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Synthesis of Active Forms of Vitamin D. I. A Facile Synthesis of 25-Hydroxycholesterol[1)]

Recently, several metabolites of vitamin D_3 (I—IV)[2-5)] have been identified and they are found to be responsible for the biological activity of vitamin D. A common characteristic feature of these metabolites is the C–25 hydroxy group. Thus, the introduction of 25-hydroxy group into an appropriate substrate would be a key reaction in the synthesis of these compounds. The reported synthesis of 25-hydroxycholecalciferol (I)[6-8)] have started from 26-nor-24-oxo-cholesterol, a degradation product of cholesterol. We have found that desmosterol acetate (V), which is now readily derived by our method[9)] from fucosterol (VI), a major sterol in brown algae,[10)] has the convenient structure for introducing the C–25 hydroxy group by several ways, as we describe in this paper.

Desmosterol acetate (V) (0.8 g) was stirred in isopropanol (100 ml) under sun-shine in the presence of rosebengal (50 mg) as a sensitizer, for 3 hr. The crude product was directly reduced with an excess of sodium borohydride in methanol to give 3,25-dihydroxycholest-5,23-diene 3-acetate (VII) (35%), mp 142—144°, NMR, δ (ppm), 0.68 (3H, s, 18-CH_3), 0.92 (3H, d, J=5.6 Hz, 21-CH_3), 1.0 (3H, s, 19-CH_3), 1.28 (6H, s, 26, 27-CH_3), 2.03 (3H, s, acetyl), 4.58 (1H, m, 3-H), 5.38 (1H, m, 6-H), and 5.60 (2H, s, 23, 24-H), and 3,24-dihydroxycholest-5,25-diene 3-acetate (VIII) (25%), mp 129°, NMR, δ (ppm), 0.67 (3H, s, 18-CH_3), 0.90 (3H, d, J=5.7 Hz, 21-CH_3), 1.0 (3H, s, 19-CH_3), 1.68 (3H, m, 26-CH_3), 2.02 (3H, s, acetyl), 3.93 (1H, t, J=5.0 Hz, 24-H), 4.81 (2H, m, 26-exomethylene), and 5.33 (1H, m, 6-H). Catalytic hydrogenation of VII over 10% Pd-charcoal in ethanol afforded 3,25-dihydroxycholest-5-ene 3-acetate (IX)[7)] (60%), mp 136—137°, NMR, δ (ppm), 0.68 (3H, s, 18-CH_3), 0.94 (3H, d, J= 5 Hz, 21-CH_3), 1.19 (6H, s, 26,27-CH_3), 2.0 (3H, s, acetyl), 4.58 (1H, m, 6-H) and 5.33 (1H, m, 3-H), with a concomitant formation of cholesterol acetate by a hydrogenolysis.

The other route to IX from V is a selective epoxidation on the 24,25-double bond, followed by treatment with $LiAlH_4$. Desmosterol acetate (V) was treated with 1.1 mole equivalent of *m*-chloroperbenzoic acid in $CHCl_3$ under ice-cooling, to give after separation by silica gel column chromatography, the 24,25-monoepoxide (X) (60%), mp 101—102°, NMR δ (ppm), 0.70 (3H, s, 18-CH_3), 1.02 (6H, 19 and 21-CH_3), 1.28 and 1.30 (6H, 26,27-CH_3), 2.02 (3H, s, acetyl), 4.7 (1H, m, 3α-H) and 5.45 (1H, m, 6-H). When the crude epoxidation products were directly subjected to reduction with $LiAlH_4$, followed by acetylation, IX was isolated in over all yield of 50%. There was no indication for the production of the isomer, 24-hydroxycholesterol diacetate, suggesting a severe regiospecificity of the epoxide opening reaction.

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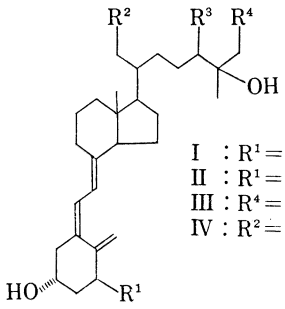
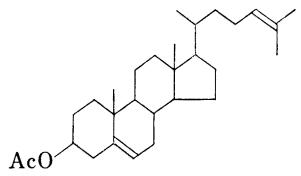


I : $R^1=R^2=R^3=R^4=H$ 25-hydroxycholecalciferol
II : $R^1=OH$, $R^2=R^3=R^4=H$ 1,25-dihydroxycholecalciferol
III : $R^4=OH$, $R^1=R^2=R^3=H$ 25,26-dihydroxycholecalciferol
IV : $R^2=OH$, $R^1=R^3=R^4=H$ 21,25-dihydroxycholecalciferol



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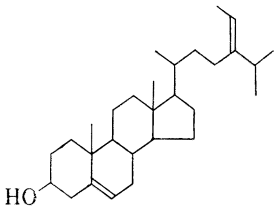

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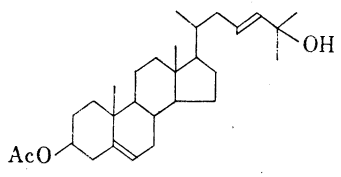

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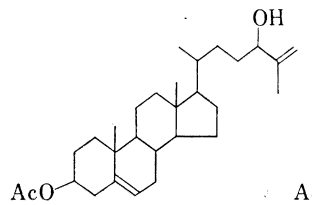

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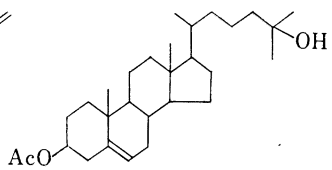
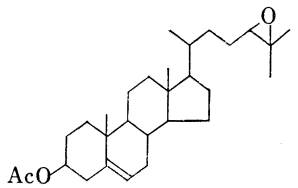


IX



X

Chart 1

The third and most convenient synthesis of IX rest on oxymercuration-demercuration reaction.[11] Desmosterol acetate (V) (50 mg) dissolved in tetrahydrofuran (0.2 ml) was added dropwise to a mixture of $Hg(OAc)_2$ (52 mg), H_2O (0.1 ml) and tetrahydrofuran (0.1 ml). The reaction mixture was stirred for 4 hr under cooling with an ice bath and further 5 hr at room temperature. Then, 50 μl of 3M NaOH was added, followed by 1 ml of $NaBH_4$ (210 mg) solution in 3M NaOH. Purification of the product by column chromatography on silica gel gave IX in 85% yield. It will be remarkable the good yield and the high regioselectivity due to the preferencial oxymercuration on 24,25-double bond over 5,6-double bond.

As the introduction of the 5,7-diene system and its conversion to vitamin D series by UV-irradiation are well known procedures,[12] the present work would pave a simple route to the biological active metabolites of vitamin D.

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