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NEW ROUTES TO 1α-HYDROXYVITAMIN D_3

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The sulphone (2) and the methyl ester (3, R=H) were used in stereoselective syntheses of derivatives of 1α-hydroxyprecalciferol$_3$ and 1α-hydroxytachysterol$_3$, which were then converted into the title compound.

1α-Hydroxyvitamin D_3 (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, 1α,25-dihydroxyvitamin D_3. The 1α-hydroxyvitamin has been obtained[1] from 1α-hydroxycholesterol, and also by a total synthesis[2] in which the diacetate (8, R=Ac) of 1α-hydroxyprecalciferol$_3$ 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 1α-hydroxyprecalciferol$_3$ in which appropriate A and CD fragments are united to generate the central 6:7-double bond.

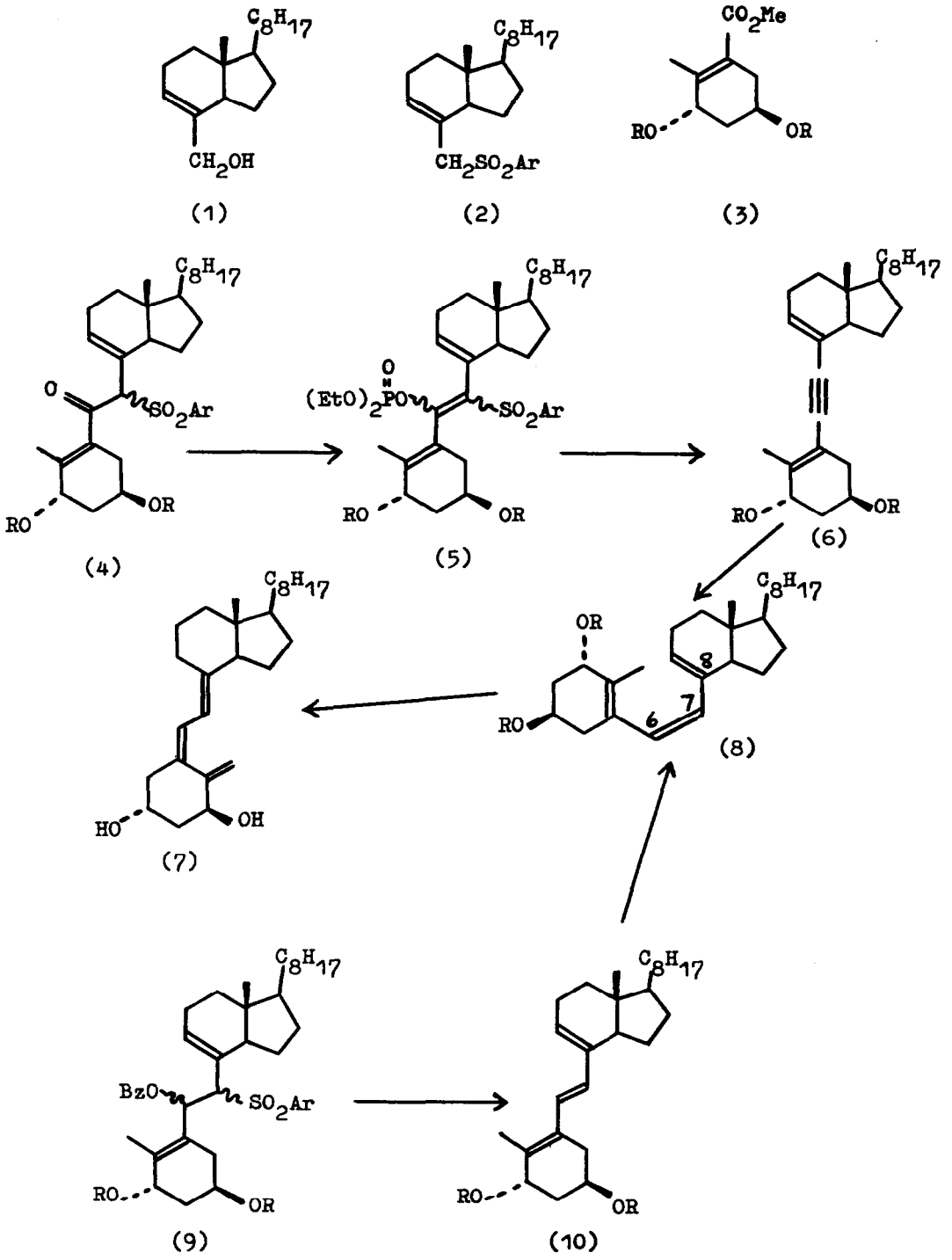
Conjugated en-yn-enes $V{\cdot}C{\equiv}C{\cdot}V^1$, where V and V^1 are vinyl or substituted vinyl groups, can be obtained[3], with retention of the original vinyl group geometries, from primary allylic aryl sulphones VCH_2SO_2Ar and conjugated methyl esters V^1CO_2Me; semihydrogenation of the triple bond then provides a stereoselective route to the central-cis- conjugated triene. In order to obtain 1α-hydroxyprecalciferol$_3$ by this approach we required the protected methyl ester (3, R= Bu^tMe_2Si) (the corresponding dihydroxy-acid has been described[2]), and the p-tolyl sulphone (2). This sulphone, m.p. 85-86°, $[\alpha]_D$ -25.4° ($CHCl_3$), 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 aldehyde[5]. Recently[6] it has been obtained from cholesterol by degradation in an overall yield of 22.5%.

Reaction of the ester (3, R= Bu^tMe_2Si) 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^tMe_2Si) (76%) which were transformed into the enol phosphates (5, R= Bu^tMe_2Si) by treatment in tetrahydrofuran-hexamethylphosphoric amide first with sodium hydride, and then with diethylphosphorochloridate. Reaction with sodium amalgam in tetrahydrofuran and dimethyl sulphoxide 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%) 1α-hydroxy-precalciferol$_3$ diacetate (8, R= Ac), which after thermal isomerisation and deacetylation provided (60%) 1α-hydroxyvitamin D_3 (7), m.p. 138-140°, $[\alpha]_D^{20}$ +28.9°(Et_2O), with spectral data identical with those of authentic material[2].

Central-trans-conjugated trienes VCH=CHV[1] can be obtained[7] from the sulphone VCH_2SO_2Ar and the aldehyde V^1CHO by the use of M. Julia's[8] reductive elimination of acyloxy-sulphones; we have found[9] that in those cases where V or V^1 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 tachysterol$_3$ (isolated as the 4-methyl-3,5-dinitrobenzoate) from the p-tolyl sulphone (2); and since tachysterol$_3$ can be converted photochemically[10] into precalciferol$_3$ in a highly efficient manner, it was apparent that a new route was available to 1α-hydroxyvitamin D_3.

The ester (3, R=Bu^tMe_2Si) 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^tMe_2Si), which were reduced with


C8H17
CH2OH
(1)
C8H17
CH2SO2Ar
(2)
CO2Me
RO
OR
(3)
O
SO2Ar
RO
OR
(4)
(EtO)2PO
SO2Ar
(5)
(6)
OR
RO
8
7
6
(8)
HO
OH
(7)
BzO
SO2Ar
(9)
(10)

sodium amalgam in tetrahydrofuran-methanol to give the 1α-hydroxytachysterol$_3$ derivative (10, R= Bu^{t}Me$_2$Si). Irradiation[10] in benzene containing fluorenone gave the corresponding 1α-hydroxyprecalciferol$_3$ derivative, and after thermal equilibration the protecting ether groups were removed with tetra-n-butylammonium fluoride in tetrahydrofuran. Crystalline 1α-hydroxyvitamin D$_3$ 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 1α,25-dihydroxyvitamin D$_3$.

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