNE / MeOH
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OH
OAc
4
OH
HO
O
5
1) TCNE / MeOH
2) Ac2O / Pyridine
OR3
R1O
OMe
OR2
6 R1=R2=R3=H
7 R1=R2=R3=Ac
8 R1=R3=Ac, R2=H
OAc
AcO
O
9
TCNE / MeOH
OAc
HO
OH
OH
10

SCHEME 1

to modify the mineral acid-catalysed hydrolysis of these epoxides and in particular there is evidence for the participation of a 3β-acetoxyl group[4,5].

The 3β-substituted epimeric epoxides were prepared by literature methods[6,7]. The 4β,5β-epoxides were prepared from 3β,17β-dihydroxyandrost-4-ene by epoxidation with 3-chloroperbenzoic acid followed by acetylation. On the other hand, epoxidation of 3β,17β-diacetoxyandrost-4-ene gave the 4α,5α-epoxide. The 3β-acetoxyl group was then subjected to mild hydrolysis with potassium carbonate.

Methanolysis of 4α,5-epoxy-3β-hydroxy-5α-androstan-17β-yl acetate (**1**) gave 4β-methoxy-5α-androstane-3β,5,17β-triol (**2**). The structure and stereochemistry of this product was established by X-ray crystallography (Fig. 1). The 4-H NMR signal (δ_H 3.08) was a doublet (J = 4 Hz) whilst the 3-H resonance (δ_H 4.09) was a doublet (J = 11 Hz) of triplets (J = 4 Hz). Methanolysis of 4α,5-epoxy-5α-androstane-3β,17β-diyl diacetate (**3**) gave a diacetate (δ_H 2.01 and 2.10) which lacked a methoxyl signal. This product possessed two CH(OAc) resonances (δ_H 4.54 (triplet, J = 8.5 Hz, 17-H) and δ_H 4.91 (doublet, J = 3.9 Hz, 4-H)). The 3-H resonance appeared at δ_H 4.25 as a doublet (J = 10.9 Hz) of double:doublets (J = 3.9 and 5.1 Hz) corresponding to one diaxial and two axial:equatorial couplings. The structure is thus 3β,5-dihydroxy-5α-androstane-4β,17β-diyl diacetate (**4**). The 3β-acetoxyl group of the starting material has migrated to C-4 through the formation of a dioxolenium ion. The rearrangement of a 3β-acetoxyl group to C-4 has been observed previously[4,5].

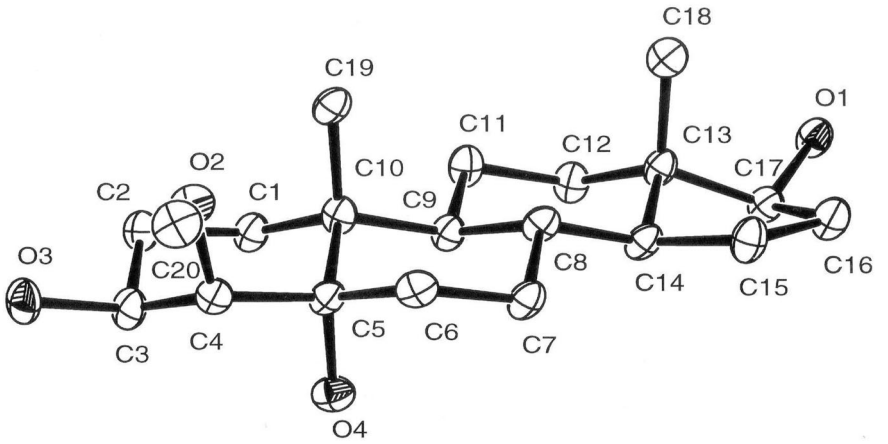

FIG. 1
X-ray structure of compound **2**

Methanolysis of 4β,5-epoxy-5β-androstane-3β,17β-diol (**5**) gave entirely 5-methoxy-5α-androstane-3β,4β,17β-triol (**6**). This compound was poorly soluble and hence it was acetylated with acetic anhydride in pyridine to give a mixture of a di- and a triacetate. The structure and stereochemistry of 5-methoxy-5α-androstane-3β,4β,17β-triyl triacetate (**7**) was established by X-ray crystallography (Fig. 2). The diacetate was assigned the structure of 4β-hydroxy-5-methoxy-5α-androstane-3β,17β-diyl diacetate (**8**), since the C-3 proton resonance (δ_H 5.05) was a doublet (J = 10 Hz) of triplets (J = 3 Hz) (cf. the triacetate, δ_H 5.12, J = 3.2, 4.8 and 12.1 Hz), whilst the C-4 proton resonance (δ_H 3.97) was a doublet (J = 3 Hz) (cf. the triacetate, δ_H 5.36, doublet, J = 3.2 Hz). We were unable to detect any of the 4α-methoxy-5β-hydroxyisomer. Thus the 3β-hydroxyl group has led to the hydrolysis taking place in one direction only.

Methanolysis of 4β,5-epoxy-5β-androstane-3β,17β-diyl diacetate (**9**) gave the triol (**10**) which lacked a methoxyl signal. The structure and stereochemistry of this product was established by X-ray crystallography (Fig. 3). The 4-H NMR signal (δ_H 3.48) was a doublet (J = 3.4 Hz) whilst the 3-H resonance (δ_H 4.07) was a doublet (J = 10.0 Hz) of triplets (J = 3.4 Hz) (see Scheme 1).

In conclusion, we have shown that the presence of 3β-hydroxyl group does not the modify the transformation of the 4α,5α-epoxide while the 3β-acetoxyl group effects the TCNE catalysed methanolysis of steroidal

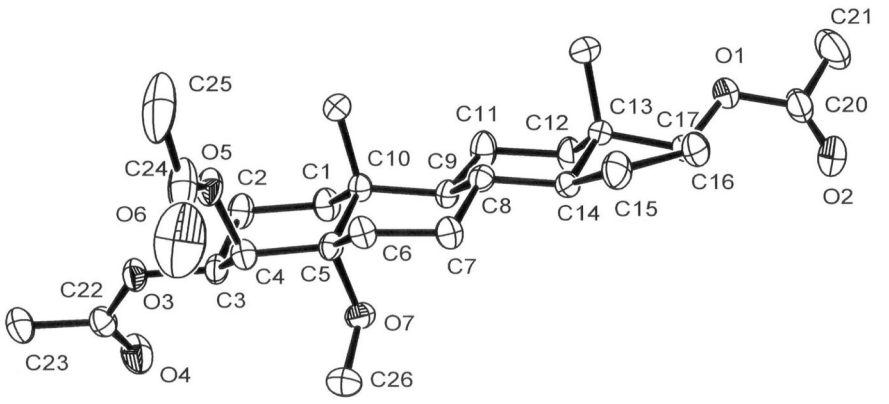

FIG. 2
X-ray structure of compound **7**

4,5-epoxides bringing about migration of a 3β-acetoxyl group to C-4 which could be interpreted in terms of a neighbouring group participation, and directing the position of the hydroxy group from the epoxide to C-4.

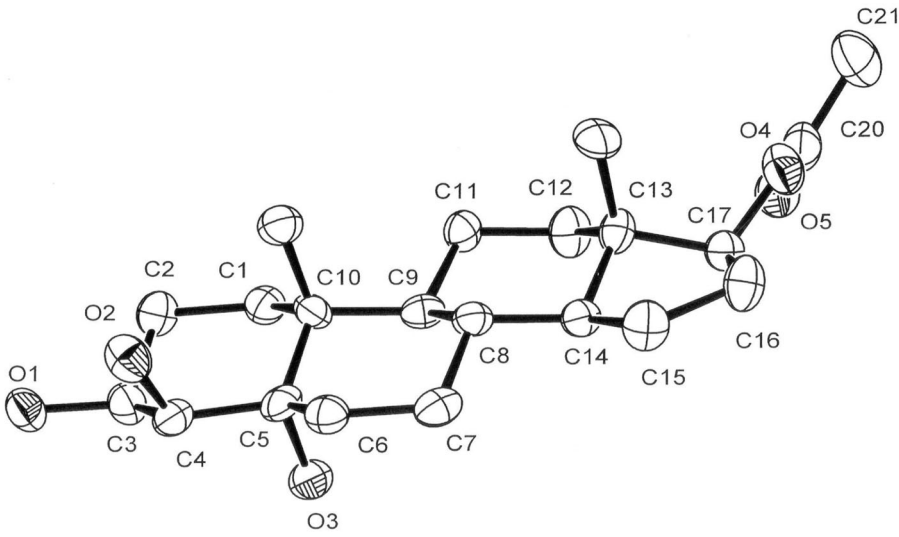

FIG. 3
X-ray structure of compound **10**

EXPERIMENTAL

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80 °C. Column chromatography was performed on silica by elution with increasing concentrations of ethyl acetate in light petroleum. Extracts were dried over anhydrous sodium sulfate. Melting points were determined using an Electrothermal IA 9200 apparatus and are uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform and pyridine-d_5 with tetramethylsilane as an internal standard reference at 300 and 500 MHz with a Bruker DPX 300 and a Bruker AMX 500 spectrometers. ^{13}C NMR spectra were recorded in deuteriochloroform at 75 and 100 MHz with a Bruker DPX 300 and a Bruker AMX 500 spectrometers. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) are given in Hz. IR spectra (wavenumbers in cm^{-1}) were recorded using Nujol mulls on a Perkin–Elmer 1710 Fourier transform spectrometer. High-resolution mass spectra (HRMS) were determined on a Bruker Daltonics Apex III mass spectrometer operating in the electrospray mode. The X-ray analysis data collection was performed using KappaCCD. The refinements were performed using SHELXL97 and the figures were drawn using ORTEP-3 for Windows.

The 3β-substituted epimeric epoxides 4α,5-epoxy-3β-hydroxy-5α-androstan-17β-yl acetate (**1**), 4α,5-epoxy-5α-androstane-3β,17β-diyl diacetate (**3**), 4β,5-epoxy-5β-androstane-3β,17β-diol (**5**) and 4β,5-epoxy-5β-androstane-3β,17β-diyl diacetate (**9**) were prepared from testosterone by literature methods[6,7].

4β-Methoxy-5α-androstane-3β,5,17β-triol (**2**)

4α,5-Epoxy-3β-hydroxy-5α-androstan-17β-yl acetate (**1**; 1.0 g, 2.8 mmol) in dry methanol (75 ml) was treated with tetracyanoethylene (250 mg, 2.0 mmol) at room temperature for 2 h (TLC control). The solvent was evaporated and the residue was chromatographed on silica. Elution with 15% ethyl acetate/light petroleum gave 4β-methoxy-5α-androstane-3β,5,17β-triol (**2**; 650 mg, 67%), m.p. 142–144 °C. IR: 3370. ^{1}H NMR ($CDCl_3$): 0.73 s, 3 H (H-18); 1.06 s, 3 H (H-19); 1.0–2.2 overlapping multiplets, 19 H; 3.08 d, 1 H, *J*(4,3) = 4.0 (H-4); 3.48 s, 3 H (4-OMe); 3.62 t, 1 H, *J*(17,16) = 8.7 (H-17); 4.09 dt, 1 H, *J*(3,2) = 11.0, *J*(3,4) = 4.0 (H-3). ^{13}C NMR ($CDCl_3$): 82.74, 78.57, 71.65, 67.82, 50.41, 47.77, 45.49, 42.54, 39.24, 36.73, 34.16, 30.71, 27.40, 25.52, 25.28, 23.27, 22.77, 19.79, 15.92, 11.97. HMRS: for $C_{20}H_{34}O_4$ + Na calculated 361.2329, found 361.2349.

3β,5-Dihydroxy-5α-androstane-4β,17β-diyl Diacetate (**4**)

Under similar conditions 4α,5-epoxy-5α-androstane-3β,17β-diyl diacetate (**3**; 1.0 g, 2.5 mmol) gave after 5 h 3β,5-dihydroxy-5α-androstane-4β,17β-diyl diacetate (**4**; 670 mg, 64%), m.p. 232–234 °C. IR: 3553, 1732, 1701. ^{1}H NMR ($CDCl_3$): 0.95 s, 3 H (H-18); 1.09 s, 3 H (H-19); 1.0–2.1 overlapping multiplets, 19 H; 2.01 s, 3 H (17-OAc); 2.10 s, 3 H (4-OAc); 4.25 ddd, 1 H, *J*(3,4) = 3.9, *J*(3,2) = 5.1, 10.9 (H-3); 4.54 t, 1 H, *J*(17,16) = 8.5 (H-17); 4.91 d, 1 H, *J*(4,3) = 3.9 (H-4). ^{13}C NMR ($CDCl_3$): 171.64, 170.10, 84.18, 83.18, 75.95, 73.03, 50.84, 47.90, 46.81, 43.12, 39.04, 37.20, 31.75, 27.94, 25.69, 25.60, 23.82, 22.20, 21.75, 21.57, 20.30, 15.98, 12.57. HMRS: for $C_{23}H_{36}O_6$ + Na calculated 431.2389, found 431.2404.

5-Methoxy-5α-androstane-3β,4β,17β-triol (**6**)

Under similar conditions 4β,5-epoxy-5β-androstane-3β,17β-diol (**5**; 1.4 g, 4.5 mmol) gave after 5 h 5-methoxy-5α-androstane-3β,4β,17β-triol (**6**; 1.03 g, 88%), m.p. 282–284 °C. IR: 3350. ^{1}H NMR ($CDCl_3$): 0.90 s, 3 H (H-18); 1.39 s, 3 H (H-19); 1.0–2.2 overlapping multiplets, 19 H; 3.13 s, 3 H (5-OMe); 3.80 t, 1 H, *J*(17,16) = 8.6 (H-17); 4.22 overlapping signals, 2 H (H-3 and H-4). ^{13}C NMR ($CDCl_3$): 87.10, 83.60, 79.20, 78.82, 50.81, 47.86, 46.52, 43.25, 38.24, 36.40, 35.23, 30.43, 27.00, 26.45, 26.32, 23.26, 21.60, 20.12, 14.87, 10.95. HMRS: for $C_{20}H_{34}O_4$ + Na calculated 361.2329, found 361.2339.

Acetylation of Triol **6**

Treatment of the triol **6** (100 mg, 0.3 mmol) with acetic anhydride in pyridine overnight gave a mixture of 5-methoxy-5α-androstane-3β,4β,17β-triyl triacetate (**7**; 55 mg, 40%) and 4β-hydroxy-5-methoxy-5α-androstane-3β,17β-diyl diacetate (**8**; 30 mg, 24%) which were separated by chromatography on silica.

5-Methoxy-5α-androstane-3β,4β,17β-triyl triacetate (**7**), m.p. 162–163 °C. IR: 1747, 1732. ^{1}H NMR ($CDCl_3$): 0.93 s, 3 H (H-18); 1.12 s, 3 H (H-19); 1.0-2.1 overlapping multiplets, 19 H; 1.93 s, 3 H (4-OAc); 2.00 s, 3 H (17-OAc); 2.07 s, 3 H (3-OAc); 3.23 s, 3 H (5-OMe); 4.55 t, 1 H, *J*(17,16) = 8.5 (H-17); 5.12 ddd, 1 H, *J*(3,4) = 3.2, *J*(3,2) = 4.8, 12.1 (H-3); 5.36 d, 1 H, *J*(4,3) = 3.2 (H-4). ^{13}C NMR ($CDCl_3$): 171.58, 170.82, 170.71, 83.19, 78.84, 70.67, 69.83, 50.81, 48.81, 45.79, 43.08, 40.26, 37.15, 34.65, 30.51, 27.96, 25.59, 23.85, 23.71, 22.82, 21.59, 21.47 (2 × C), 20.36, 16.23, 12.52. HMRS: for $C_{26}H_{40}O_7$ + Na calculated 487.2666, found 487.2671.

4β-Hydroxy-5-methoxy-5α-androstane-3β,17β-diyl diacetate (**8**), m.p. 188–190 °C. IR: 3548, 1717. ^{1}H NMR ($CDCl_3$): 0.75 s, 3 H (H-18); 1.16 s, 3 H (H-19); 0.95–2.1 overlapping multiplets, 19 H; 2.00 s, 3 H (17-OAc); 2.06 s, 3 H (3-OAc); 3.13 s, 3 H (5-OMe); 3.97 d, 1 H, J(4,3) = 3.2 (H-4); 4.54 t, 1 H, J(17,16) = 8.5 (H-17); 5.05 dt, 1 H, J(3,2) = 10, J(3,4) = 3.2 (H-3). ^{13}C NMR ($CDCl_3$): 171.65, 170.67, 83.30, 79.09, 72.89, 70.88, 50.90, 48.56, 45.99, 43.11, 40.00, 37.22, 34.71, 30.69, 27.99, 25.78, 24.15, 23.87, 22.26, 21.80, 21.61, 20.29, 16.54, 12.58. HMRS: for $C_{24}H_{38}O_6$ + Na calculated 445.2561, found: 445.2566.

3β,4β,5-Trihydroxy-5α-androstan-17β-yl Acetate (**10**)

Under similar conditions 4β,5-epoxy-5β-androstane-3β,17β-diyl diacetate (**9**; 1.2 g, 3.0 mmol) gave after 3 h 3β,4β,5-trihydroxy-5α-androstan-17β-yl acetate (**10**; 1.0 g, 88%), m.p. 212–214 °C. IR: 3510, 3392, 1701. ^{1}H NMR ($CDCl_3$): 0.75 s, 3 H (H-18); 1.11 s, 3 H (H-19); 1.0–2.28 overlapping multiplets, 19 H; 2.00 s, 3 H (17-OAc); 3.48 d, 1 H, J(4,3) = 3.4 (H-4); 4.07 dt, 1 H, J(3,4) = 3.4, J(3,2) = 10.0 (H-3); 4.54 t, 1 H, J(17,16) = 8.6 (H-17). ^{13}C NMR ($CDCl_3$): 171.72, 83.20, 78.49, 76.02, 68.69, 50.95, 47.20, 43.15, 38.85, 37.26, 34.76, 31.81, 31.07, 27.93, 26.12, 25.61, 23.83, 21.58, 20.38, 15.96, 12.58. HMRS: for $C_{21}H_{34}O_5$ + Na calculated 389.2311, found 389.2298.

X-ray Crystallographic Data and Structure Determination of 4β-Methoxy-5α-androstane-3β,5,17β-triol (**2**)

$C_{20}H_{34}O_4 \cdot 2H_2O$, M_r = 374.50, monoclinic, $P2_1/n$ (No. 4), a = 6.7033(2) Å, b = 25.0025(12) Å, c = 11.6634(5) Å, α = γ = 90°, β = 91.234(2)°, V = 1954.3(1) Å^3, Z = 4, D_{calc} = 1.27 g cm^{-3}, μ = 0.09 mm^{-1}, F(000) = 824. Data were collected on a crystal of size 0.40 × 0.40 × 0.05 mm^3 on a KappaCCD diffractometer operating for 3.86 < θ < 25.02°. 10297 Reflections were collected for $-7 \le h \le 7$, $-29 \le k \le 24$, $-13 \le l \le 13$. There were 5884 independent reflections with 5043 possessing $I > 2\sigma(I)$. The structure was refined using SHELXL97 by full-matrix least-squares on F^2. The goodness-of-fit on F^2 was 1.046. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.051, wR_2 = 0.117 and the R indices (all data) were R_1 = 0.064 and wR_2 = 0.125. The largest difference peak and hole were 0.23 and –0.19 e Å^{-3}.

X-ray Crystallographic Data and Structure Determination of 5-Methoxy-5α-androstane-3β,4β,17β-triyl Triacetate (**7**)

$C_{26}H_{40}O_7$, M_r = 464.58, monoclinic, $P\bar{1}$ (No. 4), a = 22.8421(3) Å, b = 7.5939(1) Å, c = 29.5934(12) Å, α = γ = 90°, β = 100.727(1)°, V = 5043.59(12) Å^3, Z = 8, D_{calc} = 1.22 g cm^{-3}, μ = 0.09 mm^{-1}, F(000) = 2016. Data were collected on a crystal of size 0.4 × 0.2 × 0.1 mm^3 on a KappaCCD diffractometer operating for 3.74 < θ < 227.50°. 88457 Reflections were collected for $-29 \le h \le 29$, $-9 \le k \le 7$, $-38 \le l \le 38$. There were 19694 independent reflections with 15394 possessing $I > 2\sigma(I)$. The structure was refined using SHELXL97 by full-matrix least-squares on F^2. The goodness-of-fit on F^2 was 0992. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.051, wR_2 = 0.124 and the R indices (all data) were R_1 = 0.071 and wR_2 = 0.137. The largest difference peak and hole were 0.30 and –0.21 e Å^{-3}.

X-ray Crystallographic Data and Structure Determination of 3β,4β,5-Trihydroxy-5α-androstan-17β-yl Acetate (**10**)

$C_{21}H_{34}O_5$, M_r = 384.50, orthorhombic, $P\bar{1}$ (No. 4), a = 7.2920(9) Å, b = 11.9269(9) Å, c = 23.065(2) Å, α = β = γ = 90°, V = 2006.0(3) Å^3, Z = 4, D_{calc} = 1.27 g cm^{-3}, μ = 0.09 mm^{-1}, F(000) = 840. Data were collected on a crystal of size 0.10 × 0.05 × 0.05 mm^3 on a KappaCCD diffractometer operating for 3.72 < θ < 22.99°. 6619 Reflections were collected for $-7 \le h \le 7$, $-13 \le k \le 11$, $-25 \le l \le 23$. There were 2656 independent reflections with 1733 possessing $I > 2\sigma(I)$. The structure was refined using SHELXL97 by full-matrix least-squares on F^2. The goodness-of-fit on F^2 was 0.811. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.072, wR_2 = 0.200 and the R indices (all data) were R_1 = 0.129 and wR_2 = 0.253. The largest difference peak and hole were 0.22 and –0.26 e Å^{-3}.

CCDC 742754 (for **2**), 249908 (for **7**) and 249907 (for **10**) contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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