SHORT PAPER

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The stereochemistry of osmylation of 2- and 17-methylene-5α-androstanes†

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Osmylation of 2-methylene-5α-androstan-17-one has been shown to afford the 2α-hydroxy-2β-hydroxymethyl derivative whilst 3β-hydroxy-17-methylene-5α-androstane gives the 17α-hydroxy-17β-hydroxymethyl derivative; the facial selectivity of these reactions is discussed.

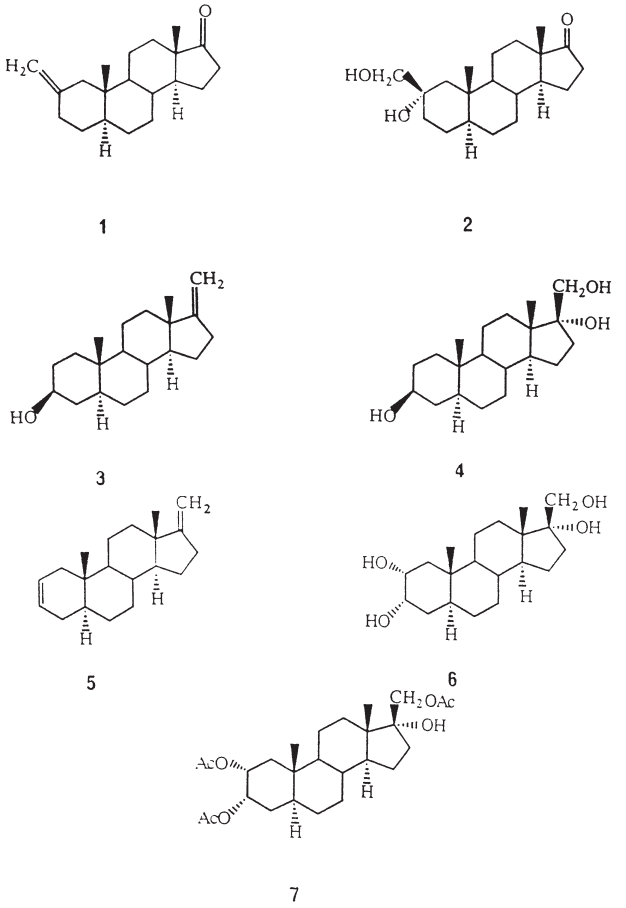
Keywords: osmylation, exocyclic methylenes

A number of factors can contribute to determining the facial selectivity of the osmylation[1‡] of exocyclic methylenes. These include the steric bulk of the reagent, torsional strain in the osmate ester, hydrogen bonding from a neighbouring hydroxyl group and hyperconjugative effects from neighbouring axial C–H bonds.[2] Attention has been drawn[3] to the effect of vicinal substituents on the stereochemistry of osmylation of methylene-4-*t*-butylcyclohexane. The presence of C-2 alkyl substituents brought about a change from the formation of O-equatorial 1,2-glycols to O-axial 1,2-glycols.

In the course of work directed at the preparation of steroidal analogues of aphidicolin, we noted[4] that osmylation of 17β-acetoxy-A-nor-2-methylene-5α-androstane gave the 2α-hydroxy-2β-hydroxymethyl glycol whilst 17β-acetoxy-3-methylene-5α-androstandrostane gave the 3β-hydroxy-3α-hydroxymethyl epimer. In the first case the osmium tetroxide has approached the alkene from the α-face and in the second approach has come from the β-face. This facial selectivity was rationalised in stereo-electronic terms. Hyper-conjugative interaction between the adjacent axial C–H and the alkene π-system[5] can increase the electron density on one face of the alkene favouring attack by the electrophilic osmium tetroxide on that face. In the light of this rationalisation, it was of interest to examine the stereochemistry of osmylation of 2-methylene-5α-androstan-17-one **1**,[6] 3β-hydroxy-17-methylene-5α-androstane **3**,[7] and 17-methylene-5α-androst-2-ene **5**.

The substrates were prepared by the Wittig olefination of the corresponding ketones.The catalytic osmylation procedure involved the use of potassium hexacyanoferrate(III) as the co-oxidant.[8] Osmylation of 2-methylene-5α-androstan-17-one **1** gave the 2β-hydroxymethyl derivative **2**. The stereochemistry of the hydroxymethyl group was established by use of the nuclear Overhauser effect (n.O.e.)(determined at 500 MHz) in the ^{1}H NMR spectrum. Irradiation of the 19-H signal (δH 0.82) produced an enhancement of 2.6% of the 2-CH_2OH signal (δ_H 3.57).

Osmylation of 3β-hydroxy-17-methylene-5α-androstane **3** gave the 17β-hydroxymethyl derivative **4**. Irradiation of the 18-H signal (δ_H 0.89) produced n.O.e. enhancements of the 17-CH_2OH signals (δ_H 3.57 and 3.72) of 2.6 and 5.8% respectively. The stereochemistry of 17β-hydroxymethyl-2α,3α, l7α-trihydroxy-5α-androstane **6**, obtained from 17-methylene-5α-androst-2-ene **5**, was established by an n.O.e. experiment on the more soluble triacetate **7**. Irradiation of the 18-H resonance (δ_H 0.74) produced n.O.e. enhancements of the 17-CH_2OAc signals (δ_H 4.09 and 4.19) of 2.4 and 5.8%



respectively. Irradiation of the 19-H resonance (δ_H 0.88) produced an enhancement of 3.3% to the signal at δ_H 4.96 which was assigned to the 2β-H. This signal possessed one diaxial coupling (*J* 12.4 Hz) and two axial:equatorial couplings (*J* 3.1 and 4.7 Hz).

In conclusion these results show that despite the consequent 1:3-diaxial interaction between the 2β-hydroxymethyl group and the angular methyl group at C-10, equatorial α-face attack takes place on the C-2 methylene. Whilst a steric approach argument may be proposed to rationalise these results, it should be pointed out that this face of the alkene has two adjacent axial C–H bonds. On the other hand the 17-methylene with the adjacent C-13 methyl group (C-18) undergoes axial attack to generate the 17β-hydroxymethyl group with a 17α-O-axial bond. The 18-methyl group hinders the β-face and the conformation of ring D does not produce an adjacent axial C–H bond at C-16. These results conform to the pattern

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

‡ See CAUTION in Experimental section.

observed previously,[3,4] and to that observed with hydroboration of these alkenes.[6]

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60-80°C. Extracts were dried over sodium sulfate. Unless otherwise stated ^{1}H NMR spectra were determined at 300MHz for solutions in deuterio-chloroform. Nuclear Overhauser effect enhancements were measured at 500MHz. IR spectra were determined as nujol mulls.

Caution: Osmium tetroxide solutions are toxic and were handled in a well ventilated fume cupboard. Excess reagent was disposed of by reduction with sodium sulfite and aqueous mannitol.

Wittig olefination reactions: A 60% suspension of sodium hydride in oil (400 mg) was thoroughly washed with hexane and dried. Dry dimethylsulfoxide (8 cm^3) was added and the mixture was heated to 70°C for 35 min. Dry tetrahydrofuran (4 cm^3) was added and the solution was cooled to 0°C. Methyl triphenylphosphonium iodide (1.28g) in dry dimethylsulfoxide (4 cm^3) was added to give a deep yellow solution of the methylenetriphenylphosphorane. 5α-Androstane-3,17-dione (400 mg) in dry tetrahydrofuran (4 cm^3) was added and the solution was heated at 60°C for 10 hours. The reaction mixture was poured into water and extracted with ether. The extracts were washed with water, dried and the solvent was evaporated to give a residue which was chromatographed on silica. Elution with light petroleum gave 3,17-dimethylene-5α-androstane (350 mg, 87%), m.p.77.5–79°C, (Found:C,88.6;H,11,3. $C_{2l}H_{32}$ requires C,88.7; H,11.3%), ν_{max}/cm^{-1} 1620; δ_H 0.78(3H,s,18-H), 0.89(3H,s,19-H), 0.68-2.22 (22H, overlapping multiplets), 4.57 and 4.62(each 2H,br.s.,3-and 17-=CH_2). Under similar conditions 5α-androst-2-en-17-one (1 g) gave 17-methylene-5α-androst-2-ene (780 mg, 78%), m.p.55–56°C,(Found: C,88.2;H, 11.3.$C_{20}H_{30}$ requires C,88.8; H,11.2%), ν_{max}/cm^{-1} 1620; δ_H 0.82 and 0.83 (each 3H,s, 18- and 19-H), 0.80-2.20(20H, overlapping multiplets), 4.66 (2H,br.s, 17-=CH_2), 5.62(2H,m, 2- and 3-H). Under similar conditions 3β-hydroxy-5α-androstan-17-one (1 g) gave 3β-hydroxy-17-methylene-5α-androstane (690 mg, 69%), m.p. 157–158°C (lit.,[7] m.p.158–159°C), ν_{max}/cm^{-1} 3560, 1654; δ_H 0.81(3H,s,18-H), 0.87(3H,s,19-H),0.90-2.00(23H, overlapping multiplets), 3.45(1H,tt, *J* 5.3 and 11.2 Hz,3-H), 4.59 and 4.61(each 1H,br.s.,17- =CH_2).

Osmylation reactions: A catalyst solution was prepared in a well-ventilated fume cupboard by dissolving osmium tetroxide (1 g) in *t*-butanol (16 cm^3) and *t*-butyl-hydroperoxide (1 cm^3). 2-Methylene-5α-androstan-17-one (80 mg) was dissolved in *t*-butanol (8 cm^3) and water (8 cm^3). Potassium hexacyanoferrate(III) (800 mg), potassium carbonate (330 mg) and 1,4-diazabicyclo[2,2,2]octane (DABCO) (33 mg) were added followed by the catalyst solution (0.26 cm^3). The reaction mixture was stirred at 40°C for 24 h. Sodium sulfite (80 mg) was added and the solution was left to stir overnight. The mixture was filtered, diluted with water and the product was extracted with ethyl acetate. The extract was dried and the solvent evaporated to give a residue which was chromatographed on silica. Elution with 50% ethyl acetate:light petroleum gave, 2α-hydroxy-2β-hydroxymethyl-5α-androstan-17-one (35 mg, 39%) as an oil (Found: M^+ 320.236; $C_{20}H_{32}O_3$ requires M^+ 320.235), ν_{max}/cm^{-1} 3540, 1742; δ_H 0.78(3H,s,18-H), 0.82(3H,s,19-H), 0.90–2.20(23H, overlapping multiplets), 3.46 and 3.59 (each,lH,d,*J* 10.9 Hz, CH_2OH), Under similar conditions 3β-hydroxy-17-methylene-5α-androstane (100 mg) gave 3β,17α-hydroxy-17β-hydroxymethyl-5α-androstane (70 mg 63%), m.p. 179–180°C, (Found: C,69.9; H,10.4; $C_{20}H_{34}O_3.H_2O$ requires C, 70.5; H,10.7%), ν_{max}/cm^{-1} 3512; δ_H 0.79(3H,s,18-H), 0.89(3H,s, 19-H),0.85–2.00 (23H, overlapping multiplets), 3.50(2H,m, 3β-H and 17β-CH_2OH), 3.72(1H,d, *J* 10.6 Hz, 17β-CH_2OH). Under similar conditions 3,17-dimethylene-5α-androstane (200 mg) gave 3β,17α-dihydroxy-3α,l7β-dihydroxymethyl-5α-androstane (180 mg, 73%), m.p. 203-205°C, (Found: C,67.2; H,10.7. $C_{21}H_{36}O_4.H_2O$ requires C,67.0; H, 10.7%), ν_{max}/cm^{-1} 3540 (broad); δ_H 0.78(3H,s,18-H), 0.82(3H,s, 19-H), 0.85-2.00(24H, overlapping multiplets), 3.61(1H,d,*J* 11 Hz), 3.62(1H,d, *J* 11 Hz), 3.69(1H,d, *J* 11 Hz), 3.78(1H,d,*J* 11Hz)(3α- and 17β-CH_2OH). Under similar conditions 17-methylene-5α-androst-2-ene (300 mg) gave 17β-hydroxymethyl-2α,3α,17α-trihydroxy-5α-androstane (258 mg 69%), m.p.165–167°C, (Found: C,67.1; H,9.8. $C_{20}H_{34}O_4.H_2O$ requires C,67.4; H,10.2%), ν_{max}/cm^{-1} 3500 (broad). The compound was not sufficiently soluble to obtain a satisfactory ^{1}HNMR spectrum and it was characterised as its acetate. The poorly soluble tetra-ol (100 mg) in pyridine (5 cm^3) was treated with acetic anhydride (0.8 cm^3) to give, after chromatography on silica, 2α,3α-diacetoxy-17β-acetoxy-methyl-l7α-hydroxy-5α-androstane (35 mg) as an oil, (Found: M^+ 464.277. $C_{26}H_{40}O_7$ requires M^+ 464.277), ν_{max}/cm^{-1} 3580, 1720; δ_H 0.74(3H,s, 18-H), 0.89(3H,s,19-H), 0.80-2.10(21H, overlapping multiplets), 1.99 (3Hs, OAc), 2.10(6H,s, 2 × OAc), 4.09 and 4.19(each 1H,d, *J* 8.4 Hz, 17β-CH_2OAc), 4.96 (1H,ddd, *J* 3.1, 4.7 and 12.4 Hz, 2β-H), 5.27(1H,m,3β-H).

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