SHORT PAPER

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The stereochemistry of the 1,2-addition of Grignard reagents to some steroidal unsaturated ketones†

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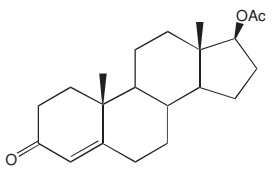
The stereochemistry of 3β,17β-dihydroxy-3α-ethylandrost-4-ene, 3α,17β-dihydroxy-3β-methylestr-4-ene and 3β-acetoxy-7α,17β-dihydroxy-7β-methylandrost-5-ene, which were obtained by Grignard reactions from the corresponding αβ-unsaturated ketones, have been established by X-ray crystallography.

Keywords: Grignard reagents, steroids, enones, crystal structures

The stereochemistry of the addition of Grignard reagents to cyclohexanones has been the subject of investigations over many years.[1] In the reactions with methylmagnesium halides in the steroid series, there is a pronounced tendency for the formation of tertiary alcohols with an equatorial methyl group.[2] In the case of steroidal unsaturated ketones attention has been focussed on the stereochemistry of conjugate addition, particularly in the presence of copper salts when there is a tendency for axial addition.[3] There are fewer well-established results for 1,2-addition to steroidal unsaturated ketones. The reaction of testosterone propionate with methylmagnesium bromide has been shown[4] to give 3,17β-dihydroxy-3-methylandrost-4-ene but the stereochemistry at C-3 was not defined. However it has been reported[5] that androst-4-ene-3,17-dione gave a 75% yield of 3β-hydroxy-3α-methylandrost-4-en-17-one. Unlike the saturated series in which a 57:43 (eq:ax) mixture of C-3 epimers was obtained,[6] the unsaturated ketones gave a single epimer.



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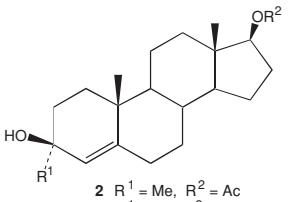
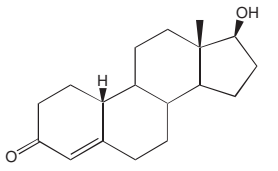


2 R^1 = Me, R^2 = Ac
3 R^1 = Et, R^2 = H



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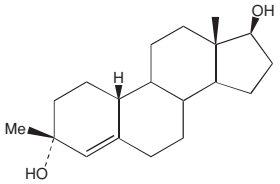

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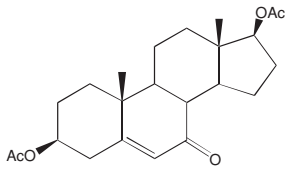

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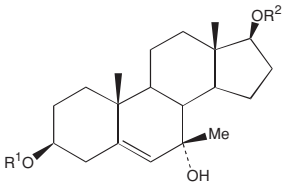

7 R^1 = Ac, R^2 = H
8 R^1 = H, R^2 = Ac

Treatment of testosterone acetate (17β-acetoxyandrost-4-en-3-one) (**1**) with methylmagnesium bromide gave a tertiary alcohol (**2**) in 76% yield. However we were unable to obtain suitable crystals for X-ray crystallography in order to establish the stereochemistry at C-3. 3β,17β-Dihydroxy-3α-ethylandrost-4-ene (**3**) was obtained from the reaction with ethylmagnesium bromide. This compound did give suitable crystals for X-ray crystallography and we were able to obtain a crystal structure (see Fig. 1) which established the 3α-ethyl-3β-hydroxy stereochemistry at C-3 in **3**. Hence **2** was assigned the stereochemistry, 17β-acetoxy-3β-hydroxy-3α-methylandrost-4-ene. Unlike the saturated series, attack of the Grignard reagent had taken place almost entirely from the α-face to introduce an axial alkyl group.

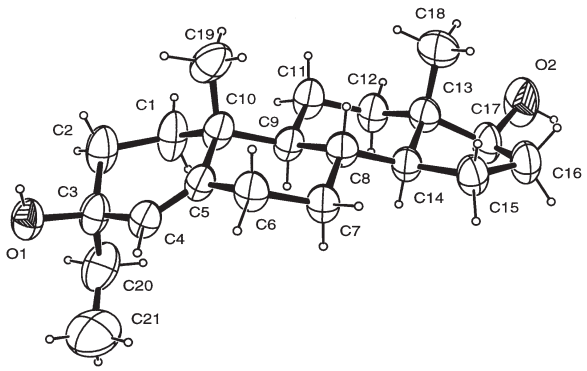

Fig. 1

Since the C-10β methyl group had a possible steric directing effect on this reaction, the stereochemistry of addition in the 19-nor series was examined.[7] Treatment of 19-nortestosterone

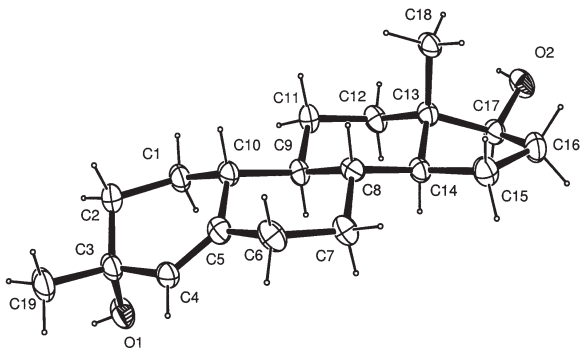

Fig. 2

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

(**4**) with methylmagnesium bromide gave a single product, the stereochemistry of which was established by X-ray crystallography (see Fig. 2). This showed that the product was 3α,17β-dihydroxy-3β-methylestr-4-ene (**5**). It was epimeric at C-3 to the product in the testosterone series.

There is a similar relationship between a Δ^5-7-ketone and the C-10β methyl group as in a Δ^4-3-ketone series. The addition of methylmagnesium iodide to a Δ^5-7-ketone has been reported on several occasions.[8] In the case of 3β,20β-diacetoxypregn-5-en-7-one, the single product which was obtained was formulated as the 7α-methylpregn-5-ene-3β,7β,20β-triol. This assignment was made on the basis of the generally preferred attack of reagents from the α-face of the steroid and the fact that dehydration of the 7-alcohol with phosphorus oxychloride in pyridine gave a 7-methylene rather than a 7(8)-alkene. Repetition of the Grignard addition with 3β,17β-diacetoxyandrost-5-en-7-one (**6**) gave a single epimer at C-7. As with other Grignard reactions this was accompanied by partial cleavage of the acetate groups. X-ray crystallography of **7** (see Fig. 3) showed that the adduct possessed the 7α-hydroxy-7β-methyl stereochemistry, *i.e.* opposite to that proposed[8] previously for the analogous compound in the pregnene series. The stereochemistry of the latter may therefore require revision. The chemical evidence would not preclude a 7α-hydroxy-7β-methyl configuration.

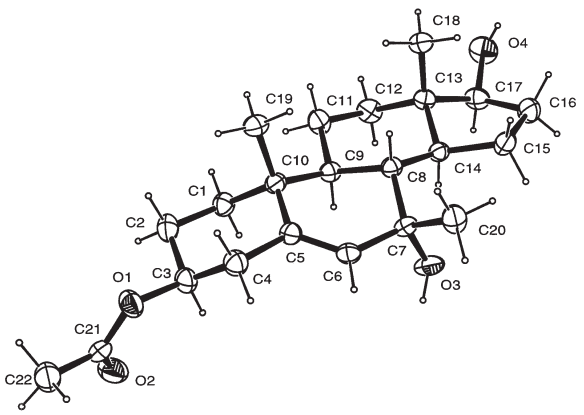

Fig. 3

In conclusion: we have shown that the stereochemistry of the Grignard reaction with unsaturated steroidal ketones at C-3 is dependent on the presence of a C-10β methyl group and that the addition at C-7 takes place from the β equatorial face.

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80 °C. ^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform. IR spectra were determined as nujol mulls. High-resolution mass spectra were obtained on a Bruker Daltonics Apex III ESI spectrometer with electrospray ionisation.

Grignard reactions: (a) A solution of methylmagnesium bromide in ether (3M, 2 cm^3) was diluted with tetrahydrofuran (25 cm^3) at 0 °C under nitrogen. 17β-Acetoxyandrost-4-en-3-one (**1**) (1 g) in tetrahydrofuran (50 cm^3) was added slowly and the mixture was left to stir overnight. Aqueous ammonium chloride (100 cm^3) was added and the solution was extracted with dichloromethane. The extract was washed with water, brine and dried. The solvent was evaporated to give 17β-acetoxy-3β-hydroxy-3α-methylandrost-4-ene (**2**) (800 mg) which crystallised from acetone as needles, m.p. 132–135 °C. (Found: M$^+$ 369.240; $C_{22}H_{34}O_3$ + Na requires 369.240) ν_{max}/cm^{-1} 3269, 1735, 1660; δ_H 0.79 (3H, s, 18-H), 1.03 (3H, s, 19-H), 1.24 (3H, s, 3α-Me), 2.02 (3H, s, 17β-Ac), 0.7–2.2 (19H, overlapping multiplets), 4.56 (1H, t, *J* 8.6 Hz, 17α-H), 5.18 (1H, s, 4-H).

(b) Under similar conditions 19-nortestosterone (**4**)(1 g) gave 3α,17β-dihydroxy-3β-methylestr-4-ene (**5**) (750 mg) which crystallised from acetone as cubes, m.p. 144-147 °C (Found: M$^+$ 313.214; $C_{19}H_{30}O_2$ + Na requires 313.214) ν_{max}/cm^{-1} 3335, 1652; δ_H 0.75 (3H, s, 18-H), 1.24 (3H, s, 3β-Me), 0.7 - 2.2 (20H, overlapping multiplets), 3.61 (1H, t, *J* 8.6 Hz, 17α-H), 5.28 (1H, s, 4-H).

(c) Under similar conditions 3β,17β-diacetoxyandrost-5-en-7-one (**6**) (750 mg) gave a mixture which was chromatographed on silica. Elution with 40% ethyl acetate : light petroleum gave 3β-acetoxy-7α,17β-dihydroxy-7β-methylandrost-5-ene (**7**)(210 mg) which crystallised from acetone as needles, m.p.186–188 °C. (Found: M$^+$ 385.235; $C_{22}H_{34}O_4$ + Na requires 385.235.) ν_{max}/cm^{-1} 3508 (br), 1715, 1671. δ_H 0.76 (3H, s, 18-H), 0.97 (3H, s, 19-H), 1.22 (3H, s, 7β-Me), 2.02 (3H, s Ac), 0.75–2.10 (19H, overlapping multiplets), 4.59(1H, tt, *J* 4.2 and 11.1 Hz, 3α-H), 5.23 (1H, s, 6-H). Further elution gave 17β-acetoxy-3β,7α-dihydroxy-7β-methylandrost-5-ene (**8**) (120 mg) which crystallised from acetone as cubes, m.p.213–215 °C. (Found: M$^+$ 385.235; $C_{22}H_{34}O_4$ + Na requires 385.235.) ν_{max}/cm^{-1} 3470 (br), 1734, 1671. δ_H 0.81 (3H, s, 18-H), 1.05 (3H, s, 19-H), 1.13 (3H, s, 7β-Me), 2.04 (3H, s, Ac), 0.90–2.10 (19H, overlapping multiplets), 3.55 (1H, m, 3α-H), 4.59 (1H, t, J 8.0 Hz, 17α-H), 5.18 (1H, s, 6-H).

(d) A solution of ethylmagnesium bromide in ether (3M, 2 cm^3) was diluted with tetrahydrofuran (25 cm^3) at 0 °C under nitrogen. 17β-Acetoxyandrost-4-en-3-one (**1**)(1 g) in tetrahydrofuran (50 cm^3) was added slowly and the mixture was left to stir overnight. Aqueous ammonium chloride (100 cm^3) was added and the solution was extracted with dichloromethane. The extract was washed with water, brine and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 50% ethyl acetate : light petroleum gave 3β,17β-dihydroxy-3α-ethylandrost-4-ene (**3**)(700 mg) which crystallised from ethyl acetate : light petroleum as needles, m.p.166–168 °C. (Found: M$^+$ 341.244; $C_{21}H_{34}O_2$ + Na requires 341.245) ν_{max}/cm^{-1} 3272 (br), 1660; δ_H 0.74 (3H, s, 18-H), 0.90 (3H, t, *J* 7.4 Hz, 3α-Et), 1.03 (3H, s, 19-H), 0.75–2.10 (23H, overlapping multiplets), 3.60 (1H, t, *J* 8.3 Hz, 17α-H), 5.18 (1H, s, 4-H).

Crystal data and structure determination: (a) Compound **3**: $C_{21}H_{34}O_2$, M_r 318.48, tetragonal, space group $P4_22_12$ (no.94), a = 24.8599(5), b = 24.8599(5), c = 7.1684(2) Å, α = β = γ = 90°, V = 4430.2(2) Å^3, Z = 8, D_{calc} = 0.96g/cm^3, F(000) 1408, μ = 0.06 mm^{-1}, λ = 0.71073 Å. Data were collected using a crystal of size 0.3 × 0.3 × 0.1 mm^3 on a KappaCCD diffractometer. A total of 12486 reflections were collected for 3.76 < θ < 25.01° and -23 ≤ h ≤ 24, -15 ≤ k ≤ 29, –6 ≤ l ≤ 8. There were 3754 independent reflections and 2995 reflections with I > 2σ(I). No absorption correction was applied. The structure was solved by direct methods and refined using SHELXL-97. The final R indices were [I > 2σ(I)] R_1 = 0.061, wR_2 = 0.154 and R indices (all data), R_1 = 0.081 and wR_2 = 0.164. The goodness-of-fit on F^2 was 1.079 and the largest difference peak and hole was 0.17 and –0.13 eÅ^{-3}.

(b) Compound **5**: $C_{19}H_{30}O_2$, M_r 290.49, monoclinic, space group C2 (No5), a = 19.6889(8), b = 7.4737(4), c = 12.4021(7) Å, α = γ = 90° β = 114.248(2)°, V = 1663.95(15) Å^3, Z = 4, D_{calc} = 1.16g cm^{-3}, F(000) 640, μ = 0.07 mm^{-1}, λ = 0.71073 Å. Data were collected using a crystal of size 0.4 × 0.05 × 0.05 mm^3 on a KappaCCD diffractometer. A total of 4538 reflections were collected for 4.28 < θ < 25.01° and –23 ≤ h ≤ 23, –7 ≤ k ≤ 8, –13 ≤ l ≤ 14. There were 2416 independent reflections and 2071 reflections with I > 2σ(I). No absorption correction was applied. The structure was solved by direct methods and refined using SHELXL-97. The final R indices were [I > 2σ(I)] R_1 = 0.048, wR_2 = 0.107 and R indices (all data), R_1 = 0.061 and wR_2 = 0.113. The goodness-of-fit on F^2 was 1.044 and the largest difference peak and hole was 0.19 and –0.17 eÅ^{-3}.

(c) Compound **7**: $C_{22}H_{34}O_4$, M_r 362.5, orthorhombic, space group $P2_12_12_1$ (No19), a = 6.05830(10), b = 11.3138(2), c = 28.4499(7) Å, α = β = γ = 90°, V = 1950.02(7) Å^3, Z = 4, D_{calc} = 1.24g/cm^3, F(000) 792, μ = 0.06 mm^{-1}, λ = 0.71073 Å. Data were collected using a crystal of size 0.3 × 0.3 × 0.2 mm^3 on a KappaCCD diffractometer. A total of 8601 reflections were collected for 3.82 < θ < 25.02° and –7 ≤ h ≤ 7, –13 ≤ k ≤ 10, –33 ≤ l ≤ 21. There were 3291 independent reflections and 2778 reflections with I > 2σ(I). No absorption correction was applied. The structure was solved by direct methods and refined using SHELXL-97. The final R indices were [I > 2σ(I)] R_1 = 0.046, wR_2 = 0.105 and R indices (all data), R_1 = 0.060 and wR_2 = 0.113. The goodness-of-fit on F^2 was 1.026 and the largest difference peak and hole was 0.20 and –0.17 eÅ^{-3}.

The data will be deposited at the Cambridge Crystallographic Data Centre.

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