

PREPARATION OF ANDROSTANES RELATED TO APHIDICOLIN

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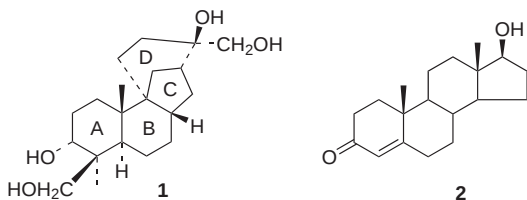
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The preparation of 3 α ,4 α ,17 β -trihydroxy-, 3 α ,4 α ,16 α ,17 α - and 2 α ,3 α ,16 α ,17 α -tetrahydroxy-5 α -androstane derivatives (**5**, **11**, **18**) from testosterone as steroidal analogues of diterpenoid inhibitor of DNA polymerase α , aphidicolin, is described. The crystal structure of 5 α -androstane-3 α ,4 α ,17 β -triyl triacetate (**6**) is reported.

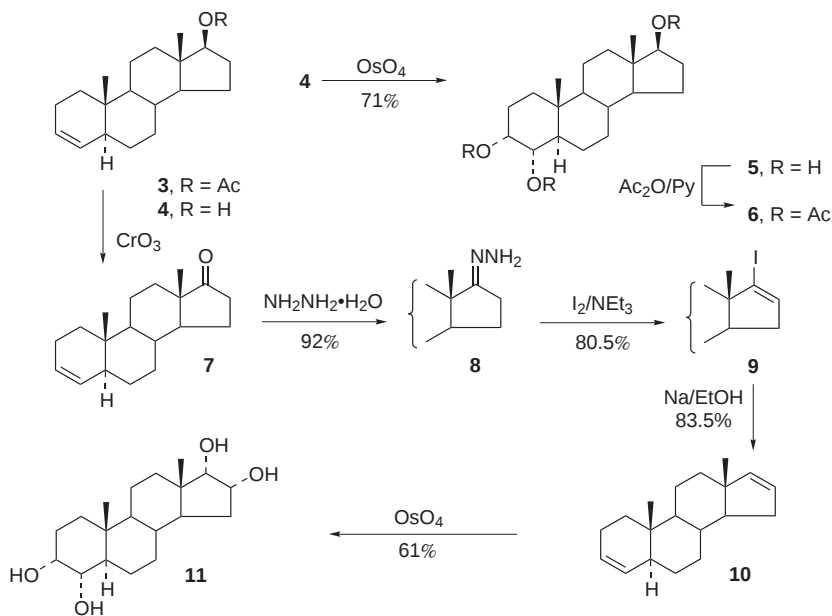
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Aphidicolin (**1**) is an inhibitor of DNA polymerase α (refs^{1,2}). Its glycinate ester reached clinical trial as a tumour inhibitory substance. The structure-activity studies which have been reported³ on this relatively expensive diterpenoid suggest that the activity may be related to the distance separating the hydroxyl groups on rings A and D of aphidicolin. There is a formal similarity between the structure of aphidicolin and the steroids and, unlike the majority of the diterpenoids, both belong to the same enantiomeric series. The binding of the steroid hormones to the steroid nuclear receptors results in the initiation of nucleic acid biosynthesis. This involves DNA polymerase activity. Consequently, we have prepared⁴⁻⁶ a number of steroids with structures that have a similarity to aphidicolin in the relative disposition of their hydroxyl groups. The C-3:C-17 and C-4 α (hydroxymethyl):C-17 distances in aphidicolin are 8.46 and 8.84 Å whilst in a typical 5 α -steroid C-3:C-17 is 8.70 and C-4:C-17 8.09 Å. Preliminary screening results suggest that some of these compounds possess tumour inhibitory activity.

In this paper we report the preparation of 5 α -androstane-3 α ,4 α ,17 β -triol (**5**), 5 α -androstane-3 α ,4 α ,16 α ,17 α -tetrol (**11**) and 5 α -androstane-2 α ,3 α ,16 α ,17 α -tetrol (**18**) from the readily available testosterone (**2**). These compounds have a 3 α -hydroxyl group typical of aphidicolin.



5 α -Androst-3-en-17 β -yl acetate⁷ (**3**) was obtained from testosterone (**2**) by treatment with boron trifluoride etherate-sodium borohydride and acetic anhydride. Hydrolysis of the 17 β -acetate gave the 17 β -alcohol⁸ **4**. Catalytic osmylation of 5 α -androst-3-en-17 β -ol (**4**) using potassium hexacyanoferrate(III) as the co-oxidant⁹, gave 5 α -androstane-3 α ,4 α ,17 β -triol (**5**) (Scheme 1). The ¹H NMR spectrum of the product, determined in pyridine-*d*₅ at 500 MHz, contained signals at δ 3.69 (1 H, dd, *J* = 3 and



SCHEME 1

11 Hz, 4-H) and δ 4.28 (1 H, q, J = 3 Hz, 3-H). The magnitude of the coupling constants was consistent with the presence of the 4 α - and 3 α -hydroxyl groups, respectively. Thus the 4-H resonance revealed a diaxial and an axial-equatorial coupling whilst the 3-H resonance contained equatorial-axial and diequatorial couplings. The stereochemistry was confirmed by an X-ray crystal structure of the triacetate **6** as shown in Fig. 1.

Oxidation of 5 α -androst-3-en-17 β -ol (**4**) with chromium trioxide gave 5 α -androst-3-en-17-one⁸ (**7**) which was converted to its hydrazone **8** with hydrazine hydrate and triethylamine. Decomposition of the hydrazone with iodine and triethylamine in tetrahydrofuran¹⁰ gave 17-iodo-5 α -androst-3,16-diene (**9**). Apart from the signals assigned to the ring A double bond, the ¹H NMR spectrum of the product contained a new alkene signal at δ 6.12. Hydrogenolysis of the iodine with sodium in ethanol afford 5 α -androst-3,16-diene (**10**) which possessed signals of olefinic protons at δ 5.69 and 5.84 (H-17 and H-16, respectively) and at δ 5.26 and 5.52 (H-4 and H-3, respectively). This method of preparing the 16-enes is preferable over that of dehydration of the 17-alcohols which can bring about rearrangement of C-18.

Catalytic osmylation of diene **10** gave 5 α -androstane-3 α ,4 α ,16 α ,17 α -tetrol (**11**). The ¹H NMR spectrum determined in pyridine-*d*₅ at 500 MHz, contained signals at δ 3.67 (doublet of doublet, J = 3 and 11 Hz), δ 3.82 (doublet, J = 5.3 Hz), δ 4.27 (quartet, J = 3 Hz) and δ 4.67 (quartet, J =

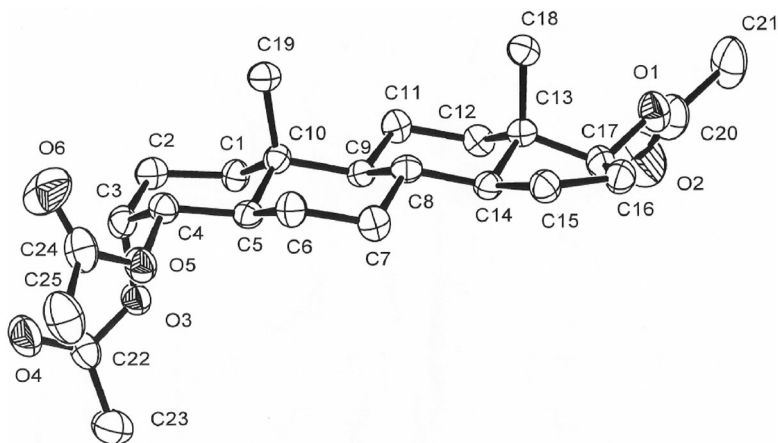
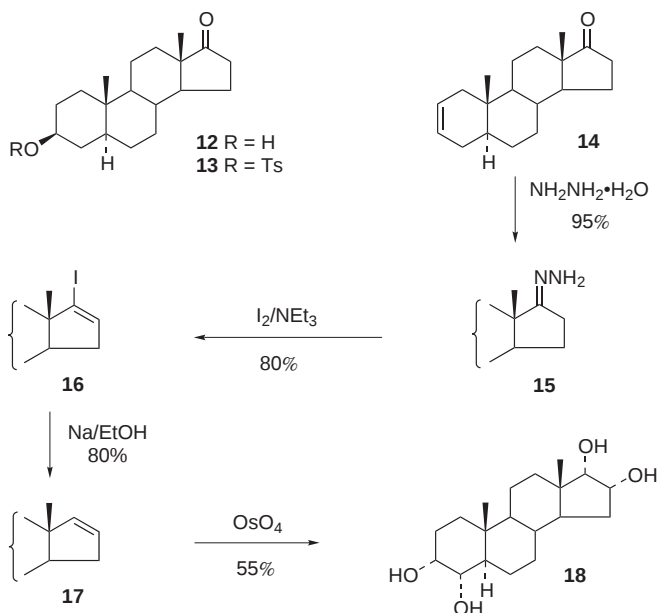


FIG. 1
X-ray structure of **6**

5.3 Hz) which were assigned to H-4, H-17, H-3 and H-16, respectively. Irradiation of the H-18 signal at δ 0.70 gave nuclear Overhauser effect enhancements of 6.4% to the H-17 signal and 4.4% to the H-16 signal, showing that both the 16- and 17-hydroxyl groups were α -oriented. Irradiation of the H-19 signal at δ 0.85 gave an NOE enhancement of 4.4% to the H-4 signal at δ 3.67. These enhancements, together with the magnitude of the coupling constants, were consistent with the 5 α -androstane-3 α ,4 α ,16 α ,17 α -tetrol stereochemistry of the compound **11**.

5 α -Androstane-2 α ,3 α ,16 α ,17 α -tetrol (**18**) was prepared by a similar route (Scheme 2) from 3 β -hydroxyandrost-5-en-17-one (**12**). 5 α -Androst-2-en-17-one¹¹ (**14**) was obtained by elimination of the 3 β -tosylate **13** with collidine and converted into 5 α -androsta-2,16-diene (**17**) via the 17-hydrazone **15** and the 17-iodo-2,16-diene (**16**) as above. Catalytic osmylation of **17** gave the tetrol **18**. The ¹H NMR spectrum contained signals at δ 3.80 (doublet, J = 5 Hz), δ 4.01 (multiplet), δ 4.30 (quartet J = 3 Hz) and δ 4.66 (multiplet) which were assigned to H-17, H-2, H-3 and H-16, respectively. Irradiation of the H-18 signal at δ 0.67 gave an NOE enhancements of 4.7% to the signal at δ 3.80 and 3.4% to the signal at δ 4.66, whilst irradiation of the H-19 signal at δ 0.82 gave an NOE enhancement of 2.6% to



SCHEME 2

the signal at δ 4.01. This, together with multiplicity of the H-3 signal, showed that the tetrol was the 5α -androstane- $2\alpha,3\alpha,16\alpha,17\alpha$ -tetrol (**18**).

In conclusion the syntheses of 5α -androstane- $3\alpha,4\alpha,17\beta$ -triol, 5α -androstane- $3\alpha,4\alpha,16\alpha,17\alpha$ -tetrol, 5α -androstane- $2\alpha,3\alpha,16\alpha,17\alpha$ -tetrol as aphidicolin models were described. The stereochemistry of osmylation followed by acetylation of 5α -androst-3-en- 17β -ol was confirmed by an X-ray crystallography.

EXPERIMENTAL

Melting points were determined using an Electrothermal IA 9200 apparatus and are uncorrected. ^1H NMR spectra were recorded in deuteriochloroform and pyridine- d_5 with tetramethylsilane as an internal standard reference at 300 and 500 MHz on a Bruker DPX 300 and Bruker AMX 500 spectrometers. ^{13}C NMR spectra were recorded in deuteriochloroform at 75 and 100 MHz on a Bruker DPX 300 and 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 SHELXL-97 and the figures were drawn using ORTEP-3 for Windows. A stock solution of osmium tetroxide (1 g, 4 mmol) in redistilled *tert*-butanol (80 ml) containing *tert*-butyl hydroperoxide (2 ml) was prepared and stored at 0 °C. Extracts were dried over anhydrous sodium sulfate. Light petroleum refers to the fraction of b.p. 60–80 °C. Silica gel for chromatography was Merck 9385.

5α -Androst-3-ene-17-one (**7**)

This compound was prepared according to the literature procedure⁸. Yield 82%, m.p. 120–122 °C (lit.⁸ gives m.p. 121–123 °C). IR: 1725 (C=O). ^1H NMR (300 MHz, CDCl_3): 0.80 s, 3 H (H-18); 0.88 s, 3 H (H-19); 5.26 dd, 1 H, $J(4,5) = 2.0$, $J(4,3) = 9.7$ (H-4); 5.52 dq, 1 H, $J(3,2) = 3.0$, $J(3,4) = 9.7$ (H-3).

5α -Androst-3-en-17-one Hydrazone (**8**)

Ketone⁸ **7** (300 mg, 1.1 mmol) in dry tetrahydrofuran (15 ml) was heated under reflux with triethylamine (0.58 ml, 4.2 mmol) and hydrazine hydrate (2 ml, 99%) for 3 h. The solution was poured into cold water (20 ml) and the mixture cooled in ice. The precipitate was collected and washed with water to give the hydrazone **8** (290 mg, 92%) which was crystallized from ethyl acetate as plates, m.p. 160–163 °C. For $\text{C}_{19}\text{H}_{30}\text{N}_2$ (286.4) calculated: 79.67% C, 10.56% H, 9.78% N; found: 79.59% C, 10.48% H, 9.67% N. IR: 3172 (N-H). ^1H NMR (300 MHz, CDCl_3): 0.70 s, 3 H (H-18); 0.88 s, 3 H (H-19); 4.74 bs, 2 H (NH_2); 5.26 dd, 1 H, $J(4,5) = 2.0$, $J(4,3) = 9.7$ (H-4); 5.52 dq, 1 H, $J(3,2) = 3.0$, $J(3,4) = 9.7$ (H-3). ^{13}C NMR (75 MHz, CDCl_3): 166.4, 131.2, 125.3, 53.7, 53.6, 45.9, 44.2, 35.0, 34.9, 34.2, 34.0, 31.4, 27.2, 24.3, 23.4, 23.3, 20.7, 17.1, 11.8.

5 α -Androst-2-en-17-one Hydrazone (15)

Under similar conditions 5 α -androst-2-en-17-one¹¹ (**14**; 300 mg, 1.1 mmol) gave the hydrazone **15** (300 mg, 95%) as a white solid, m.p. 158–160 °C. For C₁₉H₃₀N₂ (286.4) calculated: 79.72% C, 10.69% H, 9.80% N; found: 79.70% C, 10.63% H, 9.28% N. IR: 3170 (N-H), 1630 (C=C). ¹H NMR (300 MHz, CDCl₃): 0.78 s, 3 H (H-18); 0.86 s, 3 H (H-19); 4.75 bs, 2 H (NH₂); 5.55 m, 2 H (H-2 and H-3). ¹³C NMR (75 MHz, CDCl₃): 166.4, 125.8 (2 $\times$ C); 54.3, 53.6, 43.9, 41.4, 39.67, 34.9, 34.7, 34.2, 31.2, 30.2, 28.5, 24.3, 23.3, 20.5, 16.9, 11.6.

17-Iodo-5 α -androsta-3,16-diene (9)

The hydrazone **8** (300 mg, 1.05 mmol) and triethylamine (1.4 ml, 10 mmol) in dry tetrahydrofuran (15 ml) was treated with a solution of iodine (400 mg, 1.6 mmol) in tetrahydrofuran (5 ml) at room temperature under nitrogen. After the evolution of nitrogen had ceased, the solvent was evaporated and the residue was taken up in ethyl acetate. The extract was washed with dilute hydrochloric acid, water, aqueous sodium sulfite, aqueous sodium hydrogen carbonate and brine, and dried. The solvent was evaporated and the residue chromatographed on silica gel. Elution with light petroleum gave the diene **9** (320 mg, 80.5%) as a gum. IR: 1659 (C=C). ¹H NMR (300 MHz, CDCl₃): 0.74 s, 3 H (H-18); 0.80 s, 3 H (H-19); 5.26 dd, 1 H, *J*(4,5) = 2.0, *J*(4,3) = 9.7 (H-4); 5.52 dq, 1 H, *J*(3,2) = 3.0, *J*(3,4) = 9.7 (H-3); 6.12 d, 1 H, *J* = 1.2 (H-16). ¹³C NMR (75 MHz, CDCl₃): 137.4, 131.0, 125.5, 113.0, 54.5, 53.6, 50.1, 45.9, 36.2, 35.0, 34.6, 33.8, 33.7, 31.5, 27.2, 23.4, 20.8, 15.3, 11.8. HRMS: for C₁₉H₂₇I calculated: 382.1150; found: 382.1148.

17-Iodo-5 α -androsta-2,16-diene (16)

Under similar conditions the hydrazone **15** (280 mg, 0.97 mmol) gave the diene **16** (300 mg, 80%) as a gum. IR: 1659 (C=C). ¹H NMR (300 MHz, CDCl₃): 0.74 s, 3 H (H-18); 0.78 s, 3 H (H-19); 5.56 m, 2 H (H-2- and H-3); 6.12 d, 1 H, *J* = 1.2 (H-16). ¹³C NMR (75 MHz, CDCl₃): 137.4, 125.8 (2 $\times$ C); 112.9, 54.7, 54.3, 49.9, 41.5, 39.5, 36.2, 34.8, 34.6, 33.6, 31.3, 30.2, 28.5, 21.6, 15.2, 11.6. HRMS: for C₁₉H₂₇I calculated: 382.1162; found: 382.1180.

5 α -Androsta-3,16-diene (10)

The above iodoalkene **9** (250 mg, 0.6 mmol) in ethanol (40 ml) was treated with sodium (2 g, 87 mmol) under reflux for 20 min. The solution was cooled and treated with 50% aqueous ethanol (40 ml). The ethanol was evaporated in vacuo and the residue extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, aqueous sodium sulfite, water and brine, and dried. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with light petroleum gave the diene **10** (140 mg, 83.5%) as an oil. IR: 1650 (C=C). ¹H NMR (300 MHz, CDCl₃): 0.76 s, 3 H (H-18); 0.78 s, 3 H (H-19); 5.26 dd, 1 H, *J*(4,5) = 2.0, *J*(4,3) = 9.7 (H-4); 5.52 dq, 1 H, *J*(3,2) = 3.0, *J*(3,4) = 9.7 (H-3); 5.69 bs, 1 H (H-17); 5.84 dd, 1 H, *J*(16,15) = 1.8, *J*(16,17) = 4.7 (H-16). ¹³C NMR (75 MHz, CDCl₃): 143.9, 131.4, 129.5, 125.4, 56.2, 54.2, 46.1, 45.7, 35.9, 35.2, 34.2, 33.9, 32.1, 29.7, 27.4, 23.5, 21.0, 17.1, 11.9. HRMS: for C₁₉H₂₈ calculated: 256.2191; found: 256.2200.

5 α -Androsta-2,16-diene (**17**)

Under similar conditions the iodoalkene **16** (250 mg, 0.6 mmol) gave the diene **17** (135 mg, 80.5%) as an oil. IR: 1640 (C=C). ^1H NMR (300 MHz, CDCl_3): 0.78 s, 3 H (H-18); 0.80 s, 3 H (H-19); 5.56 m, 2 H (H-2 and H-3); 5.69 d, 1 H, $J(17,16) = 4.7$ (H-17); 5.84 dd, 1 H, $J(16,15) = 1.8$, $J(16,17) = 4.7$ (H-16). ^{13}C NMR (75 MHz, CDCl_3): 143.9, 129.2, 125.9 (2 $\times$ C); 56.1, 54.8, 45.5, 41.6, 39.6, 35.9, 34.9, 34.2, 31.9, 31.8, 30.3, 28.7, 20.8, 17.0, 11.6. HRMS: for $\text{C}_{19}\text{H}_{28}$ calculated: 256.2195; found: 256.2200.

5 α -Androstane-3 α ,4 α ,17 β -triol (**5**)

5 α -Androst-3-en-17 β -ol⁸ (**4**; 140 mg, 0.5 mmol) in *tert*-butanol (15 ml) and water (15 ml) was treated with potassium hexacyanoferrate(III) (1.65 g, 5 mmol), potassium carbonate (690 mg, 5 mmol), 1,4-diazobicyclo[2,2,2]octane (56 mg, 0.5 mmol) and the stock solution of osmium tetroxide (0.4 ml) at 40 °C for 24 h. Sodium sulfite (140 mg, 1.1 mmol) was added and the solution was then left to stir overnight. The mixture was filtered and extracted with ethyl acetate. The extract was dried and the solvent was evaporated to give the triol **5** (104 mg, 71%) which was crystallized from ethyl acetate as needles, m.p. 194–196 °C. For $\text{C}_{19}\text{H}_{32}\text{O}_3$ (308.5) calculated: 74.00% C, 10.52% H; found: 73.65% C, 10.37% H. IR: 3490 (O-H). ^1H NMR (500 MHz, pyridine- d_5): 0.87 s, 3 H (H-18); 0.96 s, 3 H (H-19); 3.69 dd, 1 H, $J = 3.0$, 11.0 (H-4); 3.83 t, 1 H, $J = 8.5$ (H-17); 4.28 q, 1 H, $J = 3.0$ (H-3). ^{13}C NMR (100 MHz, pyridine- d_5): 80.6, 71.1, 69.4, 55.2, 50.7, 45.4, 42.7, 36.9, 36.8, 34.8, 31.6, 31.1, 29.9, 27.3, 23.0, 22.5, 20.2, 12.3, 11.3. The triacetate **6**, prepared with acetic anhydride in pyridine, had m.p. 184–186 °C. IR: 1745 (C=O, acetate), 1716 (C=O, acetate). ^1H NMR (300 MHz, CDCl_3): 0.75 s, 3 H (H-18); 0.85 s, 3 H (H-19); 1.96 s, 3 H (17 β -OAc); 2.0 s, 3 H (4 α -OAc); 2.06 s, 3 H (3 α -OAc); 4.5 t, 1 H, $J = 8.5$ (H-17); 4.7 dd, 1 H, $J = 3.0$, 11.0 (H-4); 5.22 q, 1 H, $J = 3.0$ (H-3). ^{13}C NMR (75 MHz, CDCl_3): 171.65, 171.17, 170.89, 83.15, 72.71, 69.67, 54.49, 51.11, 44.22, 42.89, 37.89, 37.21, 35.17, 32.34, 31.13, 27.89, 25.61, 23.81, 22.65, 21.65, 21.57, 21.34, 20.71, 13.09, 12.50. HRMS: for $\text{C}_{25}\text{H}_{38}\text{O}_6 + \text{Na}$ calculated: 457.2560; found: 457.2562.

5 α -Androstane-3 α ,4 α ,16 α ,17 α -tetrol (**11**)

Under similar conditions the diene **10** (130 mg, 0.5 mmol) gave the tetrol **11** (100 mg, 61%) as a white powder, m.p. 234–236 °C. For $\text{C}_{19}\text{H}_{32}\text{O}_4 \cdot 0.5\text{H}_2\text{O}$ (333.5) calculated 68.41% C, 10.00% H; found: 68.37% C, 9.95% H. IR: 3470 broad (O-H). ^1H NMR (500 MHz, pyridine- d_5): 0.70 s, 3 H (H-18); 0.85 s, 3 H (H-19); 3.67 dd, 1 H, $J = 3.0$, 11.0 (H-4); 3.82 d, 1 H, $J = 5.3$ (H-17); 4.28 q, 1 H, $J = 3.0$ (H-3); 4.67 q, 1 H, $J = 5.3$ (H-16). ^{13}C NMR (100 MHz, pyridine- d_5): 78.9, 71.6, 71.3, 69.7, 54.6, 47.6, 46.2, 45.2, 37.5, 36.1, 35.5, 32.6, 32.3, 32.1, 28.1, 23.4, 20.3, 17.5, 12.9.

5 α -Androstane-2 α ,3 α ,16 α ,17 α -tetrol (**18**)

Under similar conditions the diene **17** (130 mg, 0.5 mmol) gave the tetrol **18** (90 mg, 55%) as a white powder, m.p. 220–223 °C. IR: 3450 broad (O-H). ^1H NMR (500 MHz, pyridine- d_5): 0.67 s, 3 H (H-18); 0.82 s, 3 H (H-19); 3.82 d, 1 H, $J(16,17) = 5.0$ (H-17); 4.01 m, 1 H (H-2); 4.30 q, 1 H, $J = 3.0$ (H-3); 4.67 m, 1 H (H-16). ^{13}C NMR (100 MHz, pyridine- d_5): 78.9, 71.6, 71.2, 69.8, 54.7, 47.6, 45.6, 41.0, 39.8, 36.3, 36.1, 35.7, 32.6, 32.3, 30.8, 28.2, 20.3, 18.1, 12.9. HRMS: for $\text{C}_{19}\text{H}_{32}\text{O}_4$ calculated: 324.2301; found: 324.2298.

X-ray Crystallographic Data and Structure Determination of
5 α -Androstane-3 α ,4 α ,17 β -triyl Triacetate (6)

C₂₅H₃₈O₆, M_r 434.55, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 7.4107(2)$ Å, $b = 10.4524(4)$ Å, $c = 30.6454(13)$ Å, $\alpha = \beta = \gamma = 90^\circ$, $V = 2373.78(15)$ Å³, $Z = 4$, $D_{\text{cal}} = 1.22$ g cm⁻³, $\mu = 0.09$ mm⁻¹, $F(000) = 944$. Data were collected on a crystal of size $0.10 \times 0.02 \times 0.02$ mm³ on a KappaCCD diffractometer operating for $3.83 \leq \theta \leq 25.1^\circ$. Reflections of 9275 were collected for $-7 \leq h \leq 8$, $-12 \leq k \leq 11$, $-36 \leq l \leq 29$. There were 4057 independent reflections with 2971 possessing $I > 2\sigma(I)$. The structure was solved by direct methods and refined using SHELXL97. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.057$, $wR_2 = 0.115$ and (all data) $R_1 = 0.093$ and $wR_2 = 0.133$. The largest difference peak and hole were 0.18 and -0.19 e Å⁻³.

CCDC 249909 contains the supplementary crystallographic data 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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