

## 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 Kraaijoel *et al.*,<sup>1</sup> has stimulated great interest in the

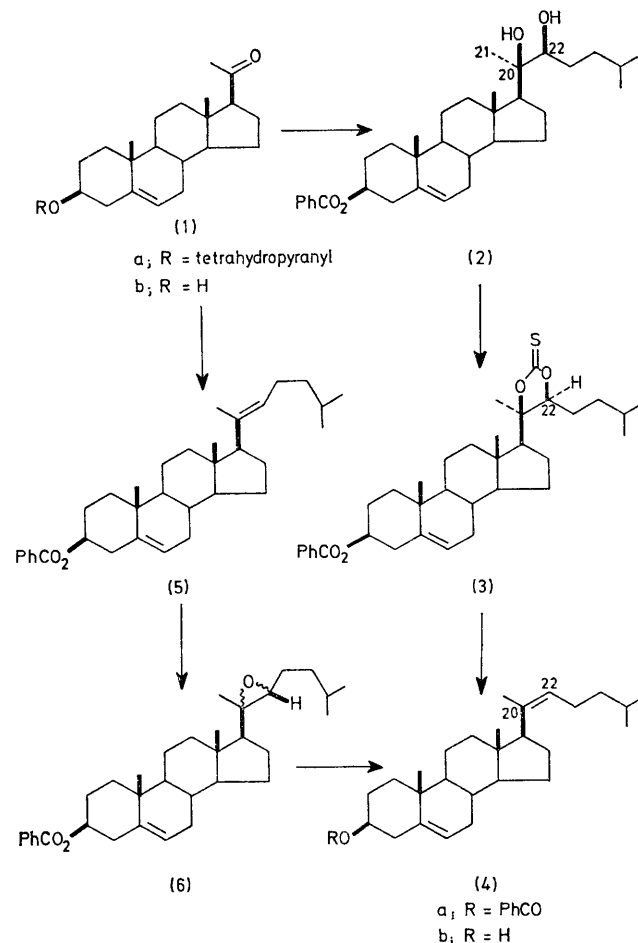
possible role of this compound in pregnenolone biosynthesis. The 20(22)-didehydrocholesterol employed in the studies of Kraaiipoel *et al.* was obtained by acid catalysed dehydration of 20-hydroxycholesterol, and therefore was a stereochemical mixture of olefins. A rigorous approach to the biosynthetic 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<sup>2</sup> in tetrahydrofuran (THF) at -25 °C for 7 h under argon gave the dithian adduct in 70% yield. Hydrolysis of this adduct with HgCl<sub>2</sub>-CaCO<sub>3</sub> 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.<sup>3</sup> 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;  $\nu_{\max}(\text{CHCl}_3)$  1310 and 1275 cm<sup>-1</sup> [-O-C(:S)-O-]; <sup>1</sup>H n.m.r.:  $\delta(\text{CDCl}_3)$  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); <sup>13</sup>C n.m.r.:  $\delta(\text{CDCl}_3)$  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<sup>4</sup> for 12 h under argon stereospecifically produced the (*Z*)-20(22)-olefin (**4a**) in 90% yield; m.p. 128–129 °C; <sup>1</sup>H n.m.r.:  $\delta(\text{CDCl}_3)$  0.69 (3H, s, 18-H), 1.71 (3H, br. s, 21-H), and 5.28 (1H, m, 22-H); <sup>13</sup>C n.m.r.:  $\delta(\text{CDCl}_3)$  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.<sup>2</sup> Hydrolysis of the 3-benzoate with KOH in MeOH-THF gave (*Z*)-20(22)-didehydrocholesterol (**4b**) in 95% yield; oil;  $[\alpha]_D^{25}$  -102° (CHCl<sub>3</sub>, *c* 0.321); *M*<sup>+</sup> at *m/e* 384.

The Wittig reaction on pregnenolone (**1b**) gave the *E*-isomer (**5**) in >80% yield;<sup>5</sup> isomerization of the (*E*)-20(22)-olefin to the *Z*-isomer was carried out following the method of Dervan and Shippey.<sup>6</sup> Oxidation of (*E*)-20(22)-didehydrocholesterol 3-benzoate (**5**) with 1.2 mol. equiv. of MCPBA in CH<sub>2</sub>Cl<sub>2</sub> 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.<sup>6</sup> 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.*<sup>7</sup> 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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