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A STEREOCONTROLLED PARTIAL SYNTHESIS OF 1α-HYDROXY VITAMIN D_3

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ABSTRACT

A novel and efficient partial synthesis of 1α-hydroxy vitamin D_3 (6), starting from 7-dehydrocholesterol (1), is reported. The crucial step in the synthesis involves a selective Diels-Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with the 6,8-diene system of previtamin D_3 (3), generating an adduct 7 suitable for the stereoselective introduction of the 1α-hydroxyl group. Cycloreversion of 13 leads to the title compound.

During the study of the metabolic pathway of vitamin D_3 (5) it was discovered that the introduction of a 1α-hydroxyl group on the vitamin skeleton is an essential metabolic event in relation to calcium absorbtion in man[2]. The scarcity of 1α-hydroxylated vitamin D derivatives has led us to look for synthetic routes amenable to large scale operation. We wish to report a novel and efficient partial synthesis of 1α-hydroxy vitamin D_3 (6), involving four distinct stages (scheme) : (a) selective Diels-Alder reaction on the 6,8-diene system of previtamin D_3 (3); (b) regioselective functionalization at C(1); (c) stereoselective introduction of the 1α-hydroxyl group; (d) stereoselective generation of the vitamin D triene system (6).

Previous syntheses were achieved by total synthesis[3] or by the photochemical and thermal isomerizations of 1α-hydroxy provitamin (cf. 2 → 4 → 6)[4]. The latter route suffers from low yields obtained during the photochemical interconversion. Since direct oxidation of vitamin D_3 was inefficient[5] an indirect approach should involve the temporary modification of the triene system of the vitamin, whilst maintaining a double bond at C(10) so as to leave C(1) as the preferred allylic position for subsequent functionalization. This strategy has recently been applied[5b] via a cyclovitamin derivative[6].

At the outset of our study it occurred to us that some remarkable structural features of the previtamin molecule (3) had not yet been synthetically exploited. Indeed, from the probable geometry of the triene system[7], a selective reaction of a dienophile on the 6,8-diene system would be anticipated[8c]. This would leave the cyclohexene ring A untouched, an ideal situation for selective introduction of the requisite 1α-hydroxyl function. Finally, concerted cycloreversion and

subsequent thermal isomerization[8], should lead to the desired 1α-hydroxy vitamin D_3 (6) (cf. 13 → 4 → 6).

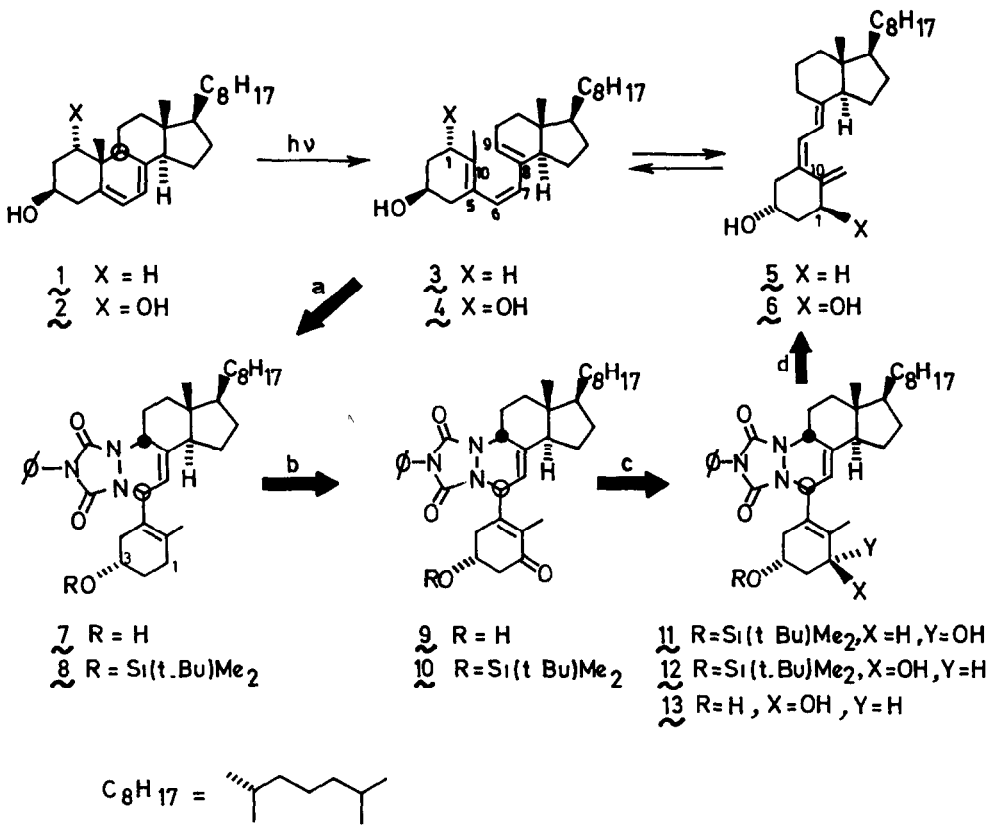
Short-time irradiation of 7-dehydrocholesterol (1)[9] and recovery of unreacted material afforded crude previtamin D_3 (3) which upon treatment with 4-phenyl-1,2,4-triazoline-3,5-dione[10] (CH_2Cl_2, 0°C, N_2, 2 min) led to adduct 7[11]. Ready purification occurred via recrystallization from acetone (m.p. 147-148°C; 50 % isolated yield based on converted 1). Only a single previtamin adduct, originating from the anticipated reaction from the least hindered α-face of the trans-hydrindane system on the more reactive diene, was isolated. Its structure was proven by X-ray diffraction[12].

After protection of the C(3)-hydroxyl group (t-BudiMeSiCl, imidazole, DMF; m.p. 137°C; 95 % yield) 8 was oxidized with CrO_3-3,5-DMP[13] to enone 10[11] in 33 % yield. Alternatively, allylic bromination of 7 with NBS (CCl_4, AIBN, N_2, 120°C, 20 min) was highly regioselective and led to diastereoisomeric bromides at C(1) (crude yield > 80 %), which were directly converted to 11 and 12 upon stirring with silicagel-water-collidine-hexane for 24 hr at r.t. (64 % overall yield from 7). Although both isomers 11 and 12 (ratio 7:3) can be separated by column chromatography (benzene-ethyl acetate, 8:2), for synthetic purposes the crude mixture was converted to the corresponding enone 10 (PDC, CH_2Cl_2, 4 hr, r.t.; 57 % yield from 7).

After cleavage of the silyl ether in 10 (n.butyric acid, $(n.Bu)_4NF$, THF, -10°C to -20°C, 3 hr) the keto-alcohol 9 (m.p. 101-102°C; 90 % yield) was reduced with aluminumhydride in THF at -70°C yielding 13[11] with high stereoselectivity (better than 9:1 as deduced from ^1H NMR; m.p. 165°-167°C from ether; 84 % yield after column chromatography on silica gel with benzene-acetone 8:2). The anticipated stereochemical result is rationalized by the prior formation of an alkoxymetal hydride complex with the hydroxyl group at C(3), followed by intramolecular hydride transfer to the carbonyl group.

Deprotection of the 6,8-diene by heating 13 at 80°C in 15 N KOH-MeOH for 24 hr under argon restored with complete stereocontrol[14] the previtamin triene system (4), which, under these reaction conditions, was directly isomerized to 1α-hydroxy vitamin D_3 (6). Ready column chromatographic purification and recrystallization (m.p. 134°C from hexane) gave pure 6[11] (64 % isolated yield), which was found identical with an authentic sample[15].

Starting from 7-dehydrocholesterol (1) the present method yields 1α-hydroxy vitamin D_3 in 8 % (7 steps) or in 13 % overall yield via the longer route involving 11 and 12 (9 steps). The main advantage of the present sequence resides in its broad scope and in the possibility for gramscale preparation of the title compound (without tedious chromatographic separations).



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11. Satisfactory spectral data were obtained for all isolated compounds. Relevant ^1H NMR (360 MHz, $CDCl_3$) data are : 7 : δ(ppm) : 0.78 (3H, s), 0.87 (6H, 2d, J = 6.5 Hz), 0.92 (3H, d, J = 5 Hz), 1.81 (3H, s), 3.99 (1H, m), 4.46 (1H, m), 5.15 (1H, m), 5.35 (1H, m), 7.31-7.49 (5H, m). 10 : δ(ppm) : 0.80 (3H, s), 1.92 (3H, s), 2.50 (1H, dd, J = 12 Hz), 2.74 (1H, 2d, J = 4 Hz), 3.99 (1H, m), 4.55 (1H, m), 5.15 (1H, m), 5.37 (1H, m), 7.32-7.52 (5H, m). 13 : δ(ppm) : 0.78 (3H, s), 0.87 (6H, 2d, J = 6.5 Hz), 0.92 (3H, d, J = 5 Hz), 1.93 (3H, s), 4.09 (1H, m), 4.27 (1H, m), 4.48 (1H, m), 5.19 (1H, m), 5.29 (1H, m), 7.32-7.48 (5H, m). 6 : δ(ppm) : 0.55 (3H, s), 0.87 (6H, 2d, J = 6.5 Hz), 0.92 (3H, d, J = 6.5 Hz), 4.24 (1H, m), 4.43 (1H, m), 5.01 (1H, m), 5.33 (1H, m), 6.02 (1H, d, J = 11 Hz), 6.39 (1H, d, J = 11 Hz).
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15. We thank Prof. Lythgoe for kindly sending us a sample of authentic 1α-hydroxy vitamin D_3.

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