Synthesis of 25-Hydroxycholesterol from 3β-Hydroxyandrost-5-en-17-one. A Method for Stereospecific Construction of a Sterol Side-chain

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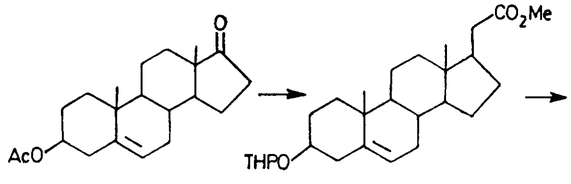
Summary The side-chain of 25-hydroxycholesterol was constructed stereospecifically on the androstane skeleton *via* addition of an ethyl acetate unit to C-17 and subsequent alkylation of the resulting ester C-20 with a C_5 unit; the remaining carbon atom (C-27) was added by a Grignard reaction.

RECENTLY there has been growing interest in developing efficient methods for the preparation of 25-hydroxycholesterol[1] required as a key intermediate in the synthesis of 1α,25-dihydroxy-vitamin D$_3$. We report the first stereospecific synthesis of this compound from an easily accessible androstane derivative.

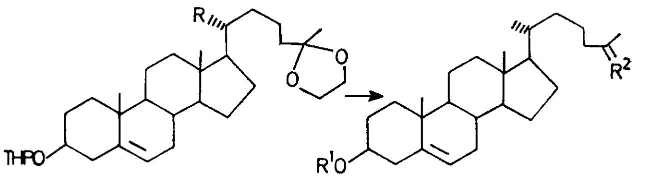
Our approach to the stereospecific construction of a side chain on the androstane skeleton was based on the assumption that C-20 alkylation of the ester (**2**) would give predominantly the needed product (**3a**) with the (20*R*) configuration. Also, the (20*S*) epimer, if formed, could be converted into the (20*R*) epimer upon equilibration (*cf.* refs. 2 and 3). The androstene acetate (**1**) was transformed into the ester (**2**)† by treatment with ethyl bromoacetate under Reformatsky conditions followed by dehydration, selective hydrogenation of the 17–20 double bond,[4] and exchange of the protecting groups.[5] The ester (**2**) was alkylated with the dioxolan[6] (**5**) by the procedure of Cregge *et al.*[7] A solution of (**2**) in tetrahydrofuran under argon at −78 °C was treated with di-isopropyl-lithium amide (3 equiv.) and the bromo-compound (**5**) (2 equiv.) in hexamethylphosphorotriamide was added stepwise to the resulting solution of the enolate anion. The product (**3a**) was isolated by extraction with ether; m.p. 159—165 °C (from MeOH); δ (100 MHz, CDCl$_3$) 5·36 br (s, 1H, 6-H), 4·72 br (s, 1H, THP-H), 3·92 (s, 4H, dioxolan-H), 3·87 (m, 1H, 3α-H), 3·65 (s, 3H, OMe), 3·50 (m, 2H, THP-H), 1·28 (s, 3H, 26-H), 1·00 (s, 3H, 19-H), and 0·70 (s, 3H, 18-H) (66% yield).

Compound (**3a**) was reduced with LiAlH$_4$ to the alcohol (**3b**) which was tosylated to give (**3c**). Hydrogenolysis of the tosyloxy-group in (**3c**) by LiAlH$_4$ gave the 21-unsubstituted compound (**4a**). Hydrolysis of (**4a**) furnished the alcohol (**4b**) which was acetylated (Ac$_2$O in pyridine) to (**4c**).

The homogeneity of the acetate (**4c**) was confirmed by t.l.c. and high-pressure liquid chromatography. Its physical properties (m.p. 138—139·5 °C, $[\alpha]_D$ −44°) were in good agreement with those of an authentic sample. The 21-Me signal in its ^{1}H n.m.r. spectrum was in a position which is typical of the (20*R*) epimer (δ 0·95, d, *J* 7 Hz); there was no signal at δ 0·86 corresponding to the (20*S*) epimer.

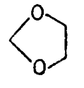


(1) (2)

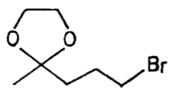


(3) (4)

a; R = CO$_2$Me
b; R = CH$_2$OH
c; R = CH$_2$OTs

a; R^1 = THP, R^2 =


b; R^1 = H, R^2 = O
c; R^1 = COMe, R^2 = O
d; R^1 = H, R^2 = CH(OH)Me



(5)

THP = tetrahydropyranyl
Ts = toluene-*p*-sulphonyl

Reaction of the acetoxy ketone (**4b**) with MeMgI gave the 25-hydroxycholesterol (**4d**), in 42% overall yield from (**1**) and 53% from (**2**).

We thank Dr. Uskokovic for an authentic sample of (**4c**).

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† Satisfactory elemental analyses were obtained for all new compounds.

[1] J. J. Partridge, S. Faber, and M. R. Uskoković, *Helv. Chim. Acta*, 1974, **57**, 764; T. A. Narwid, K. E. Cooney, and M. R. Uskoković, *ibid.*, p. 771; J. P. Moreau, D. J. Aberhart, and E. Caspi, *J. Org. Chem.*, 1974, **39**, 2018; A. Rotman and Y. Mazur, *J.C.S. Chem. Comm.*, 1974, 15.

[2] D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *Chem. Comm.*, 1970, 939; R. Hayatsu, *Pharm. Bull. (Japan)*, 1957, **5**, 452.

[3] A. Bowers, T. G. Halsall, and G. C. Sayer, *J. Chem. Soc.*, 1954, 3070, and references therein.

[4] T. Reichstein, H. Müller, C. Meystre, and M. Sutter, *Helv. Chim. Acta*, 1939, **22**, 741; Pl. A. Plattner and W. Schreck, *ibid.*, 1939, **22**, 1178; D. Magrath, D. S. Morris, V. Petrow, and R. Royer, *J. Chem. Soc.*, 1950, 2393.

[5] J. Wicha, and K. Bal, *Roczniki Chem.*, in the press.

[6] C. A. Grob and R. Mösch, *Helv. Chim. Acta*, 1959, **42**, 728.

[7] R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richmann, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 2425.