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FACILE, STEREOSELECTIVE SYNTHESIS OF (24R)-24,25-DIHYDROXYVITAMIN D_3 USING D-GLYCERIC ACID AS A CHIRAL SYNTHON

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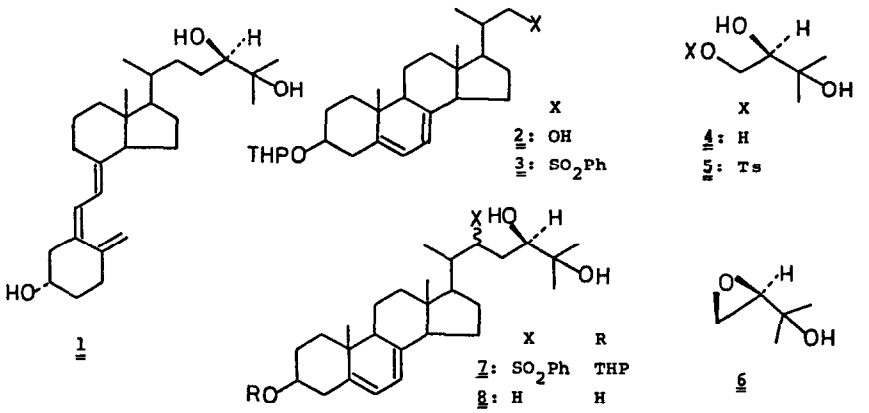
Summary: A facile, stereoselective, and efficient synthesis of (24R)-24,25-dihydroxyvitamin D_3, using D-glyceric acid as a chiral synthon to construct the side chain and ergosterol as a precursor of the secosteroid skeleton, is described.

Since its discovery[1] and structural elucidation[2], (24R)-24,25-dihydroxyvitamin D_3 (1) has received increasing attention and recently the specialized activities of 1 in the function of vitamin D_3 have been suggested.[3] However, the biological importance of the metabolite has been debatable[4] and the role of 24-hydroxylated vitamin D has still been remained to be clarified.[5]

Although several syntheses of 1 have been reported[6], they involve resolution of diastereomers in their processes and a completely stereoselective synthesis has not been known. We now wish to report the first stereoselective synthesis of 1 using chiral template.

In our synthesis, ergosterol was used as a precursor of the secosteroid skeleton and its C(23)-C(28) part of the side chain was cleaved off for the purpose of the later introduction of the side chain with desired structure. The bisnorcholadiene derivative (2) [mp 151-152°] was obtained from ergosterol by modifying the Barton's method.[7] In order to activate the 22-position for the subsequent C-C bond forming reaction, the alcohol (2) was converted to the phenylsulphone (3) [mp 175-177°; IR(KBr) 1135, 1295 cm^{-1}] in three steps [(a) TsCl, pyridine; (b) LiBr, $LiCO_3$ in DMF, 75°; (c) $PhSO_2Na$ in DMF, 75°] in 61% overall yield. As a precursor of the C(23)-C(27) part of the target molecule having the desired stereochemistry, D-glyceric acid was chosen and its methyl ester was transformed into (R)-3-methylbutane-1,2,3-triol-1-tosylate (5) [mp 103-104°][8] in four steps [(a) PPTS in dimethoxypropane; (b) MeMgBr in THF; (c) PPTS in 70% aq. MeOH; (d) TsCl, pyridine] in 54% overall yield. The phenylsulphone (3) was reacted with the epoxide (6), prepared *in situ* from the tosylate (5) under the reaction conditions, in the presence of n-BuLi [THF, -20°] to give the 22ξ-phenylsulphonyl derivative (7) [major isomer; MS: m/e 640(M^+); IR($CHCl_3$) 1135, 1300 cm^{-1} UV: λ_{max}(EtOH) 271, 282, 294 nm; ^1H NMR: δ($CDCl_3$) 0.38(3H,s), 0.89(3H,s), 1.02 (3H,d,J=5Hz), 1.19(3H,s), 1.25(3H,s), 4.72(1H,m), 5.32(1H,d,J=5Hz), 5.52(1H,d,J=5Hz), 7.4-8.0(5H,m)] in 86% yield, which on reductive desulphonylation[5% Na-Hg, Na_2HPO_4 in MeOH, r.t] followed by deprotection of the hydroxyl group[PPTS in EtOH]

afforded the desired provitamin D (8) [mp 216-218°; UV: λ_{max}(EtOH) 272, 282, 294 nm][6,9] in 75% yield. The provitamin D(8) was transformed into the vitamin D (1) by the usual method, irradiation by high pressure mercury lamp through Vycor filter followed by thermal isomerization. The UV, MS, and ^{1}H NMR spectra of 1 were in good agreement with those reported.[6,10]



Further studies on the stereoselective synthesis of the metabolites of vitamin D using chiral template are in progress.

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9) The UV, MS, and ^{1}H NMR spectra[δ(CDCl3) 0.64(3H,s), 0.94(3H,s), 1.15(3H,s), 1.19 (3H,s), 3.3-3.8(2H,m), 5.38(1H,d,J=5Hz), 5.56(1H,d,J=5Hz)] were consistent with those reported except for its MP being higher than that described: H-Y Lam, H. K. Schnoes, H. F. DeLuca, and T. C. Chen, Biochemistry, 12, 4851(1973).
10) 1: m/e 416, 136, 118; λ_{max}(EtOH) 265 nm; δ(CDCl3) 0.55(3H,s), 0.93(3H,d,J=4Hz) 1.17(3H,s), 1.22(3H,s), 3.33(1H,m), 3.95(1H,m), 4.85(1H,bs), 5.07(1H,bs), 6.08(1H,d,J=11Hz), 6.25(1H,d,J=11Hz). The biological activity of 1 was identical with that of the authentic (24R)-24,25-(OH)$_2$-D$_3$ in the competitive protein binding assay: K. Kano, J. Hosoki, J. Yata, H. Yoshida, E. Abe, and T. Suda, Vitamins(Japan), 53, 11 (1979).

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