Stereoselective Synthesis of 19(10→9β)*abeo*-10α-Testosterone

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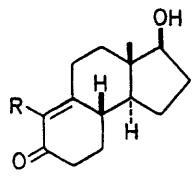
Summary Conjugate methylation of a steroidal 4,5-seco-Δ^9-5-ketone afforded the 9β-methyl compound which was converted into 19(10→9β)*abeo*-10α-testosterone.

THE synthesis of a simple representative (**3**) of the 19-(10→9β)*abeo*-10α-steroids was undertaken in order to supplement information obtained during studies of the degradation products of the cucurbitacins.[1] Simple paths to the desired skeleton may be envisaged through adaptation of known[2] rearrangements of 10β- to 9β-methyl compounds. However, it was considered that a totally synthetic approach commencing with precursors of 19-norsteroids would provide a more versatile path. Accordingly, the conjugate alkylation of 17β-hydroxy-des-A-oestr-9-en-5-one[3] (**1a**)† and the derived 4,5-seco-steroid (**1b**) was examined. There is ample precedent[4] for expecting steric control in the reaction, leading to B,C-*cis* products.

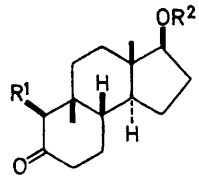
Treatment of (**1a**) with an excess of dimethyl copper lithium (DCL)[5] in diethyl ether at 0° afforded a single product (**2a**)‡ (100%). C.d. evidence ($\Delta\epsilon$ + 0·51 at 288 nm) supported[6] the assignment of 9β-stereochemistry and this was confirmed by n.m.r. examination of the derived[7] t-butyl ether (**2b**) under the influence of added tris-(1,1,1-2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium(III) [Eu(fod)$_3$].[8]

† We thank Dr. G. Nominé of Roussel-Uclaf for a gift of this material.

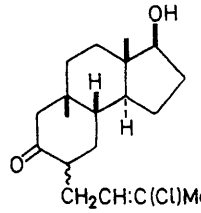
‡ Satisfactory analytical and spectral data were obtained for all new compounds.



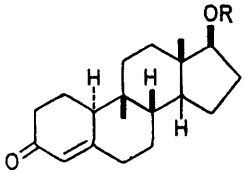
(1) a; R = H
b; R = $CH_2CH{:}C(Cl)Me$



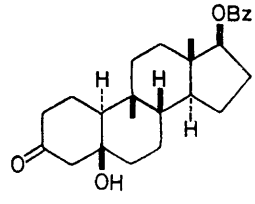
(2) a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = Bu^t$
c; $R^1 = CH_2CH{:}C(Cl)Me, R^2 = H$
d; $R^1 = CH_2CH{:}C(Cl)Me, R^2 = Bu^t$
e; $R^1 = CH_2CH{:}C(Cl)Me, R^2 = Bz$
f; $R^1 = (CH_2)_2Ac, R^2 = Bz$



(5)



(3) a; R = H
b; R = Bz



(4)

The 4,5-seco-steroid (**1b**) was prepared (59%) by treatment of the pyrrolidine dienamine derivative of (**1a**) with 1,3-dichlorobut-2-ene (DCB) and potassium iodide in dry dimethylformamide at 20°. The reaction of (**1b**) with DCL proceeded more sluggishly than with (**1a**), and afforded the 9β-methyl compound (**2c**) (41%) together with starting material (**1b**). The structural assignment was confirmed by $Eu(fod)_3$ n.m.r. spectroscopy of the derived t-butyl ether (**2d**).

The compound (**2c**) was converted into the 17β-benzoate (**2e**) which was treated with sulphuric acid in dichloromethane to give the diketone (**2f**) (63%). Annelation of (**2f**) with 4N-potassium hydroxide in ethanol at 20° afforded the products (**3a**) (47%), (**3b**) (24%), and (**4**) (5%). The configuration of (**3a**) was demonstrated by c.d. spectroscopy [$\Delta\epsilon$ + 2·2 (315 nm) and −8·7 (246 nm)], which clearly displayed the characteristic $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions associated with 9β,10α-stereochemistry.[9]

Attempted base-catalysed alkylation of the hydroxyketone (**2a**) with DCB failed to add the desired A-ring elements at the 10-position. It was expected[10,11] that enolization of the carbonyl function would proceed preferentially toward C-10, but after prolonged treatment of (**2a**) with sodium hydride and DCB in toluene under reflux, the only alkylated product, which was isolated in poor yield, was assigned the structure (**5**).

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[1] J. R. Bull, *J.C.S. Perkin I*, 1972, 627, and other papers in this Series.
[2] J. W. ApSimon, R. R. King, and J. J. Rosenfeld, *Canad. J. Chem.*, 1969, **47**, 1989; J. W. ApSimon and J. M. Rosenfeld, *Chem. Comm.*, 1970, 1271; O. E. Edwards and T. Sano, *Canad. J. Chem.*, 1969, **47**, 3489; D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Comm.*, 1969, 227.
[3] L. Velluz, G. Nominé, and J. Mathieu, *Angew. Chem.*, 1960, **72**, 725.
[4] J. A. Marshall, W. I. Fanta, and H. Roebke, *J. Org. Chem.*, 1966, **31**, 1016; J. A. Marshall and H. Roebke, *ibid.*, 1968, **33**, 840.
[5] H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31**, 3128.
[6] M. Legrand, and J. Mathieu, *Bull. Soc. chim. France*, 1961, 1679.
[7] H. C. Beyerman and G. J. Heiszwolf, *Rec. Trav. chim.*, 1965, **84**, 203.
[8] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.
[9] P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Francisco, 1965, ch. 9; E. Farkas, J. M. Owen, and D. J. O'Toole, *J. Org. Chem.*, 1969, **34**, 3022.
[10] L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Internat. Edn.*, 1965, **4**, 181.
[11] J. N. Gardner, B. A. Anderson, and E. P. Oliveto, *J. Org. Chem.*, 1969, **34**, 107, and references cited therein.