Total Synthesis of Des-AB-cholestane-8β,9α-diol

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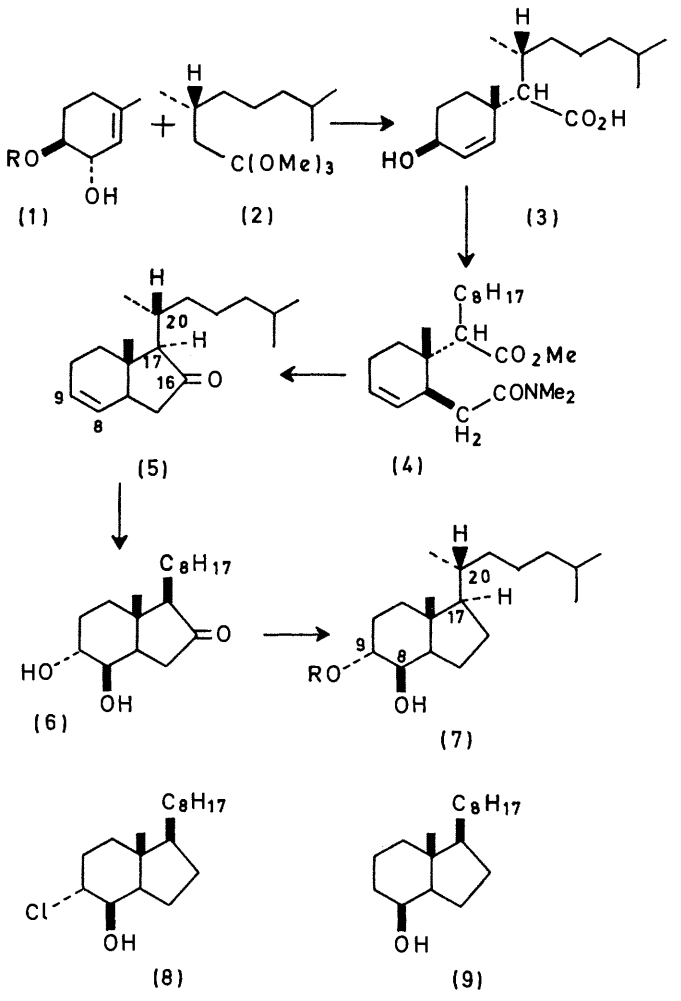
Summary A brief and highly stereoselective total synthesis gives the title compound (7; R = H), from which 9α-chloro-des-AB-cholestan-8β-ol, used for the synthesis of precalciferol$_3$ can be prepared.

9α-CHLORO-DES-AB-CHOLESTAN-8β-OL (8),† used for the synthesis[1] of precalciferol$_3$ is a product of total synthesis by virtue of its preparation from des-AB-cholestan-8β-ol (9).† The latter has been obtained[2] *via* relay compounds from 4-methoxycarbonyl-3-methylcyclohex-2-en-1-one, although only in very small (*ca.* 0·001%) yield. With the aim of providing a more efficient start to the synthesis of precalciferol$_3$, we have devised a brief and stereoselective total synthesis of the title diol (7; R = H), from which the chlorohydrin (8) is easily prepared.

The synthesis takes its form and starting materials from the method used to secure the 20β-configuration.[3] We noted that the readily available (*R*)-dihydrocitronellic acid contains configurational and structural features which fit it to provide the iso-octyl side-chain together with C-17 and C-16 of the ketone (5). Model experiments showed that the orthoacetate variant[4] of the Claisen rearrangement, hitherto used for the transfer of the $\cdot CH_2 \cdot CO_2Et$ group in acyclic systems, could be extended to the transfer of $\cdot CHR \cdot CO_2Et$ groups in cyclohex-2-en-1-ols; this suggested the use of the orthoester (2). To unite it with a ring-c

† All the structures in this communication denote absolute configurations.

fragment, the methods outlined in the preceding communication[5] were developed; they allow the assembly of all eighteen carbon atoms of the ketone (5) in two synthetic steps, with the absolute configurations of three of its four asymmetric centres predetermined by those of the starting materials.



The orthoester (2) was obtained by standard methods from the dihydro-compound, $[\alpha]_D^{23}$ −4·6° (neat), of citronellonitrile M.[6] Reaction of the orthoester (3 mols) with the mesitoate[7] (1; R = $Me_3C_6H_2CO$), followed by vigorous alkaline hydrolysis of the product, gave the hydroxy-acid (3); its methyl ester was then converted into the dimethylamide (4), which was hydrolysed to the corresponding dibasic acid. Cyclisation as previously described of the dimethyl ester gave a (near-equilibrium) mixture (*ca.* 6 : 1 by g.l.c.) of the crystalline (low-melting) hydrindenone (5), $[\alpha]_D^{21}$ −93° (chloroform), and its 17α-epimer. They were separated chromatographically, and the latter epimer was re-treated with acid to obtain more of the former. The 17β-epimer (5) formed an 8α,9α-epoxide m.p. 83°, reaction of which with dilute sulphuric acid in acetone gave the 8β,9α-diol (6), m.p. 113—114°, $[\alpha]_D^{22}$ −122° (chloroform). After acetylation and reaction with ethane dithiol and boron trifluoride etherate, the thioacetal was desulphurised with Raney nickel; deacetylation then gave the diol (7; R = H), m.p. 142—143°, $[\alpha]_D^{22}$ + 49° (chloroform), identical with material prepared[8] from des-AB-cholest-8-ene.[1,9] In these preliminary experiments the diol (7; R = H) was obtained in 13% yield from the mesitoate (1; R = $Me_3C_6H_2CO$). We expect that the use of other esters of the diol (1; R = H), may result in improvements; they will be reported in the full paper.

Selective monotosylation of the diol (7; R = H) gives[9] in good yield the monotosy late (7; R = $MeC_6H_4SO_2$), which is converted by standard methods into the 8β,9β-epoxide, and thence into the chlorohydrin (8). In conjunction with the results[1] already obtained, therefore, the present work provides a complete total synthesis of precalciferol$_3$.

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