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

By MASAJI ISHIGURO, NAOYUKI KOIZUMI, MITSUHIRO YASUDA, and NOBUO IKEKAWA*

(*Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology, Nagatsuta Midori-ku, Yokohama* 227, *Japan*)

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]

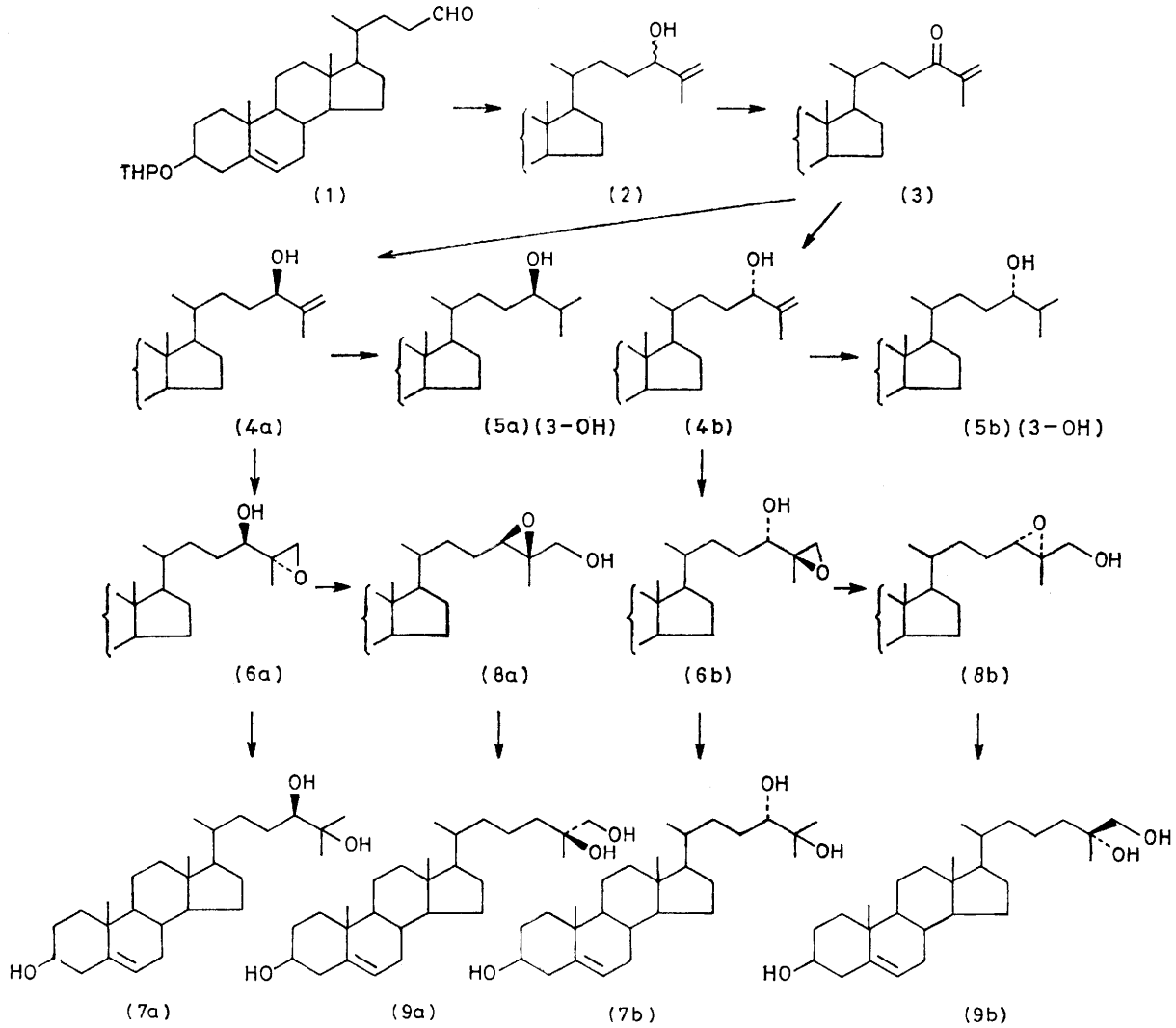
The 24-aldehyde 3-THP (tetrahydropyran-2-yl) ether (**1**),[7] prepared from the cholenic acid, was treated with propenylmagnesium bromide to give 3β,24-dihydroxycholesta-5,25-diene 3-THP ether (**2**), m.p. 120—126 °C, which was oxidized to the 24-oxo-compound (**3**)† (90% yield), m.p. 136—138 °C, 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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