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# A SYNTHESIS OF 25-HYDROXYCHOLESTEROL

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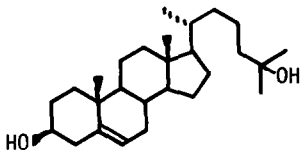
The intense interest in the Vitamin $D_3$ metabolites has engendered the need for syntheses of 25-hydroxycholesterol (1). We report here one of a number[1] evaluated by us.

One of our approaches[1b], as well as one reported by the Roche group[2], proceeded via the bromide (2) or iodide (3), derived in turn from the alcohol (4) and the aldehyde (5). Although each step in the preparation of (2) or (3) is efficient, it appeared to us that an unnecessarily large number of steps is involved.

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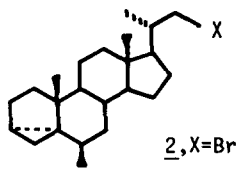
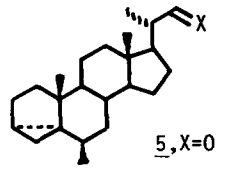



2, X=Br
3, X=I
4, X=OH

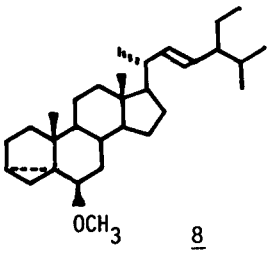



5, X=O
6, X=$CBr_2$
7, X=$CCl_2$

Accordingly, the aldehyde (5) derived from the ozonolysis of the 3α,5α-cyclo-6β-methoxy derivative of stigmasterol (8) was allowed to react with dibromomethylenetriphenylphosphorane, $\phi_3P{=}CBr_2$, derived from triphenylphosphine and carbon tetrabromide.[3] This led in high yield to the 20R-dibromovinyl pregnane (6) m.p. (ex acetone) 85-89°. NMR ($CDCl_3$) δ 0.30-0.63m; 0.77s(3H); 1.03s(3H); 1.03d, J=7Hz(3H); 2.77 broad triplet, J=ca 2Hz(1H); 3.32s(3H) 6.18d, J=10 Hz(1H). No racemization of the chiral center at C-20 was observed.[4]

Although this reaction proceeded well, the separation of triphenylphosphine oxide from the product was tedious. In addition, the combination of triphenylphosphine and carbon tetrabromide was unattractively and, in the outcome, unnecessarily expensive. We found that a combination of hexamethylphosphoroustriamide and bromotrichloromethane[5] led to the dichlorovinyl compound (7) in 85% yield, with the advantages of cheapness and ease of workup. The dichloroölefin (7) crystallized from acetone/methanol m.p. 135-137°. NMR ($CDCl_3$) δ 0.30-0.63; 0.77s(3H); 1.03s(3H); 1.03d, J=7 Hz(3H); 2.77 broad triplet, J=ca 2Hz(1H); 3.32(3H); 5.67d, J=10 Hz(1H).

The dihalovinylpregnane (6) or (7) was now treated with two equivalents of n-butyl lithium at -68° to produce the lithium acetylide (9), from which the ethynylpregnane (10)was obtained by hydrolysis.[6]

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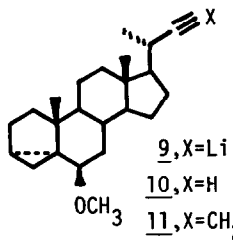
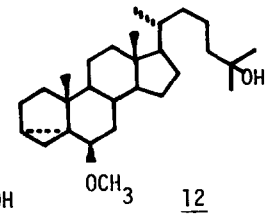



9, X=Li
10, X=H
11, X=$CH_2 \cdot C(CH_3)_2OH$

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Alternatively, and more efficiently, the acetylide (9) was treated directly with dry 2-methyl-propan-1,2-oxide after the addition of hexamethylphosphorictriamide (HMPA) (ca 10% of the reaction volume). Reaction in the absence of HMPA was very sluggish.[7] In the presence of HMPA reaction took place overnight at room temperature, or at 60° under pressure within 3 hours[8], to give (11) in yields of ca 70%.

The acetylenic alcohol (11) was obtained pure by chromatography over deactivated alumina[9], although it has resisted all attempts to crystallize. NMR ($CDCl_3$) δ 0.30-0.63; 0.77s(3H); 1.03d(3H);1.20d, J=7 Hz(3H); 1.27s(6H); 2.33bd, J=ca 2(2H); 2.78bt, J=ca 2(1H); 3.33s(3H).

Hydrogenation of the triple bond over platinum oxide at 50 psi in ethyl acetate yielded, essentially quantitatively, the desired alcohol (12), converted as described[1b,2], to 25-hydroxycholesterol (1).

## References


1. a) J.A.Campbell, D.M.Squires and J.C. Babcock, *Steroids* 13, 567 (1969); b) W.G.Salmond and K.D.Maisto, *Tetrahedron Letters*, in press.
2. J.J.Partridge, S.Faber and M.R.Uskokovic, *Helvetica* 57, 764 (1974).
3. F.Ramirez, N.B.Desai and N.McKelvie, *J.A.C.S.* 84, 1745 (1962); E.J.Corey and P.L.Fuchs, *Tetrahedron Letters*, 3769 (1972).
4. The 20R-aldehyde was prepared by epimerization of the 20S-aldehyde (5) in aqueous ethanolic alkali. The corresponding 20S-dibromovinylpregnane was easily distinguished from (6) by NMR.
5. W.G.Salmond, accompanying paper.
6. The acetylene (10) crystallized from ethanol m.p. 74-76°. NMR ($CDCl_3$): δ 0.3-0.63; 0.77s(3H); 1.03s(3H); 1.20d, J=7 Hz(3H); 1.27s(6H); 2.33 bd, J=ca 2(2H); 2.78 bt, J=ca 2(1H); 3.33s(3H).
7. For difficulties experienced in the ring opening of epoxides with acetylides see for example: H.H.Inhoffen, K.Weissermal, G.Quinkert, and D.Bartling, *Berichte* 89, 853 (1956); R.T.Arnold and G.Smolinsky, *J.A.C.S.* 82, 4918 (1960); J.Fried, S.Heim, S.J.Etheredge, P.Sunder-Plassman, T.S.Santhanakrishnan, J.Himizu, and C.H.Lin, *Chemical Communications*, 634 (1968).
8. Care must be taken to ensure complete dryness, otherwise the acetylene (10) is obtained as a by-product.
9. We have found that i-ethers are susceptible to highly activated absorbents. The use of alumina or silica gel deactivated with 10% water has given good results in our hands.