

Zn^{II}-Promoted D-Homorearrangement of 17 α -Hydroxy-3 β -methoxyandrost-5-ene-17 β -carbaldehyde

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The synthesis of 17 α -hydroxy-3 β -methoxyandrost-5-ene-17 β -carbaldehyde and a highly efficient method for its *D*-homorearrangement is described. The transformation produced by the action of Zn^{II} afforded 17 α -hydroxy-3 β -methoxy-*D*-homoandrost-5-en-17 α -one in a fast, stereospecific, and high-yield reaction.

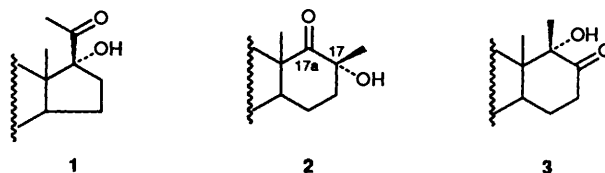
During the past four decades much attention has been paid to the *D*-homoannulation of 17-hydroxy-20-oxopregnanes (for reviews see ref. 1). Kirk and McHugh² have established the main features of the Lewis acid-catalysed process, by which 17 α -hydroxy-20-oxopregnanes **1** rearrange into 17 α -hydroxy-17 β -methyl-17 α -ketones **2**. Although the C-16/C-17 bond migration occurs only in compounds of type **1** when treated with Lewis acids such as boron trifluoride, alumina, or aluminium *t*-butoxide, recently we found that zinc iodide promotes rearrangement of compounds **1** into 17 α -hydroxy-17 β -methyl-17-oxo derivatives **3** with 100% optical purity and in 100% yield.³ The observed stereospecificity prompted us to investigate the reaction on other 17-hydroxy-20-oxosteroids.

To the best of our knowledge *D*-homorearrangements of 17 α -hydroxy-17 β -carbaldehydes have not yet been accomplished. This paper deals with the synthesis and rearrangement of 17 α -hydroxy-3 β -methoxyandrost-5-ene-17 β -carbaldehyde **4**.

Results and Discussion

The synthesis of aldehyde **4** was carried out as described by Reid,⁴ using 3 β -methoxyandrost-5-en-17-one **5** as the starting material (Scheme 1) and introducing some modifications as described in the Experimental section. All compounds were characterised by ¹H and ¹³C NMR spectroscopy (see Experimental section).

Treatment of the steroid **4** with zinc dust and a few crystals of iodine in boiling dichloromethane resulted in a fast (0.5 h), stereospecific, and high yielding (95%) reaction, from which 17 α -hydroxy-3 β -methoxy-*D*-homoandrost-5-en-17 α -one **10** was isolated. The evidence for a 17 α -hydroxy-17 α -ketone product was provided by its proton NMR spectrum. The presence of a proton signal at δ 4.72 as a double doublet instead of a singlet indicated that the rearranged product **10** was a 17-hydroxy-17 α -ketone and not the isomeric 17 α -hydroxy-17-ketone. Coupling-constant-values for the C-17 proton (7 and 11 Hz) were in agreement with those calculated for both an axial-equatorial and an axial-axial splitting, indicating a 17 α -hydroxy configuration. Molecular mechanics calculations (using the MM2 force field (PC Model, Serena Software) afforded coupling-constant-values of 5 and 10 Hz for compound **10**, while for the alternative 17 β -hydroxy-17 α -ketone these values were 2.5 and 3.8 Hz. Taking into account our previous results³ on 17 α -hydroxy-20-oxopregnanes **1** the reaction path probably involves initial conversion of aldehyde **4** into the acyloin **9**. The formation of *O*-metallated zinc enolates derived from ketones is a well established process⁵ which may operate in the reaction conditions described above. This fact would let the initial product **9** be transformed into the more stable *D*-homo-hydroxy ketone **10** (Scheme 2).

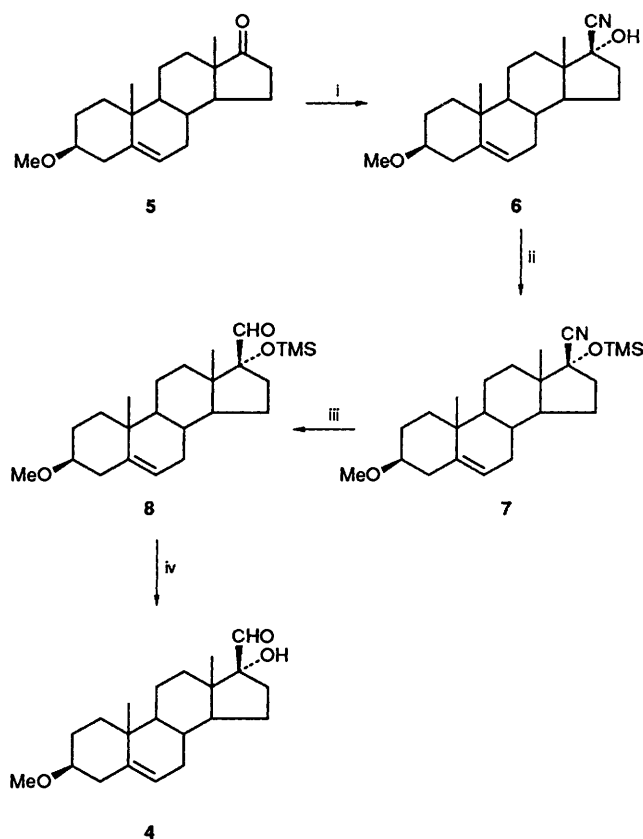


Experimental

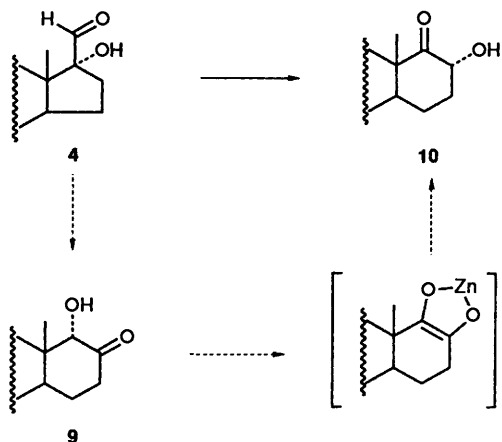
M.p.s (uncorrected) were determined on a Fisher-Johns apparatus. ¹H and ¹³C NMR spectra (Fourier transform) were determined at 100.1 and 25.2 MHz, respectively, in deuteriochloroform. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Extractive work-up included exhaustive extraction with dichloromethane, washing with water, drying with anhydrous sodium sulfate, and evaporation of the solvent under reduced pressure at ~40–60 °C. The homogeneity of all compounds was confirmed by TLC.

17 α -Hydroxy-3 β -methoxyandrost-5-ene-17 β -carbonitrile 6 from Ketone 5.—To a stirred solution of 3 β -methoxyandrost-5-en-17-one **5** (430 mg) and KCN (460 mg) in methanol (4 cm³), was added AcOH (120 mm³) during 30 min. The reaction mixture was kept at room temperature for 12 h and further AcOH (0.3 cm³) was then added. The mixture was diluted with water (10 cm³) and filtered. The solid was washed with water and dried to afford pure cyanohydrin **6** (450 mg), m.p. 163–165 °C (from MeOH) (Found: C, 76.3; H, 9.2; N, 4.3. C₂₁H₃₁NO₂ requires C, 76.6; H, 9.5; N, 4.2%); δ_{H} 0.95 (3 H, s, 18-H₃), 1.02 (3 H, s, 19-H₃), 3.06 (1 H, m, 3-H), 3.35 (3 H, s, OMe) and 5.37 (1 H, m, 6-H); δ_{C} 16.2 (C-18), 19.4 (C-19), 20.5 (C-11), 24.1 (C-15), 27.9 (C-2), 29.6 (C-16), 31.9 (C-7), 32.4 (C-8), 36.9 (C-10), 37.2 (C-1), 38.2 (C-12), 38.6 (C-4), 48.4 (C-9), 49.1 (C-13), 49.6 (C-14), 55.5 (OMe), 77.9 (C-17), 80.3 (C-3), 120.8 (C-20), 120.9 (C-6) and 140.7 (C-5).

3 β -Methoxy-17 α -(trimethylsiloxy)androst-5-ene-17 β -carbonitrile 7 from Cyanohydrin 6.—To a stirred solution of compound **6** (390 mg) and 4-(dimethylamino)pyridine (DMAP) (20 mg) in tetrahydrofuran (THF) (10 cm³) were added triethylamine (TEA) (4 cm³) and chlorotrimethylsilane (TMSCl) (2 cm³). The reaction mixture was kept overnight at room temperature and then was diluted with water (20 cm³). Extractive work-up afforded the siloxy cyanide **7** (450 mg), m.p. 137–138 °C (from MeOH) (Found: C, 71.6; H, 9.5; N, 3.3. C₂₄H₃₉NO₂Si requires C, 71.8; H, 9.8; N, 3.5%); δ_{H} 0.23 (9 H, s, OSiMe₃), 0.92 (3 H, s, 18-H₃), 1.02 (3 H, s, 19-H₃), 3.06 (1 H, m, 3-H), 3.36 (3 H, s, OMe) and 5.35 (1 H, m, 6-H); δ_{C} 1.10 (OSiMe₃), 15.9 (C-18), 19.4 (C-19), 20.5 (C-11), 24.1 (C-15), 27.9 (C-2), 29.8 (C-16), 31.9 (C-7), 32.4 (C-8), 36.8 (C-10), 37.1 (C-1),



Scheme 1 Reagents: i, KCN, AcOH, MeOH; ii, TMSCl, DMAP, TEA; iii, DIBAL, THF-CH₂Cl₂ (2:1); iv, AcOH-water-THF (3:1:1.5)



Scheme 2 Reagents and conditions: ZnI₂, CH₂Cl₂, reflux

38.7 (C-4), 38.9 (C-12), 48.4 (C-9), 49.5 (C-14), 49.9 (C-13), 55.4 (OMe), 78.7 (C-17), 80.1 (C-3), 120.7 (C-20), 120.9 (C-6) and 140.7 (C-5).

3β-Methoxy-17α-(trimethylsilyloxy)androst-5-ene-17β-carbaldehyde 8 from 7.—To a stirred solution of compound 7 (250 mg) in anhydrous THF-CH₂Cl₂ (2:1) (6 cm³) kept under N₂ at -10 °C was added diisobutylaluminium hydride (DIBAL) (1 mol dm⁻³ in hexane; 1 cm³) dropwise. After 4 h, the reaction was quenched with aq. AcOH (50%; 4 cm³) and the resulting mixture was stirred at room temperature for 10 min. Extractive

work-up gave a solid, compound 8, which upon purification by preparative TLC (PLC) [silica; CH₂Cl₂-MeOH (99:1)] afforded pure *siloxane aldehyde* 8 (214 mg), m.p. 88–89 °C (from MeOH) (Found: C, 71.1; H, 10.0. C₂₄H₄₀O₃Si requires C, 71.2; H, 10.0%); δ_H 0.12 (9 H, s, OSiMe₃), 0.70 (3 H, s, 18-H₃), 1.00 (3 H, s, 19-H₃), 3.06 (1 H, m, 3-H), 3.36 (3 H, s, OMe), 5.35 (1 H, m, 6-H) and 9.61 (1 H, s, 20-H); δ_C 1.85 (OSiMe₃), 14.6 (C-18), 19.4 (C-19), 20.5 (C-11), 24.2 (C-15), 28.0 (C-2), 31.1 (C-16), 31.8 (C-8), 32.1 (C-7), 36.9 (C-10), 37.2 (C-1), 38.7 (C-4 and -12), 49.3 (C-9*), 51.0 (C-14* and -13), 55.5 (OMe), 80.3 (C-3), 91.3 (C-17), 121.2 (C-6), 140.8 (C-5) and 203.3 (C-20).

17α-Hydroxy-3β-methoxyandrost-5-ene-17β-carbaldehyde 4 from the Siloxane 8.—A solution of the siloxane aldehyde 8 (170 mg) in AcOH-water-THF (3:1:1.5; 5.5 cm³) was stirred at 50 °C for 4 h. The reaction mixture was then diluted with water and, after extractive work-up, the product was purified by PLC [silica; toluene-AcOEt (73:27)] to yield starting material 8 (33 mg recovery) and pure *hydroxy aldehyde* 4 (112 mg), m.p. 134–135 °C [from MeOH-water (9:1)] (Found: C, 75.7; H, 9.7. Calc. for C₂₁H₃₂O₃: C, 75.9; H, 9.7%); δ_H 0.98 (3 H, s, 18-H₃), 1.01 (3 H, s, 19-H₃), 3.06 (1 H, m, 3-H), 3.35 (3 H, s, OMe), 5.37 (1 H, m, 6-H) and 9.79 (1 H, s, 20-H); δ_C 15.3 (C-18), 19.5 (C-19), 20.3 (C-11), 25.3 (C-15), 28.1 (C-2), 30.3 (C-16), 31.4 (C-8), 32.1 (C-7), 32.8 (C-12), 36.9 (C-10), 37.3 (C-1), 38.7 (C-4), 49.7 (C-9*), 51.0 (C-13), 51.3 (C-14*), 55.6 (OMe), 80.2 (C-3), 87.9 (C-17), 121.2 (C-6), 140.8 (C-5) and 205.6 (C-20).

17α-Hydroxy-3β-methoxy-D-homoandrost-5-en-17a-one 10 from aldehyde 4.—To a solution of the aldehyde 4 (100 mg) in CH₂Cl₂ (5 cm³) were added zinc dust (80 mg) and a few crystals of iodine. The mixture was stirred and heated under reflux for 30 min, and was then cooled and filtered. The filtrate was concentrated to dryness and purified by PLC (silica; CH₂Cl₂) to afford the *D-homosteroid* 10 (95 mg), m.p. 127–128 °C [from MeOH-water (8:2)] (Found: C, 75.9; H, 9.6. C₂₁H₃₂O₃ requires C, 75.9; H, 9.7%); δ_H 1.00 (3 H, s, 19-H₃), 1.18 (3 H, s, 18-H₃), 3.06 (1 H, m, 3-H), 3.36 (3 H, s, OMe), 4.72 (1 H, dd, J_{7,11}, 17β-H) and 5.35 (1 H, m, 6-H); δ_C 16.7 (C-18), 19.4 (C-19 and -11), 22.1 (C-15), 28.0 (C-2), 31.6 (C-8), 32.0 (C-7 and -12), 36.5 (C-10), 36.9 (C-16), 37.2 (C-1), 38.5 (C-4), 49.1 (C-9 and -13), 52.9 (C-14), 55.7 (OMe), 71.3 (C-17), 80.1 (C-3), 120.7 (C-6), 140.6 (C-5) and 218.3 (C-17a).

* Assignments may be interchanged.

References

- N. L. Wendler, *Molecular Rearrangements*, ed. P. de Mayo, Interscience, New York, 1964, vol. 2, pp. 1099–1101 and 1114–1121;
- D. N. Kirk and M. P. Hartshorn, *Steroid Reaction Mechanisms*, Elsevier, Amsterdam, 1968, pp. 294–301.
- D. N. Kirk and C. R. McHugh, *J. Chem. Soc., Perkin Trans. 1*, 1978, 173 and references therein.
- L. Schor, A. M. Seldes and E. G. Gros, *J. Chem. Soc., Perkin Trans. 1*, 1990, 163.
- J. G. Reid and T. Debiak-Krook, *Tetrahedron Lett.*, 1990, 31, 3669.
- M. M. Hansen, P. A. Bartlett and C. H. Heathcock, *Organometallics*, 1987, 6, 2069.

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