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DIRECT TOTAL SYNTHESIS OF VITAMINS D_2 AND D_3

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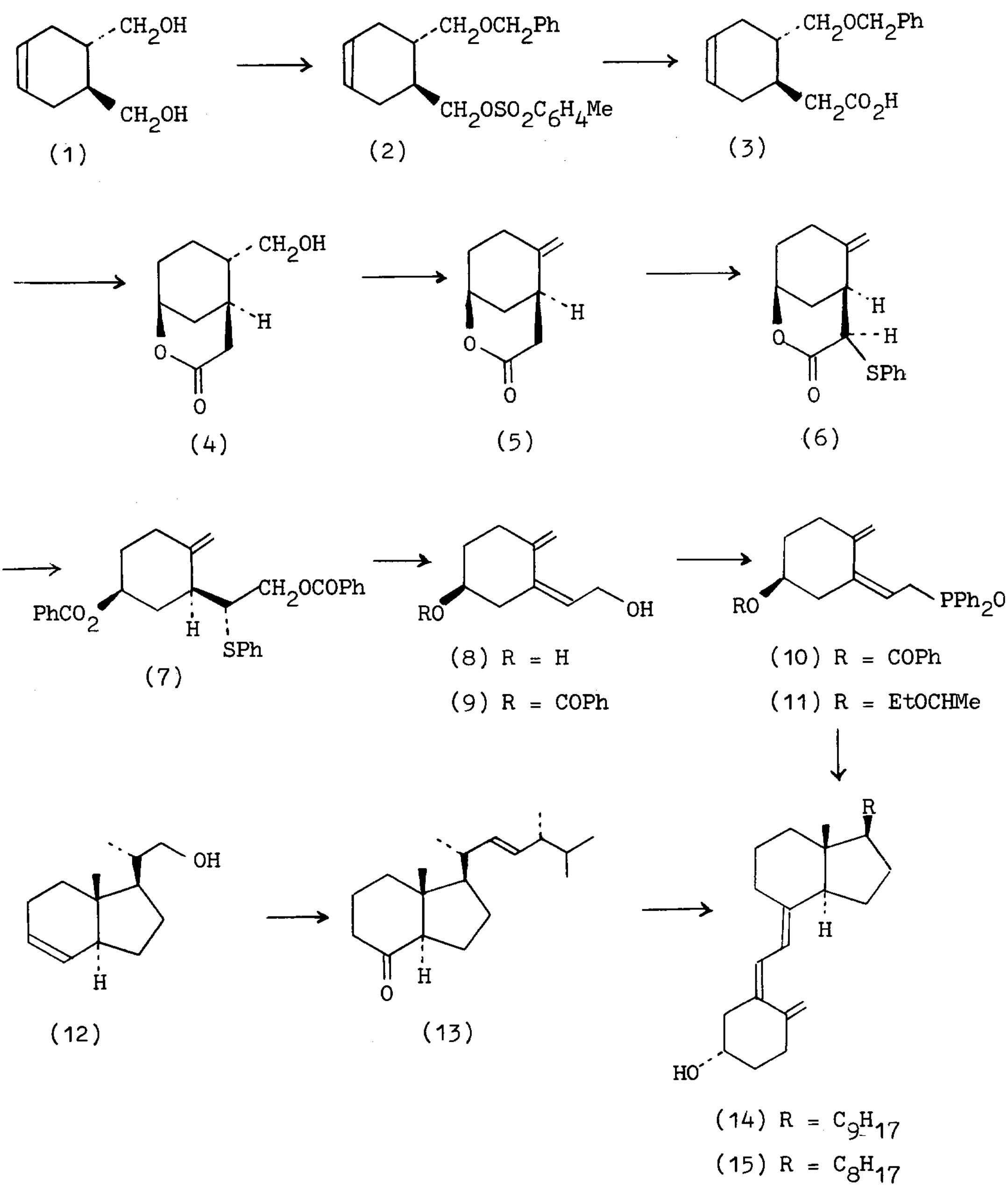
In existing total syntheses[1,2] of vitamin D_3 the conjugated triene system is not constructed directly; instead, an isomeric triene, either 5-trans-vitamin D_3[1b] or precalciferol$_3$,[2] is first elaborated, and is then transformed into the vitamin itself by photochemical or thermal isomerisation. Vitamin D_2 has not hitherto been obtained by total synthesis, although partial syntheses[3,1b] have been described. We now report direct total syntheses, not involving intermediate trienes, of both vitamin D_2 and vitamin D_3. They are effected by reaction[4] between the Z-allylic phosphine oxide (11) and the appropriate bicyclic ketone, e.g. (13), and they proceed stereospecifically, the 5,6-double bond of the product (14) retaining completely the (natural) Z-geometry of the precursor (11), and the newly formed 7,8-double bond having exclusively the natural E-geometry.

As an intermediate in the preparation of the phosphine oxide (11) we used the (Z)-dienediol (8), a compound originally isolated[5] as a product of degradation of vitamin D_2, but now obtained by total synthesis from the readily available[6] (+)-cyclohex-4-ene-1,trans-2-dimethanol (1). Tosylation of the monobenzyl ether gave the compound (2), which was homologated by a nitrile synthesis to give the acid (3). Iodolactone formation, deiodination, and hydrogenolysis of the benzyl group gave the lactonic alcohol (4); the corresponding iodide gave on treatment with diazabicycloundecane (DBU) the unsaturated lactone (5), m.p. 51·5°. Reaction of the lithio-derivative with diphenyl disulphide gave a mixture of two epimeric thioethers, of which the major isomer (6) was crystalline (m.p. 132-134°); its liquid epimer gave more of the crystalline isomer when equilibrated with DBU in benzene at 25°. Reduction and benzoylation of (6) then led to the sulphide (7); the corresponding sulphoxide gave on thermolysis followed by hydrolysis the (Z)-dienediol (8), m.p. 101-102°, $[\alpha]_D$ + 26·8°.[7] It was obtained in 10·6% yield from the (+)-diol (1).

The secondary benzoate (9) was obtained by selective reaction of the diol (8) with trichloroethyl chloroformate, followed by benzoylation and removal of the protecting group. The primary alcohol group was converted,[4] first into the chloride, and then into the phosphine oxide (10), m.p. 184-186°, $[\alpha]_D$ + 44°. Alkaline hydrolysis, followed by reaction with ethyl vinyl ether, gave the phosphine oxide (11) in an overall yield of 4·1% from the diol (1).

The lithio-derivative of (11) reacted with the Windaus-Grundmann[8] ketone (13) to give, after removal of the protecting group, crystalline vitamin D_2 (14) (yield ca. 60%), identified by its spectral characteristics, and by conversion into the 3,5-dinitrobenzoate, m.p. 148°, $[\alpha]_D$ + 90·3°. Since the ketone (13) has recently[9] been obtained by total synthesis from the hydrindenylpropanol[10] (12), the above work constitutes the first total synthesis of vitamin D_2.

Similar reaction between the phosphine oxide (11) and des-AB-cholestan-8-one gave vitamin D_3 (15), isolated as the 3,5-dinitrobenzoate, m.p. 129·5-131°, $[\alpha]_D$ + 96·6°, in ca. 53% yield from the phosphine oxide (11).



(1)

(2)

(3)

(4)

(5)

(6)

(7)

(8) R = H

(9) R = COPh

(10) R = COPh

(11) R = EtOCHMe

(12)

(13)

(14) R = C_9H_{17}

(15) R = C_8H_{17}

N.B. All the structures in this paper represent absolute configurations.

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