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A SYNTHESIS OF 25-HYDROXYCHOLESTEROL

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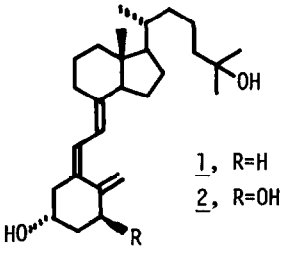
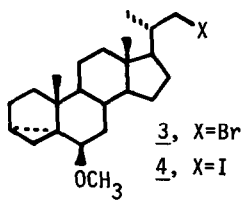
Recent synthetic studies[1] have shown the importance of 25-hydroxycholesterol as an intermediate to the Vitamin D_3 metabolites 25-hydroxycholecalciferol (1) and 1,25-dihydroxycholecalciferol (2). We report here a simple approach to this valuable material.

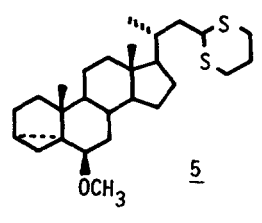


1, R=H
2, R=OH

Reaction of 2-lithiodithian[2] in dry tetrahydrofuran at 0° with the bromide (3)[3] for 16 hrs. or with the iodide (4)[4] for 3 hrs. leads in yields of about 80% to the dithioacetal (5), m.p. (ex-ethanol) 117-118°. NMR ($CDCl_3$): 0.30-0.67m; 0.73s(3H); 0.82d, J=6Hz,(3H); 0.85s(3H); 2.66-3.00m; 3.30s(3H); 3.94-4.08m(1H). R_f: (5% ethyl acetate/hexane) 0.45. Isolation of the intermediate dithioacetal (5) is, however, unnecessary; it may be treated *in situ* with n-butyl lithium (one molar equivalent) at -20° for 3 hrs. to convert it to its conjugate anion. After this period condensation of the anion with 2-methylpropan-1,2-oxide[5] overnight at 0° leads to the alcohol (6) in 70% yield, m.p. (ex cyclohexane) 152.5-154°. NMR ($CDCl_3$): 0.30-0.67m; 0.82s(3H); 1.03s(3H); 1.20d, J=6Hz, J=Hz(3H); 1.35s(6H); 2.30s(2H); 2.50-3.16m; 3.33s(3H). R_f: (5% ethyl acetate/hexane) 0.10.



3, X=Br
4, X=I



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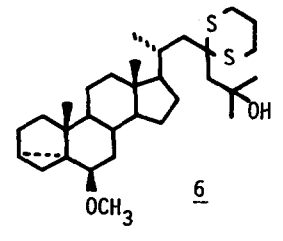

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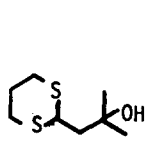
Condensation of 2-lithiodithian with 2-methylpropan-1,2-oxide gave the alcohol (7) b.p. 104-110° at ca. 0.5 mm. NMR ($CDCl_3$): δ 130s(6H); 1.95d, J=6.5Hz(2H); 1.95m(2H); 2.42s(1H) exchanged with D_2O; 2.92m(4H); 4.22t, J=6.5(1H). However, attempts to condense the conjugate

dianion of alcohol (7) with either the bromide (3)or the iodide (4) failed. This lack of reactivity may be attributed to steric hindrance or perhaps to the stabilization and therefore the deactivation of the carbanion by virtue of lithium bridging as depicted in (8).



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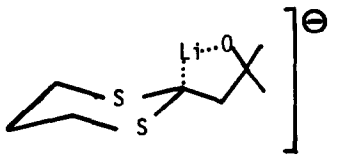

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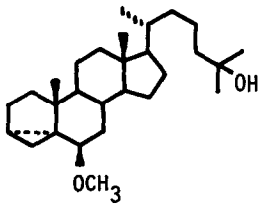
Efforts to desulfurize the dithioacetal (6) with Raney nickel did not lead to the desired compound (9). The dithioacetal moiety was indeed removed but the i-ether residue was also hydrogenolyzed, presumably to (11).[6] This lack of selectivity was circumvented by the use of Mukaiyama's reagent[7], lithium aluminum hydride and titanium tetrachloride. Boiling the alcohol (6) with this reagent in tetrahydrofuran for 15 minutes led to the desired 3d,5α-cyclo-6β-methoxy-25-hydroxycholestane (9).



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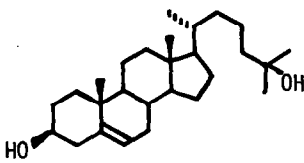

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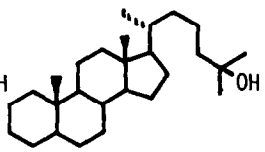

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Boiling of the i-ether (9) in acetic acid for 15 minutes led in high yield to 25-hydroxycholesteryl acetate, easily hydrolyzed to 25-hydroxycholesterol (10)[1].

References

1. For other syntheses of 25-hydroxycholesterol see for example: a) J.W.Blunt and H.F.DeLuca, *Biochem.* 8,671(1969); b) S.J.Halkes and N.P.VanVliet, *Rec. Trav. Chim.* 88,1080(1969); c) J.A.Campbell, D.M.Squires, and J.C.Babcock, *Steroids*,13,567(1969); M.Morisaki, J.Rubiolightbourn and N.I.Kekawa, *Chem. Pharm. Bull.* 21,457(1973); e) A.Rotman and Y.Mazur, *J. Chem. Soc. Chem. Commun.* 1974,15; f) J.J.Partridge, S.Faber and M.R.Uskokovic, *Helvetica* 57,764 (1974); and g) T.A.Narwid, K.E.Cooney and M.R.Uskokovic, *ibid*, 771.
2. E.J.Corey and D.Seebach, *Angew. Chem. Internat. Ed.* 4,1075(1965).
3. See Reference 1f.
4. See Reference 1f and S.K.Dasgupta, D.R.Crump and M.Gut, *J. Org. Chem.* 39,1658.
5. D.J.Pasto and C.C.Cumbo, *J. Org. Chem.* 30,1271(1965).
6. This was not proved rigorously, but NMR of the crude product showed no methoxyl or cyclopropyl signals.
7. T.Mukaiyama, M.Hayashi and K.Narasaka, *Chemistry Letters*, 291(1973).