Regioselectivity in the Hydroboration of Steroidal Δ^3-Allylic Alcohols†

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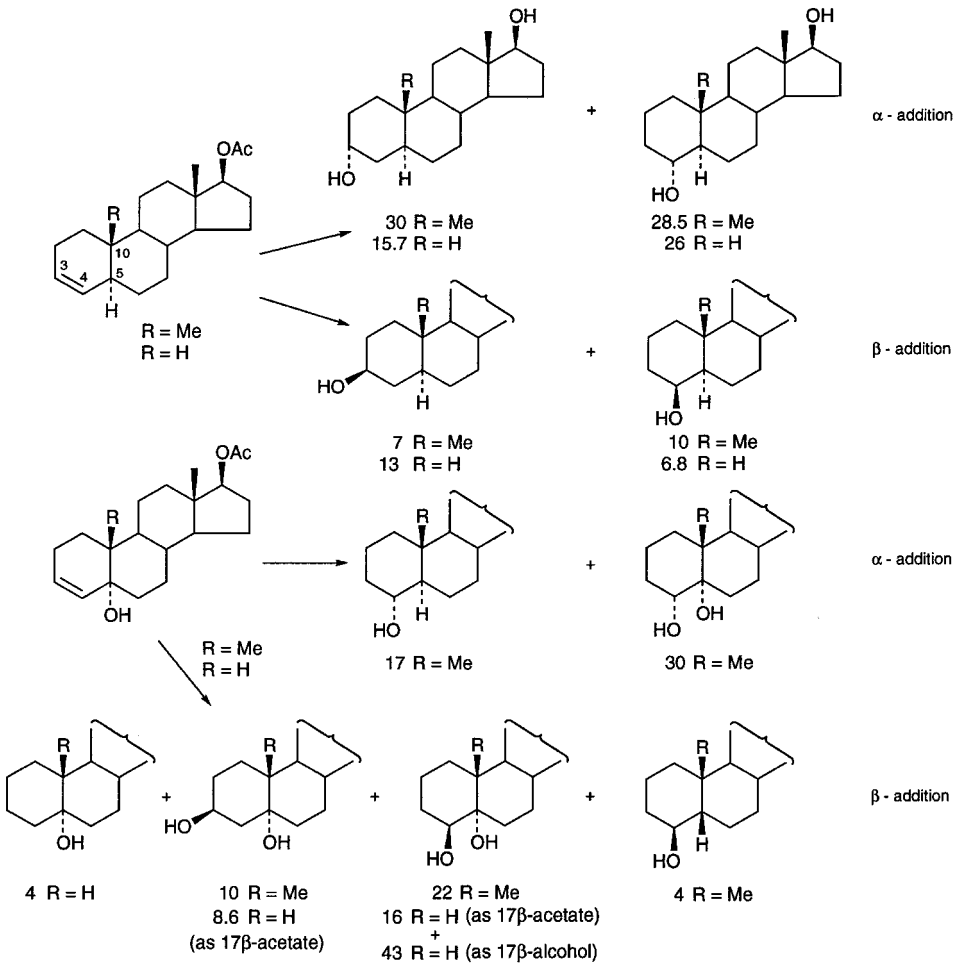
The presence of an allylic 5α-hydroxy group in an androst-3-ene increases the proportion of addition of a borane to the adjacent C-4 compared to the unsubstituted steroid and directs the addition to the face of the alkene *anti* to the hydroxy group with stereochemical effects that may oppose those of the C-10β-methyl group.

Hydroboration proceeds in a *cis*-manner on the less-hindered face of an alkene with anti-Markownikoff regioselectivity.[1,2] The directing effects of electronegative substituents in allyl derivatives modify the regiospecificity favouring addition of the borane at the 2-position.[3] In cyclohex-2-en-1-ols, the hydroxy group also affects the stereospecificity and directs the addition of the borane to the opposite face of the alkene.[4] Other directing effects in cyclic systems may arise from transannular diaxial interactions between the borane and sterically bulky groups. The relative contributions of these effects require evaluation. In the steroid series, the directing effect of an allylic hydroxy group on the hydroboration of the trisubstituted alkene, androst-4-ene, is sufficient to overturn the normal directing effect of the C-10 methyl group.

The C-10 angular methyl group can also affect the stereochemistry of reactions of the disubstituted androst-3-enes. The absence of a Markownikoff effect can afford greater potential for an adjacent hydroxy group to modify both the regiochemistry and stereochemistry of hydroboration. The hydroboration of 17β-acetoxy-5α-hydroxyandrost-3-ene and 17β-acetoxy-5α-hydroxy-19-norandrost-3-ene was compared to 17β-acetoxy-5α-androst-3-ene and 17β-acetoxy-19-nor-5α-androst-3-ene to contrast the directing role of the 10β-methyl group with that of the pseudo-axial 5α-hydroxy group.

Table 1 Yields (%) of hydroboration products of androst-3-enes



The results are shown in Table 1. The structures of the products were readily established from the multiplicity of the C*H*(OH) resonances in the ^{1}H NMR spectra[6] and by comparison with literature data.[7]

The 5α-hydroxy group increased the proportion of addition at C-4 in the hydroboration of androst-3-enes despite the fact that this is a more hindered position than C-3. The *trans* directing effect of the 5α-hydroxy group opposed the steric hindrance of the 10β-methyl group and increased the amount

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of addition to the β-face of the 3-ene. In the case of the 19-nor steroid, lacking this methyl group, only products arising from addition to the β-face were obtained when a 5α-hydroxy group was present. Comparison of the results of hydroboration of 5α-hydroxyandrost-3-ene and the corresponding 19-nor steroid suggests that the 10β-methyl group and the 5α-hydroxy group have approximately equivalent directing effects.

Experimental

General experimental details have been described previously.[5] Steroids were crystallized from ethyl acetate or acetone–light petroleum mixtures.

Hydroboration Experiments.—17*β-Acetoxy*-5α-*androst*-3-*ene*. The steroid (1 g) in dry THF (30 cm^3) was treated with borane in THF (30 cm^3, 1 M) for 4 h. Water (10 cm^3) was added and the solution cooled to 0 °C. Aqueous sodium hydroxide (20 cm^3, 10%) was added followed by the dropwise addition of hydrogen peroxide (20 cm^3, 30%). The mixture was stirred overnight. Sodium sulfite (2 g) was added followed by acetic acid (1 cm^3), water (50 cm^3), dil. hydrochloric acid (50 cm^3) and ethyl acetate (100 cm^3). The organic layer was separated, washed with water, brine and then dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave successively (i) 3β,17β-dihydroxy-5α-androstane (64 mg), needles, mp 167–169 °C (lit.,[7] 168–169 °C), ν_{max}/cm^{-1} 3450, 3304; δ_H (3 H, s, 18-H), 0.79 (3 H, s, 19-H), 3.61 (2 H, m, 3α- and 17α-H); (ii) 4α,17β-hydroxy-5α-androstane (263 mg), prisms, mp 231–233 °C (lit.,[8] 235–237 °C), ν_{max}/cm^{-1} 3506, 3433; δ_H 0.73 (3 H, s, 18-H), 0.81 (3 H, s, 19-H), 3.45 (1 H, dt, *J* 4.6 and 10.5 Hz, 4β-H), 3.63 (1 H, t, *J* 8.6 Hz, 17α-H); (iii) 4β,17β-dihydroxy-5α-androstane (92 mg), needles, mp 179–181 °C (lit.,[8] 176–178 °C), ν_{max}/cm^{-1} 3490, 339; δ_H 0.72 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 3.62 (1 H, t, *J* 8.6 Hz, 17α-H), 3.88 (1 H, m, 4α-H); (iv) 3α,17β-dihydroxy-5α-androstane (278 mg), prisms, mp 220–223 °C (lit.,[7] 222–224 °C), ν_{max}/cm^{-1} 3490, 3400; δ_H 0.73 (3 H, s, 18-H), 0.79 (3 H, s, 19-H), 3.62 (1 H, t, *J* 8.6 Hz, 17α-H), 4.05 (1 H, brs, 3β-H).

17*β-Acetoxy*-19-*nor*-5α-*androst*-3-*ene*. The 19-nor steroid (1 g) gave (i) 4β-17*β-dihydroxy*-19-*nor*-5α-*androstane* (63 mg), needles, mp 167–169 °C (Found: C, 77.5; H, 10.8. $C_{18}H_{30}O_2$ requires C, 77.6; H, 10.9%); ν_{max}/cm^{-1} 3305; δ_H 0.74 (3 H, s, 18-H), 3.64 (1 H, t, *J* 8.2 Hz, 17α-H), 3.76 (1 H, brs, 4α-H); (ii) 4α,17*β-dihydroxy*-19-*nor*-5α-*androstane* (240 mg), plates, mp 200–220 °C (Found: C, 77.5; H, 10.9. $C_{18}H_{30}O_2$ requires C, 77.5; H, 10.9%); ν_{max}/cm^{-1} 3230; δ_H 0.75 (3 H, s, 18-H), 3.21 (1 H, td, *J* 10.5 and 4.6 Hz, 4β-H), 3.64 (1 H, t, *J* 8.2 Hz, 17α-H); (iii) 3α,17*β-dihydroxy*-19-*nor*-5α-*androstane* (145 mg), needles, mp 163 °C (Found: C, 77.6; H, 11.0. $C_{18}H_{30}O_2$ requires c, 77.6; H, 10.9%); ν_{max}/cm^{-1} 3279; δ_H 0.72 (3 H, s, 18-H), 3.64 (1 H t, *J* 8.2 Hz, 17α-H), 4.12 (1 H, brs, 3β-H); (iv) 3β,17*β-dihydroxy*-19-*nor*-5α-*androstane* (120 mg), needles, mp 141–143 °C (Found: C, 77.5; H, 10.7. $C_{18}H_{30}O_2$ requires C, 77.6; H, 10.9%); ν_{max}/cm^{-1} 3348; δ_H 0.74 (3 H, s, 18-H), 3.57 (1 H, t, *J* 10.5 and 4.5 Hz, 3α-H) 3.62 (1 H, t, *J* 8.1 Hz, 17α-H).

17*β-Acetoxy*-5α-*hydroxyandrost*-3-*ene*. The 5α-hydroxy steroid (1 g) gave 4α,17β-dihydroxy-5α-androstane (147 mg) and 4β,17β-dihydroxy-5β-androstane (30 mg) which were identified by their ^1H NMR spectra. Further chromatography gave 4α,5α,17*β-trihydroxyandrostane* (90 mg), prisms, mp 219–220 °C (Found: C, 71.7; H, 10.3. $C_{19}H_{32}O_3 \cdot 0.5H_2O$ requires C, 71.9; H, 10.5%); ν_{max}/cm^{-1} 3498, 3409, 3335; δ_H 0.73 (3 H, s, 18-H), 0.94 (3 H, s, 19-H), 3.65 (2 H, m, 4β- and 17α-H). The 4α,17*β-diacetate*, prepared with acetic anhydride in pyridine, had mp 170–172 °C (Found: C, 70.7; H, 9.5. $C_{23}H_{36}O_5$ requires C, 70.4; H, 9.2%); ν_{max}/cm^{-1} 3380, 1720; δ_H 0.71 (3 H, s, 18-H), 0.91 (3 H, s, 19-H), 1.96 and 1.99 (each 3 H, s, OAc), 4.51 (1 H, t, *J* 7.8 Hz, 17α-H), 4.91 (1 H, dd, *J* 6.0 and 10.5 Hz, 4β-H). Further chromatography gave 4β,5α,17*β-trihydroxyandrostane* (281 mg), prisms, 223–225 °C (Found: C, 71.5; H, 10.3. $C_{19}H_{32}O_3 \cdot 0.5H_2O$ requires C, 71.9; H, 10.5%); ν_{max}/cm^{-1} 3490, 3400, 3367; δ_H 0.74 (3 H, s, 18-H), 1.18 (3 H, s, 19-H), 3.54 (1 H, t, *J* 2.8 Hz, 4α-H), 3.64 (1 H, t, *J* 8.4 Hz, 17α-H). The 4β,17*β-diacetate*, prepared with acetic anhydride in pyridine, had mp 181–183 °C (Found: C, 70.2; H, 9.0. $C_{23}H_{36}O_5$ requires C, 70.4; H, 9.2%); ν_{max}/cm^{-1} 3240, 1740, 1720; δ_H 0.74 (3 H, s, 18-H), 1.10 (3 H, s, 19-H), 1.96 and 1.99 (each 3 H, s, OAc), 4.54 (1 H, t, *J* 7.8 Hz, 17α-H), 4.65 (1 H, t, *J* 2.6 Hz, 4α-H). Further elution gave 3β,5α,17β-trihydroxyandrostane (201 mg), mp 192–194 °C (lit.,[9] 193–196 °C).

17*β-Acetoxy*-5α-*hydroxy*-19-*norandrost*-3-*ene*. The 5α-hydroxy-19-nor steroid (1 g) gave successively (i) 5α,17β-dihydroxy-19-norandrostane (40 mg) as a gum, *m/z* 292 (M^+), 274 ($M-H_2O$) 256 ($M-2H_2O$); ν_{max}/cm^{-1} 3512; δ_H 0.75 (3 H, s, 18-H), 3.65 (1 H, t, *J* 8.2 Hz, 17α-H); (ii) 17*β-acetoxy*-4β,5α-*dihydroxy*-19-*norandrostane* (160 mg), plates, mp 187–189 °C (Found: C, 71.3; H, 9.7. $C_{20}H_{32}O_4$ requires C, 71.4; H, 9.6%); ν_{max}/cm^{-1} 3320, 1742; δ_H 0.78 (3 H, s, 18-H), 2.02 (3 H, s, OAc), 3.47 (1 H, t, *J* 3.0 Hz, 4α-H), 4.58 (1 H, t, *J* 8 Hz, 17α-H); (iii) 17*β-acetoxy*-3β,5α-*dihydroxy*-19-*norandrostane* (80 mg), needles, mp 218–220 °C (Found: C, 70.7; H, 9.6. $C_{20}H_{32}O_4$ requires C, 71.4; H, 9.6%); ν_{max}/cm^{-1} 3358, 1720; δ_H 0.75 (3 H, s, 18-H), 2.04 (3 H, s, OAc), 3.98 (1 H, tt, *J* 9.6 and 4.5 Hz, 3α-H), 4.62 (1 H, t, *J* 8.2 Hz, 17α-H); (iv) 4β,5α-17*β-trihydroxy*-19-*norandrostane* (410 mg), prisms, 203–205 °C (Found: C, 71.5; H, 10.2. $C_{18}H_{30}O_3 \cdot 0.5H_2O$ requires C, 71.2; H, 10.3%); ν_{max}/cm^{-1} 3450; δ_H 0.74 (3 H, s, 18-H), 3.48 (1 H, t, *J* 2.8 Hz, 4α-H), 3.65 (1 H, t, *J* 8 Hz, 17α-H).

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