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# TOTAL SYNTHESIS OF 1α-HYDROXY-VITAMIN $D_3$

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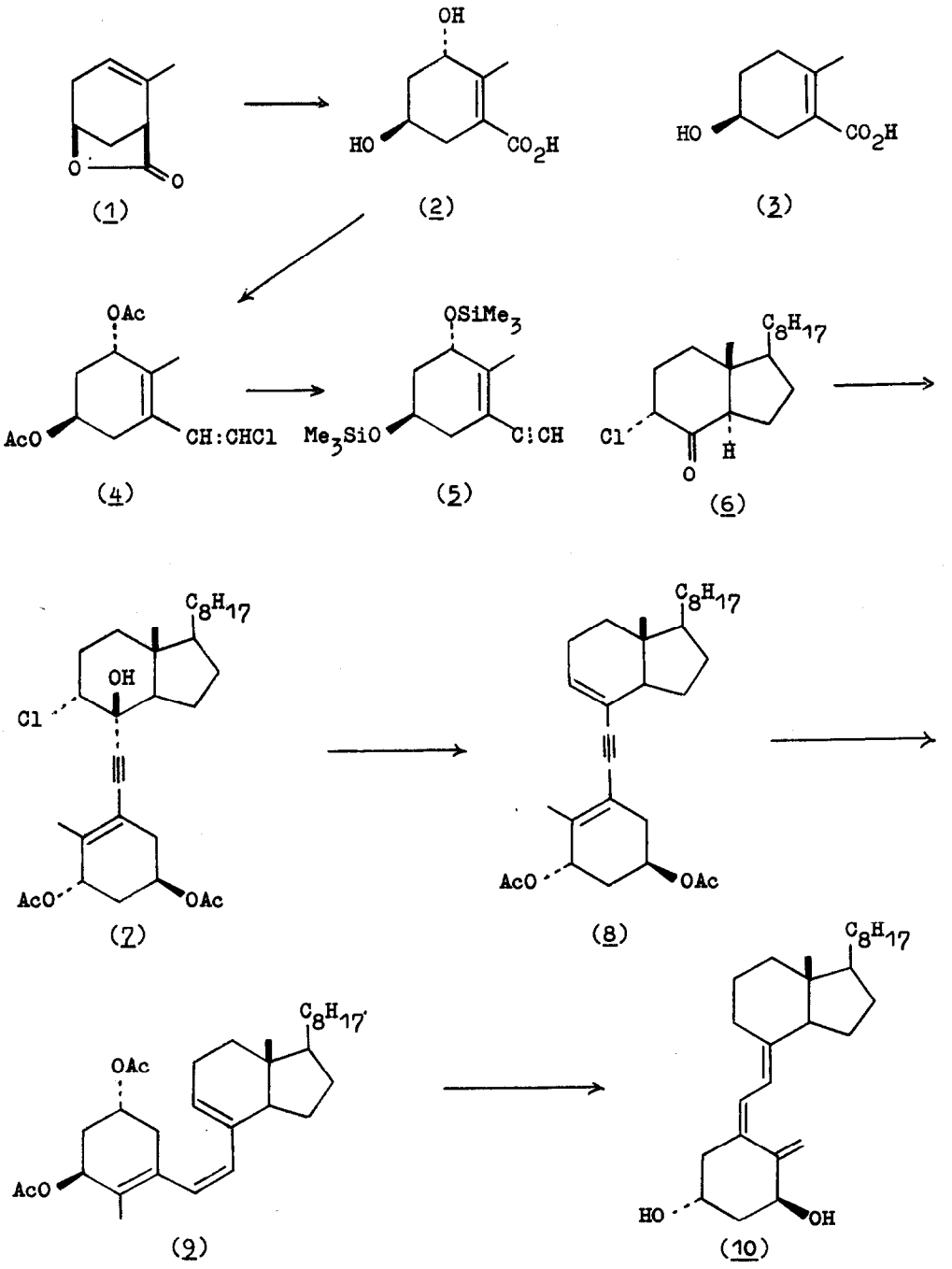
1α,25-Dihydroxycholecalciferol, which has been identified[1,2] as the active form of vitamin $D_3$ in physiological calcium transport, is formed from it by hydroxylation at C-25 in the liver, and then at C-1α in the kidney. The chemical preparation of this metabolite from derivatives of cholesterol has been announced recently[3], although without disclosure of the m.p., [α], or $\varepsilon_{max.}$ of the product. For vitamin $D_3$ itself, total synthesis is much less convenient as a preparative procedure than partial synthesis from cholesterol. For 1α,25-dihydroxycholecalciferol, however, where both ends of the cholesterol molecule need modification before ring B is opened by irradiation, the efficiency gap between total and partial synthesis should be diminished, although it may remain considerable. It was therefore of interest to extend previous studies[4] to the field of vitamin D metabolites, and we now report the total synthesis of 1α-hydroxy-vitamin $D_3$ (10).

The optically active lactone[5] (1) gave with m-chloroperbenzoic acid only one epoxide; from steric considerations this should be the α-epoxide. Treatment with methanolic sodium methoxide, and then with water, gave a

conjugated dihydroxy acid (2), m.p. 149°, $[\alpha]_D$ -165° (EtOH). Since the acid (3) has $[\alpha]_D$ -52° (EtOH), Mills' rule[6] suggests an α-configuration for the allylic hydroxy group, and this is supported by n.m.r. data on (2) and its derivatives. We converted the acid (2) into its diacetoxy acid chloride, the diacetoxy aldehyde, and then, by existing methods[7], into the chloro-diene (4) and the protected en-yne (5) $\lambda_{max.}^{EtOH}$ 230 nm. (ε 11,300) (yield 17% from the lactone 1).

The lithio-derivative of (5) reacted with 9α-chloro-des-AB-cholestan-8-one[8] (6) to give, after hydrolysis and acetylation, the chlorohydrin (7), and this was converted by existing methods[4] into the en-yn-ene (8) $\lambda_{max.}^{EtOH}$ 273 nm. (ε 20,000) and then into the precalciferol derivative (9) $\lambda_{max.}^{Et_2O}$ 260 nm. (ε 8,700). Heating in benzene, followed by saponification, gave 1α-hydroxy-vitamin $D_3$ (10), m.p. 134-136°, $[\alpha]_D^{25}$ + 28° ($Et_2O$), $\lambda_{max.}^{Et_2O}$ 264-265 nm. (ε 18,000); the n.m.r. and mass spectral data confirmed its structure. Taking account of recovered starting materials, it was obtained in 22% yield from (6).

Very recently, two groups[9,10] have announced partial syntheses of 1α-hydroxy-vitamin $D_3$ from cholesterol, and it has been shown to have a biological activity comparable with that of 1α,25-dihydroxycholecalciferol. DeLuca's group[9] give no m.p., [α], $\varepsilon_{max.}$, or n.m.r. data for their product. Barton *et al.*[10], whose preparative route is particularly convenient, quote constants which are, in general, in satisfactory agreement with our own. Small discrepancies occur however in respect of $\varepsilon_{max.}^{Et_2O}$, for which Barton *et al.*[10] quote 20,200[11], and of the position of one of the two C-19 proton resonances, which they place at δ 4·85 and 5·30 (solvent not quoted), whereas we find values of δ 5·02 and 5·33 ($CDCl_3$).


OH
HO
CO2H
(1)
(2)
(3)
OAc
AcO
CH:CHCl
OSiMe3
Me3SiO
C:CH
C8H17
Cl
H
O
(4)
(5)
(6)
OH
Cl
AcO
OAc
(7)
(8)
OAc
AcO
(9)
HO
OH
(10)

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