

NEW ROUTES TO 1 α -HYDROXYVITAMIN D₃

Philip J. Kocienski, Basil Lythgoe* and Ian Waterhouse

Department of Organic Chemistry, The University, Leeds LS2 9JT

The sulphone (2) and the methyl ester (3, R=H) were used in stereoselective syntheses of derivatives of 1 α -hydroxyprecalciferol₃ and 1 α -hydroxytachysterol₃, which were then converted into the title compound.

1 α -Hydroxyvitamin D₃ (7), which is highly active in promoting calcium transport in man, is also of interest as a model for the development of synthetic routes to the hormone, 1 α ,25-dihydroxyvitamin D₃. The 1 α -hydroxyvitamin has been obtained¹ from 1 α -hydroxycholesterol, and also by a total synthesis² in which the diacetate (8, R=Ac) of 1 α -hydroxyprecalciferol₃ was obtained by the union of fragments corresponding to rings A and CD so as to generate the 7:8-bond, and was then subjected to thermal isomerisation. We now report new routes to derivatives of 1 α -hydroxyprecalciferol₃ in which appropriate A and CD fragments are united to generate the central 6:7-double bond.

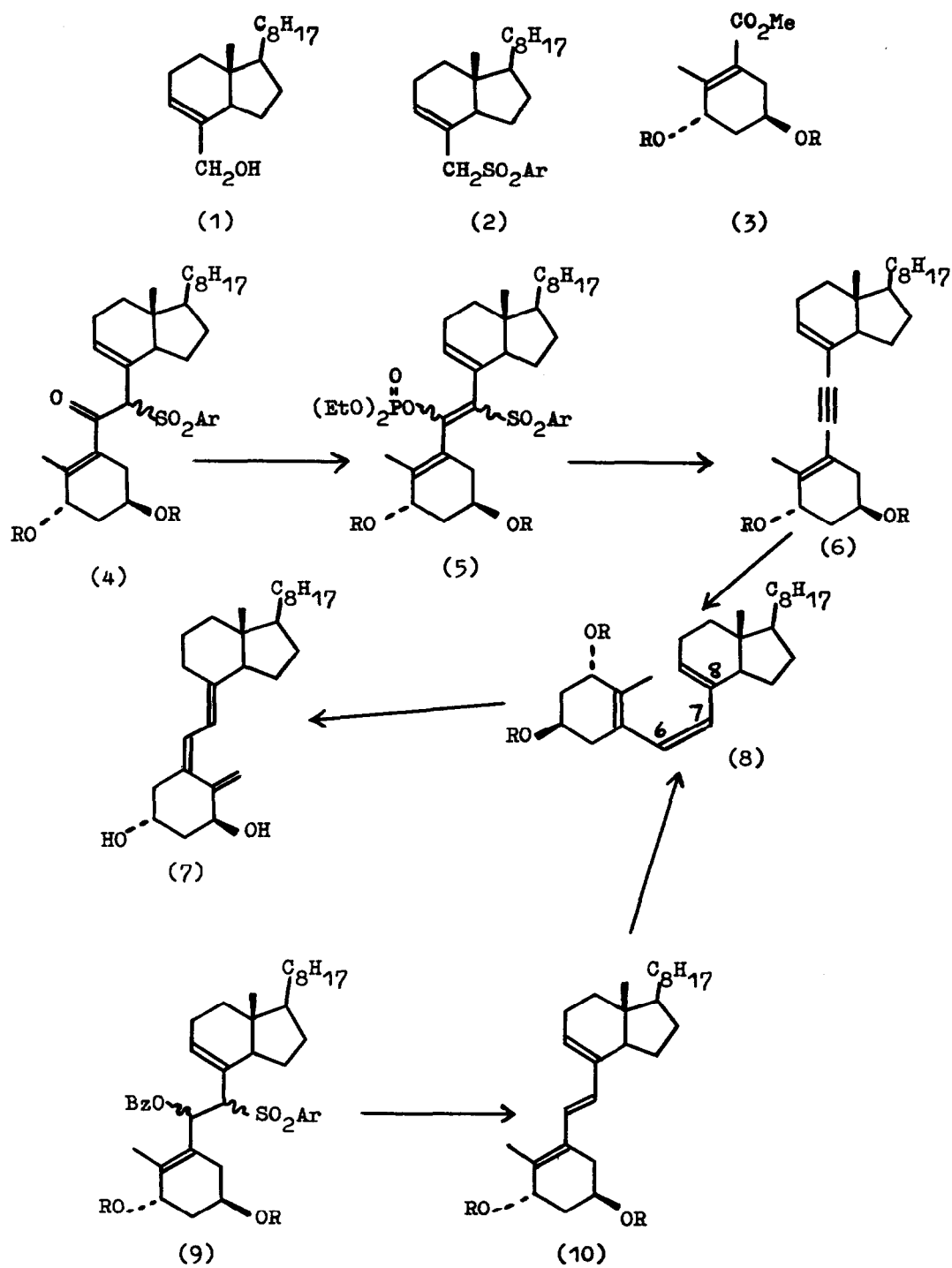
Conjugated en-yn-enes V·C:C·V¹, where V and V¹ are vinyl or substituted vinyl groups, can be obtained³, with retention of the original vinyl group geometries, from primary allylic aryl sulphones VCH₂SO₂Ar and conjugated methyl esters V¹CO₂Me; semihydrogenation of the triple bond then provides a stereoselective route to the central-cis-conjugated triene. In order to obtain 1 α -hydroxyprecalciferol₃ by this approach we required the protected methyl ester (3, R= Bu^tMe₂Si) (the corresponding dihydroxy-acid has been described²), and the p-tolyl sulphone (2). This sulphone, m.p. 85-86°, [α]_D -25.4° (CHCl₃), was prepared in 92% yield from 8-hydroxymethyl-des-AB-cholest-

8-ene (1)⁴ by conversion into the corresponding chloride, followed by reaction with sodium toluene-*p*-sulphinate in dimethylformamide. The allylic alcohol (1) has been obtained by total synthesis by reduction of the corresponding aldehyde⁵. Recently⁶ it has been obtained from cholesterol by degradation in an overall yield of 22.5%.

Reaction of the ester (3, R= Bu^tMe₂Si) with the magnesium bromide derivative of the *p*-tolyl sulphone (2) (2 mols) gave, after separation of the unused sulphone, diastereoisomeric keto-sulphones (4, R= Bu^tMe₂Si) (76%) which were transformed into the enol phosphates (5, R= Bu^tMe₂Si) by treatment in tetrahydrofuran-hexamethylphosphoric amide first with sodium hydride, and then with diethylphosphorochloridate. Reaction with sodium amalgam in tetrahydrofuran and dimethyl sulfoxide at 0°, followed by replacement of the protecting ether groups by acetate residues gave (53%) the en-yn-ene diacetate (6, R= Ac)². Semihydrogenation over Lindlar catalyst gave (86%) 1 α -hydroxy-precalfiferol₃ diacetate (8, R= Ac), which after thermal isomerisation and deacetylation provided (60%) 1 α -hydroxyvitamin D₃ (7), m.p. 138-140°, $[\alpha]_D^{20} +28.9^\circ$ (Et₂O), with spectral data identical with those of authentic material².

Central-trans-conjugated trienes VCH=CHV¹ can be obtained⁷ from the sulphone VCH₂SO₂Ar and the aldehyde V¹CHO by the use of M. Julia's⁸ reductive elimination of acyloxy-sulphones; we have found⁹ that in those cases where V or V¹ bear an alkyl branch adjacent to the new double bond the reaction is highly trans-stereoselective. By this method we have effected a synthesis of tachysterol₃ (isolated as the 4-methyl-3,5-dinitrobenzoate) from the *p*-tolyl sulphone (2); and since tachysterol₃ can be converted photochemically¹⁰ into precalfiferol₃ in a highly efficient manner, it was apparent that a new route was available to 1 α -hydroxyvitamin D₃.

The ester (3, R= Bu^tMe₂Si) was reduced with lithium aluminium hydride, and the product was oxidised with manganese dioxide in light petroleum to give the corresponding aldehyde. Reaction with the lithium derivative of the *p*-tolyl sulphone (2), followed by treatment with benzoyl chloride, gave the mixed isomeric benzoyloxy-sulphones (9, R= Bu^tMe₂Si), which were reduced with



sodium amalgam in tetrahydrofuran-methanol to give the 1α -hydroxytachysterol₃ derivative (10, R = Bu^tMe₂Si). Irradiation¹⁰ in benzene containing fluorenone gave the corresponding 1α -hydroxyprcalciferol₃ derivative, and after thermal equilibration the protecting ether groups were removed with tetra-n-butylammonium fluoride in tetrahydrofuran. Crystalline 1α -hydroxyvitamin D₃ was so obtained in a yield of 57% overall from the allylic alcohol (1), or about 12.8% from cholesterol. This route therefore provides a relatively efficient approach to the compound (7), and it may be suitable for extension to $1\alpha,25$ -dihydroxyvitamin D₃.

References

1. M.F.Holick, E.J.Semmler, H.K.Schnoes, and H.F.DeLuca, Science, 1973, **180**, 190; D.H.R.Barton, R.H.Hesse, M.M.Pechet, and E.Rizzardo, J.Amer.Chem.Soc., 1973, **95**, 2748; A.Fürst, M.Labler, and K.-H.Pfoertner, Helv.Chim.Acta, 1973, **56**, 1708.
2. R.G.Harrison, B.Lythgoe, and P.W.Wright, J.C.S.Perkin I, 1974, 2654.
3. B.Lythgoe and I.Waterhouse, Tetrahedron Letters, 1978, 2625; J.C.S.Perkin I, 1979,
4. R.S.Davidson, W.H.H.Günther, S.M.Waddington-Feather, and B.Lythgoe, J.Chem.Soc., 1964, 4907.
5. P.S.Littlewood, B.Lythgoe, and A.K.Saksena, J.Chem.Soc.(C), 1971, 2955.
6. P.J.Kocienski, B.Lythgoe, and D.A.Roberts, J.C.S.Perkin I, 1980,
7. P.J.Kocienski, B.Lythgoe, and S.Ruston, J.C.S.Perkin I, 1978, 829.
8. M.Julia and J.-M.Paris, Tetrahedron Letters, 1973, 4833.
9. P.J.Kocienski, B.Lythgoe, and I.Waterhouse, to be published.
10. A.E.C.Snoeren, M.R.Daha, J.Lugtenburg, and E.Havinga, Rec.Trav.chim., 1970, **89**, 261.

We thank the S.R.C. for a post-doctoral award (to P.J.K.).

(Received in UK 31 August 1979)