Stereoselective Introduction of Hydroxy-groups into the 24-, 25-, and 26-Positions of the Cholesterol Side Chain

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Summary Asymmetric reduction of steroidal 25-en-24-ones by a complex of $LiAlH_4$ and 2,2′-dihydroxy-1,1′-binaphthyl led to a steroselective introduction of hydroxy-groups into the 24-, 25-, and 26-positions of the cholesterol side chain.

THE recent discovery of various biologically active steroids, such as vitamin D metabolites,[1] insect-moulting hormones (ecdysteroids),[2] plant-growth promoters (brassinolide),[3] and bile alcohols,[4] has led to interest in the stereo-controlled preparation of steroids with hydroxy-substituted side chains. We have already reported methods for the stereoselective introduction of hydroxy-groups at C-22 and C-23.[5] We now report a method for the stereoselective construction of steroidal side chains having hydroxy-groups at C-24, C-25, and C-26.[6]

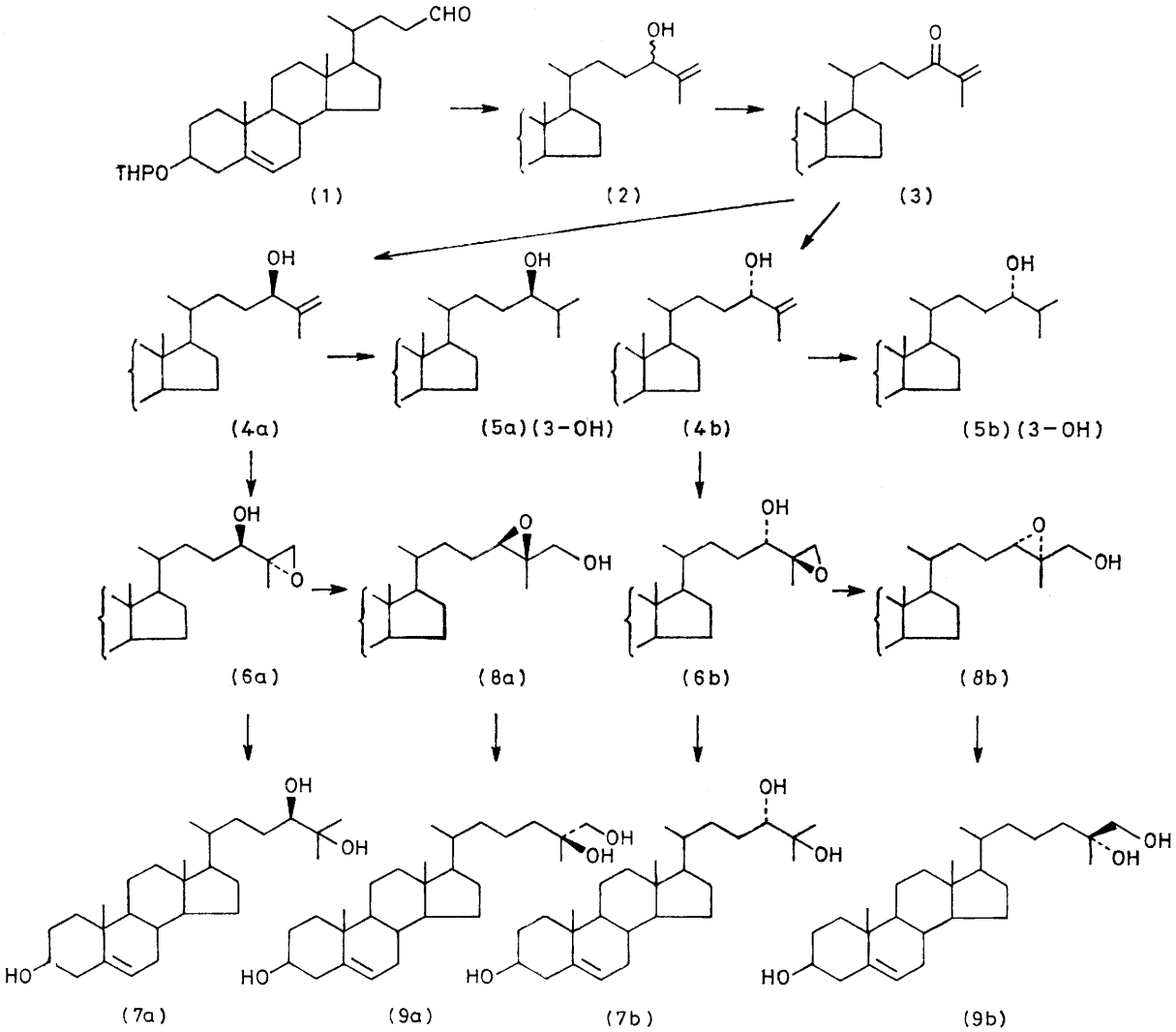
The 24-aldehyde 3-THP (tetrahydropyran-2-yl) ether (**1**),[7] prepared from the cholenic acid, was treated with propenylmagnesium bromide to give 3β,24-dihydroxycholesta-5,25-diene 3-THP ether (**2**), m.p. 120—126 °C, which was oxidized to the 24-oxo-compound (**3**)† (90% yield), m.p. 136—138 °C, by treatment with pyridinium dichromate in methylene chloride–dimethylformamide[8] for 3 h at room temperature. After several attempts at asymmetric reduction of the carbonyl group, we finally achieved a highly stereoselective reduction by use of a

† Satisfactory elemental analyses and spectral data were obtained for all new compounds: *e.g.*, (**6a**): δ ($CDCl_3$) 0·68 (3H, s, 18-H), 0·92 (3H, d, *J* 6 Hz, 21-H), 1·00 (3H, s, 19-H), 1·34 (3H, s, 27-H), 2·58, and 2·88 (2H, d, *J* 6 Hz, 26-H); (**6b**): δ 1·35 (3H, s, 27-H), 2·60, and 2·89 (2H, d, *J* 6 Hz, 26-H); (**8a**): δ 0·68 (3H, s, 18-H), 0·93 (3H, d, *J* 6 Hz, 21-H), 1·00 (3H, s, 19-H), 1·26 (3H, s, 27-H), and 3·00 (1H, m, 24-H); (**8b**): δ 1·29 (3H, s, 27-H) and 3·00 (1H, m, 24-H). Optical rotations were measured in $CHCl_3$ solution except those for (**9a**) and (**9b**).

complex of $LiAlH_4$, ethanol, and 2,2′-dihydroxy-1,1′-binaphthyl which was developed by Noyori.[9] When the ketone (**3**) was reduced by the complex (3 equiv.) of (*R*)-(+)-dihydroxybinaphthyl in tetrahydrofuran (THF) at −90 °C for 20 h, a mixture of 24-hydroxy-compounds (**4a**) and (**4b**), m.p. 118—120 °C, was obtained in 75% yield. Since (**4a**) and (**4b**) could not be separated sufficiently for determination of the optical yield of the reduction, the product was converted into the dibenzoate derivative and reduced with Pd/C in ethanol–THF. Analysis by h.p.l.c. using a Sorbax SIL column and hexane–methylene chloride (20 : 1) as eluant[10] indicated that the major product (95%) was identical with the 3,24-dibenzoate of (24*R*)-24-hydroxycholesterol (**5a**), contaminated with the (24*S*)-isomer [3,24-dibenzoate of (**5b**)] (5%) as minor product. Recrystallization of the asymmetric reduction product from acetone gave pure (24*R*)-3β,24-dihydroxycholesta-5,25-diene 3-THP ether (**4a**), m.p. 130—132 °C, $[\alpha]_D^{25}$ −19° (*c* 1). When (*S*)-(−)-dihydroxybinaphthyl was employed, compound (**3**) was reduced to the (24*S*)-24-hydroxy-25-ene (**4b**) in 95% optical yield, from which the pure (24*S*)-compound (**4b**), m.p. 135—137 °C, $[\alpha]_D^{25}$ −27·8° (*c* 1) was obtained.

Epoxidation of the geminally disubstituted olefin (**4a**) with t-butyl hydroperoxide catalysed by VO(acetylacetonate)$_2$[11] in dry benzene at room temperature gave a single product, the 25,26-epoxy-24-ol (**6a**), in 70% yield, m.p. 145—147 °C, $[\alpha]_D^{25}$ −28° (*c* 1), which should have the (24*R*,25*S*)-configuration according to the mechanism proposed by Sharpless.[12] By the same procedure the (24*S*)-24-hydroxy-25-ene (**4b**) gave the (24*S*,25*R*)-25,26-epoxy-24-ol (**6b**), m.p. 148—150 °C, $[\alpha]_D^{25}$ −26·8° (*c* 1). Treatment of the epoxy alcohol (**6a**) with $LiAlH_4$ in refluxing THF gave (24*R*)-24,25-dihydroxycholesterol (**7a**)[13] 3-THP ether, m.p. 159—161 °C, $[\alpha]_D^{25}$ −21·1° (*c* 0·18), quantitatively. The stereoisomer (**6b**) was also reduced to the (24*S*)-stereoisomer (**7b**), m.p. 160—162 °C, $[\alpha]_D^{25}$ −50·0° (*c* 0·2).

Treatment of the epoxide (**6a**) with potassium carbonate in refluxing propan-2-ol for 2 h afforded the 24,25-epoxy-26-ol (**8a**) in 85% yield, m.p. 140·5—142 °C, $[\alpha]_D^{25}$ −114·6° (*c* 0·67), which was reduced by $LiAlH_4$ to provide (25*S*)-



25,26-dihydroxycholesterol (**9a**) 3-THP ether, m.p. 161—163 °C. Subsequent acidic hydrolysis gave (**9a**), m.p. 192—193 °C, $[\alpha]_D^{25}$ −32·9° (*c* 0·17, MeOH). By the same procedure, (**6b**) was transformed into (**8b**), m.p. 147—149 °C, $[\alpha]_D^{25}$ −195·6° (*c* 0·45), which was transformed into (25*R*)-25,26-dihydroxycholesterol (**9b**) 3-THP ether, m.p. 138—140 °C, and (**9b**), m.p. 190—192 °C, $[\alpha]_D^{25}$ −4·8° (*c* 0·17, MeOH). Thus, an epimeric pair of 25,26-dihydroxycholesterols could be prepared by an unambiguous procedure.[14]

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[1] H. F. DeLuca and H. K. Shnoes, *Annu. Rev. Biochem.*, 1976, **45**, 631.
[2] K. Nakanishi, 'The Chemistry of Natural Products 7,' Butterworth, London, 1971, p. 167.
[3] M. D. Grove, G. F. Spencer, W. K. Rohwedder, N. Mandava, J. F. Worley, J. D. Warthen Jr., G. L. Steffens, J. L. Flippen-Andersen, and J. C. Cook, Jr., *Nature* (*London*), 1979, **281**, 216.
[4] M. Murata, T. Kuramoto, and T. Hoshita, *Steroids*, 1978, **31**, 319; M. Yasuhara, T. Kuramoto, and T. Hoshita, *ibid.*, p. **333**; B. Dayal, G. S. Tint, S. Shefer, and G. Salen, *ibid.*, 1979, **33**, 327.
[5] (a) M. Ishiguro, H. Saito, A. Sakamoto, and N. Ikekawa, *Chem. Pharm. Bull.*, 1978, **26**, 3715; (b) N. Ikekawa, Y. Hirano, M. Ishiguro, J. Oshida, T. Eguchi, and S. Miyasaka, *ibid.*, 1980, **28**, 2852.
[6] A. stereoselective preparation of 24,25-dihydroxycholesterol was reported by J. J. Partridge, V. Toome, and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1976, **98**, 3739; ref. 5(a) gives a method for inversion of the configuration of hydroxy-groups on the side chain.
[7] N. Koizumi, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 1978, 2899.
[8] E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
[9] R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem. Soc.*, 1979, **101**, 3129; R. Noyori, I. Tomino, and M. Nishizawa, *ibid.*, p. 5843.
[10] N. Koizumi, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 1975, 2203.
[11] K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, 1973, **95**, 6136.
[12] B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless, *Tetrahedron Lett.*, 1979, 4733.
[13] M. Seki, N. Koizumi, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 1975, 15.
[14] The physical data of the corresponding 3,26-diacetates of both isomers (**9a**) and (**9b**) (270 MHz n.m.r. spectra and m.p.) were opposite to those previously reported;[7] the previous assignment of the configuration at C-25 should be reversed, and we have proved this using [*carbonyl*-^{18}O]-labelled 24,25-epoxy-26-ol 26-benzoate (details will be reported elsewhere). Recently, the French group also revised their previous assignment: M. Cesario, J. Guilhem, C. Pascard, and J. Redel, *Tetrahedron Lett.*, 1980, 1588; *cf.* 1978, 1097.