Stereospecific Synthesis of (*Z*)-20(22)-Didehydrocholesterol

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Summary Two efficient, stereospecific syntheses of (*Z*)-20(22)-didehydrocholesterol (**4b**), utilizing deoxygenation of 20,22-oxygenated cholesterols, are described.

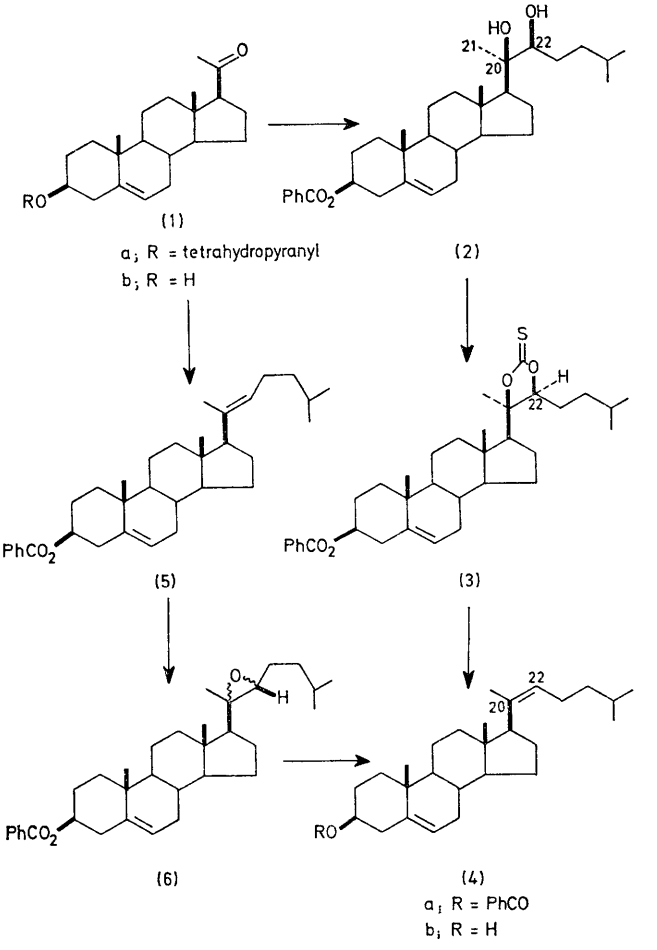
The biosynthetic conversion of 20,22-didehydrocholesterol to pregnenolone in bovine adrenal mitochondria, observed by Kraaipoel *et al.*,[1] has stimulated great interest in the

possible role of this compound in pregnenolone biosynthesis. The 20(22)-didehydrocholesterol employed in the studies of Kraaipoel *et al.* was obtained by acid catalysed dehydration of 20-hydroxycholesterol, and therefore was a stereochemical mixture of olefins. A rigorous approach to the biosynthetic problem requires stereochemically pure 20(22)-olefins.

Two stereospecific syntheses of (*Z*)-20(22)-didehydrocholesterol (**4b**) are described. The first gives the desired olefin in two steps from (20*R*,22*S*)-20,22-dihydroxycholesterol 3-benzoate in 83% yield; the second affords the desired olefin in 52% yield from pregnenolone (**1b**) in four steps.

The key step of the first method involves the stereospecific removal of the 20- and 22-oxygen atoms from (20*R*, 22*S*)-20,22-dihydroxycholesterol. Treatment of pregnenolone tetrahydropyranyl (THP) ether (**1a**) with 1·1 mol. equiv. of 2-lithio-2-isopentyl-1,3-dithian[2] in tetrahydrofuran (THF) at −25 °C for 7 h under argon gave the dithian adduct in 70% yield. Hydrolysis of this adduct with $HgCl_2$–$CaCO_3$ in MeCN–THF–water under reflux for 50 h gave (20*R*)-20-hydroxy-22-oxocholesterol in 51% yield. Reduction of (20*R*)-20-hydroxy-22-oxocholesterol 3-benzoate with sodium borohydride afforded predominantly the 20*R*,22*S*-diol (**2**) in 81% yield [3] Treatment of the diol (**2**) with an excess of *NN'*-thiocarbonyldi-imidazole (pyridine, 110 °C, 12 h) gave the thiocarbonate (**3**) in 91% yield; m.p. 238—240 °C; $\nu_{max}(CHCl_3)$ 1310 and 1275 cm^{-1} [–O–C(:S)–O–]; ^1H n.m.r.: $\delta(CDCl_3)$ 0·91 (3H, s, 18-H), 1·63 (3H, s, 21-H), and 4·28 (1H, dd, *J* 3·5 and 8·5 Hz, 22-H); ^{13}C n.m.r.: $\delta(CDCl_3)$ 12·7 (18-C), 93·7 (20-C), 94·0 (22-C), and 191·9 [–O–C(:S)–O–]. Refluxing the thiocarbonate (**3**) in excess of triethyl phosphite[4] for 12 h under argon stereospecifically produced the (*Z*)-20(22)-olefin (**4a**) in 90% yield; m.p. 128—129 °C; ^1H n.m.r.: $\delta(CDCl_3)$ 0·69 (3H, s, 18-H), 1·71 (3H, br. s, 21-H), and 5·28 (1H, m, 22-H); ^{13}C n.m.r.: $\delta(CDCl_3)$ 14·0 (18-C), 22·8 (21-C), 129·6 (22-C), and 134·1 (20-C). The *Z*-20(22)-stereochemistry of (**4a**) was validated by epoxidation of (**4a**) with 1·2 mol. equiv. of *m*-chloroperbenzoic acid (MCPBA) which gave (20*R*,22*S*)-20,22-epoxycholesterol, a known epoxide.[2] Hydrolysis of the 3-benzoate with KOH in MeOH–THF gave (*Z*)-20(22)-didehydrocholesterol (**4b**) in 95% yield; oil; $[\alpha]_D^{23}$ −102° ($CHCl_3$, *c* 0·321); M^+ at *m/e* 384.

The Wittig reaction on pregnenolone (**1b**) gave the *E*-isomer (**5**) in >80% yield;[5] isomerization of the (*E*)-20(22)-olefin to the *Z*-isomer was carried out following the method of Dervan and Shippey.[6] Oxidation of (*E*)-20(22)-dehydrocholesterol 3-benzoate (**5**) with 1·2 mol. equiv. of MCPBA in CH_2Cl_2 at 0 °C for 2 h gave a *ca.* 2:1 mixture of (20*S*,22*S*)- and (20*R*,22*R*)-20,22-epoxides in 71% yield. Conversion of the mixture of epoxides into the *Z*-olefin was affected stereospecifically with the trimethylsilyl anion.[6] Treatment of the epoxides (**6**) with excess of hexamethyldisilane and potassium methoxide in hexamethylphosphoramide at 100 °C for 2 h furnished (*Z*)-20(22)-didehydrocholesterol (**4b**) in 95% yield. This constitutes a convenient synthesis of (*Z*)-20(22)-didehydrocholesterol.



Recently, Burstein *et al.*[7] published results showing that neither (*E*)- nor (*Z*)-20(22)-didehydrocholesterol yields significant amounts of pregnenolone when incubated with their acetone-powder preparation of bovine adrenal cortex mitochondria.

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