Calciferol and its Relatives. Part 28.[1] A Stereoselective Synthesis of 1α-Hydroxyprecalciferol$_3$ from 8-Hydroxymethyl-des-AB-cholest-8-ene

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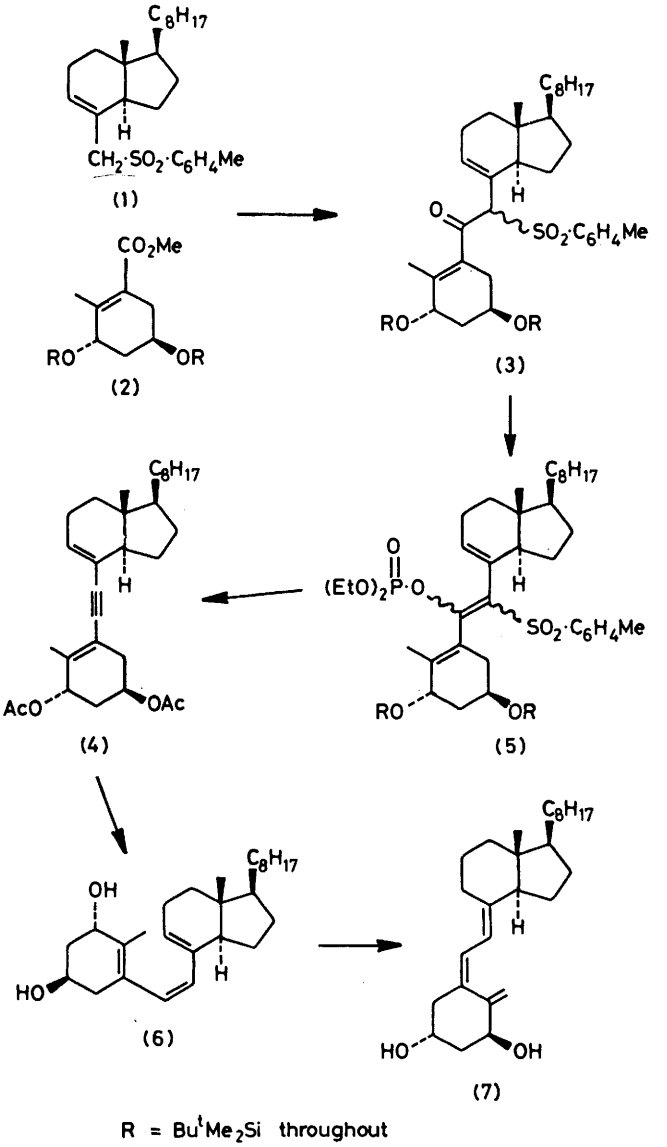
8-*p*-Tolylsulphonylmethyl-des-AB-cholest-8-ene (1) † and methyl (3*S*,5*R*)-3,5-bis-t-butyldimethylsilyloxy-2-methylcyclohex-1-enecarboxylate (2) were combined to give a 6-oxo-7-sulphone from which 1α,3β-diacetoxy-9,10-seco-cholesta-5(10),8-diene-6-yne (4) was obtained. Semihydrogenation and deacetylation gave 1α-hydroxyprecalciferol$_3$ (6), which was converted by thermal isomerisation into 1α-hydroxyvitamin D$_3$ (7).

THE precalciferols are distinguished by the *cis*-geometry of the disubstituted (6,7) double bond which is the central double bond of their conjugated triene system. Their 6-*trans*-isomers, the tachysterols, can be obtained stereoselectively [2] by uniting two fragments, corresponding to ring A and rings CD, so as to construct the 6,7-double bond, and it seemed of interest to find a parallel stereoselective route to the precalciferols. A possible approach was offered by a general synthesis [3] of conjugated en-yn-enes from allylic aryl sulphones and αβ-unsaturated esters, followed by semi-hydrogenation of the acetylene link to give the central *cis*-double bond of the required triene system. We here report the application of this method to the synthesis of 1α-hydroxyprecalciferol$_3$ (6).

The necessary starting materials, the *p*-tolyl sulphone (1),† and the protected dihydroxy-ester (2) were described in the preceding paper. Condensation of the magnesium bromide derivative (2 mol) of the sulphone with the protected ester (1 mol) gave a mixture of diastereoisomeric β-oxo-sulphones (3) in a yield of 76% based on unrecovered sulphone (1). The mixture was treated in tetrahydrofuran and hexamethylphosphoric triamide, first with sodium hydride and then with diethyl phosphorochloridate in order to form (yield, 60%) the enol phosphate (5). After reductive elimination in tetrahydrofuran and dimethyl sulphoxide, which generated the acetylene link, the protecting silyl ether groups were removed and replaced by acetate groups to give (yield, 53%) the en-yn-ene (4), identified by comparison of its spectral data with those of material obtained by an earlier [4] route.

The en-yn-ene (4) has already [4] been converted by semihydrogenation into 1α-hydroxyprecalciferol$_3$ diacetate, and thence by thermal isomerisation and hydrolysis into 1α-hydroxyvitamin D$_3$. By similar methods the present sample was converted into 1α-hydroxyprecalciferol$_3$ and then into 1α-hydroxyvitamin D$_3$. The final crystalline product was obtained in 53% yield from the en-yn-ene (4), or 12.4% from the starting sulphone (1). This is modest compared with that obtained by the route described in the preceding paper, and the individual steps in the present route could undoubtedly be greatly improved by careful repetition. However, the interest of the present route lies less in its potential efficiency than in the success of the general approach when applied to the synthesis of a fairly complex central-*cis*-conjugated triene.

† All the structures in this paper represent absolute configurations.



R = Bu^{t}Me$_2$Si throughout

EXPERIMENTAL

For general instructions, see the preceding paper.

The Oxo-sulphones (3).—1.5M-Ethereal ethylmagnesium bromide (2.8 cm^3) was added to a stirred solution of the *p*-

tolyl sulphone (1) (1.639 g) in dry benzene (15 cm³) at 20 °C. The mixture was heated under reflux under nitrogen for 1.5 h and then cooled to 20 °C and stirred during the addition of the ester (2) (816 mg) in tetrahydrofuran (6 cm³). Stirring was continued at 20 °C for 19 h; the mixture was then poured into 0.2N-hydrochloric acid and the product was isolated with ether, acid being removed by washing with aqueous sodium hydrogencarbonate. Chromatography on silica gel (230 g) with ethyl acetate and light petroleum (1 : 19) gave the mixed oxo-sulphones (3) (1.158 g), $\nu_{max.}$ ($CHCl_3$) 840s, 994s, 1 080s, 1 130s, 1 150s, 1 258, 1 306s, 1 317s, 1 600m, and 1 696s cm^{-1}; τ 2.21 (2 H, d, J 9 Hz, ArH), 2.70 (2 H, d, J 9 Hz, ArH), 4.65 (1 H, m, −CH=), 4.95 and 5.08 (together 1 H, s, >CH·SO_2 of major and minor isomers respectively), 5.8—6.15 (2 H, m, 2 >CH−O), 7.60 (3 H, s, $ArCH_3$), 8.28 (3 H, m, =C(CH)−CH_3), 9.40 (3 H, s, CH_3-18), and 9.91 and 9.97 (each 6 H, s, CH_3Si). Further elution of the chromatogram with the same solvent gave the crystalline sulphone (1) (850 mg).

The Enol Phosphate (5).—The mixed oxo-sulphones (3) (1.154 g) and sodium hydride (100 mg) were stirred together under nitrogen in tetrahydrofuran (5 cm³) and hexamethylphosphoric triamide (2 cm³) at 20 °C for 3 h. The mixture was cooled to 0 °C and diethyl phosphorochloridate (0.8 cm³) was added; stirring was then continued at 20 °C for 20 h. The solution was diluted with water, and the product was isolated with ether. As t.l.c. showed that some loss of protecting silyl groups had taken place, re-silylation was was added, and the mixture was washed with aqueous sodium hydrogencarbonate, and was dried. The solvent was evaporated, and the residue was acetylated with acetic anhydride and pyridine in the usual way. Purification by p.l.c. (ethyl acetate–light petroleum, 1 : 9) gave the en-yn-ene [4] (4) (213 mg), $[\alpha]_D^{22}$ −114° ($CHCl_3$); $\lambda_{max.}$ (EtOH) 273.5 (ε 17 900) and 288 nm (13 900) (inflection at 267 nm); $\nu_{max.}$ (film) 1 025m, 1 235s, 1 740s, and 2 180w cm^{-1}; τ 4.02 (1 H, m, −CH=), 4.53 (1 H, t, J 4 Hz, >CH−OAc), 4.7—5.1 (1 H, m, >CH−OAc), 7.92 (3 H, s, Ac), 7.96 (3 H, s, Ac), 8.12br (3 H, s, =C(CH)−CH_3), and 9.29 (3 H, s, CH_3-18).

1α-*Hydroxyvitamin* D_3 (7).—Hydrogenation of the en-yn-ene (4) (195 mg) in light petroleum (10 cm³) with presaturated Lindlar palladium catalyst (220 mg), poisoned with quinoline (0.5 mg) at 17 °C resulted in the uptake of 1.1 mol hydrogen in 18 min. Filtration, evaporation, and separation by p.l.c. (ethyl acetate–benzene, 3 : 97) gave unchanged en-yn-ene (42 mg) as the more polar compound, and 1α-hydroxyprecalciferol$_3$ diacetate (132 mg, 86%) as the less polar. After deacetylation with sodium methoxide (from 38 mg sodium) in methanol (7.5 cm³) at 20 °C under nitrogen for 2 h, and normal work-up, the product was heated under reflux in benzene (nitrogen) for 8 h, and then subjected to p.l.c. (ethyl acetate–light petroleum, 3 : 7). The less polar material (51.5 mg) separated from ether–light petroleum at −20 °C giving 1α-hydroxyvitamin D_3 as needles (44.5 mg), m.p. 138—140°, $[\alpha]_D^{20}$ +28.9° ($CHCl_3$); $\lambda_{max.}$ (Et_2O) 264 nm (ε 17 900); the i.r. and ^1H n.m.r.