Stereoselective Conversion of Vitamin D_3 into its 3β-Halogenated Derivatives. The Synthesis of a 1α-Hydroxy-3β-fluorovitamin D_3 Analogue

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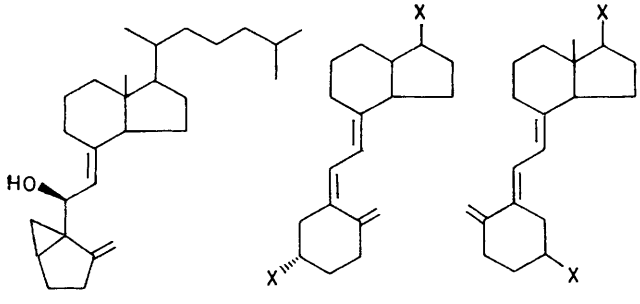
Summary (6*R*)-Hydroxy-3,5-cyclovitamin D_3 was converted with HF, HCl, and HBr into 3β-fluoro-, 3β-chloro-, and 3β-bromo-3-deoxyvitamin D_3 respectively, and with NaI–$ZnCl_2$ into the corresponding 3β-iodo derivative; a 3β-fluoro-1α-hydroxyvitamin D_3 analogue was prepared from 1α-hydroxyvitamin D_3 tosylate using the 3,5-cyclovitamin derivative as an intermediate.

THE similarity between the hormonal mode of action of the corticoids and of the hydroxylated analogues of vitamin D_3 (all of which act by binding to specific receptor proteins), and the enhanced activity of some fluorinated corticoids suggests that the fluorinated hydroxy-vitamin D derivatives may also possess increased activity.[1] We synthesized the 1α-hydroxy-3β-fluorovitamin D_3 analogue (**7b**), since it contains the 1α-hydroxy function necessary to elicit the biological activity which should not be impaired by the absence of the hydroxy-group at C-3.[2]

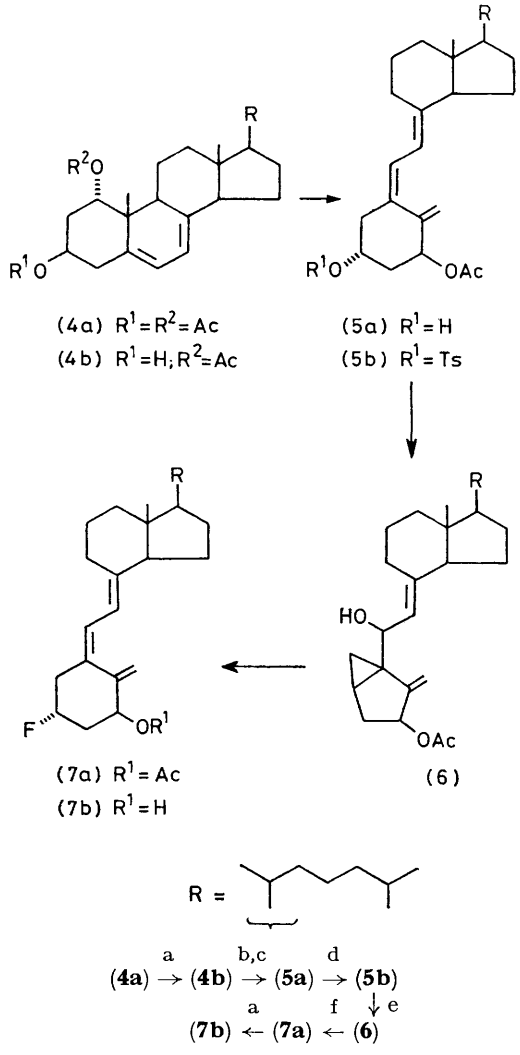
The simplest way to prepare this and other halogenated vitamin D and analogues would have been the nucleophilic substitution of the hydroxy, or the sulphonyloxy groups in the vitamin, or its sulphonic esters, by halides or halogenating reagents. However, only a small yield of the epimeric mixture of halides was obtained; the main products resulted from elimination reactions. To prevent this elimination, and at the same time to retain the configuration at C-3, it was necessary to protect the vitamin D triene system for which the only suitable way was the utilization of the 3,5-cyclovitamin D_3 system previously described by us.[3]



(1) (2) (3)

a, X = F
b, X = Cl
c, X = Br
d, X = I

Thus the (6*R*)-hydroxy-cyclovitamin (**1**) (obtained by solvolysis of the vitamin tosylate in aq. acetone[3b]) was treated with either HF in benzene at room temperature or with HCl or HBr in tetrahydrofuran at 0 °C to give the fluoro-, chloro-, and bromo-analogues of the vitamin (**2a**),[4] (**2b**), and (**2c**),[5]† respectively. In addition, in all the three cases *ca.* 10% of the corresponding 3β-halogenated *trans*-vitamin analogues (**3a**), (**3b**), and (**3c**) was formed. This method, however, was unsuitable for the formation of the iodo-vitamin derivative (**2d**), since it resulted mainly in elimination products. Instead, we rearranged the 6*R*-



(4a) $R^1 = R^2 = Ac$
(4b) $R^1 = H; R^2 = Ac$
(5a) $R^1 = H$
(5b) $R^1 = Ts$
(7a) $R^1 = Ac$
(7b) $R^1 = H$
(6)

R =

a b,c d
(**4a**) → (**4b**) → (**5a**) → (**5b**)
a f e
(**7b**) ← (**7a**) ← (**6**)

SCHEME. Reagents: a, MeOH–KOH, 0 °C; b, *hν*; c, 70 °C, 3 h; d, *p*-$MeC_6H_4SO_2Cl$–pyridine; e, aq. Me_2CO, $KHCO_3$; f, HF in C_6H_6.

† The three compounds were previously obtained by irradiation of the respective 3β-halogeno-cholesta-5,7-dienes. However only u.v. data are available for (**2b**) and (**2c**) and no n.m.r. data are given for (**2a**).

hydroxy-cyclovitamin (**1**) with $ZnCl_2$ and NaI to give a 4:6 mixture of vitamin and *trans*-vitamin iodo-derivatives (**2d**) and (**3d**).‡

The retention of the original configuration in the halogenated vitamin analogues was evident from their $[\alpha]_D$ values [+58, +62, and +72° for (**2a**), (**2b**) and (**2c**), respectively]. The u.v. spectra of these compounds are similar to those of vitamin D_3 whereas the ^1H n.m.r. spectra differ only in the chemical shift of the C-3 proton,[6] (**2a**): two equally intense 7-line patterns at δ 4·55 and 4·73 (J_{HF} 50, J_{trans} 7·2, J_{cis} 3·6 Hz); (**2b**): δ 4·00 (J_{trans} 8·0, J_{cis} 4·0 Hz); (**2c**): δ 4·25 (J_{trans} 8·0, J_{cis} 4·0 Hz); (**2d**): δ 4·22 (J_{trans} 7·5, J_{cis} 3·7 Hz).

These coupling constant values indicate a *ca.* 1:1 ratio of the two ring A conformers in a dynamic equilibrium. We have not observed changes in the ^1H n.m.r. spectra of these compounds down to −100 °C which indicates a low energy barrier for the ring A interconversion, analogous to that for vitamin D.[7]

In the mass spectra the characteristic fragment of the vitamin D system, due to C-7, C-8 double bond cleavage[8] was strong for (**2b**) and (**2c**), fairly strong for (**2a**), and absent for (**2d**).

The fluoro analogue of the 1α-hydroxyvitamin D_3 (**7b**) [u.v.: λ 264 nm, ε, 16,500; ^1H n.m.r. δ 6·21 and 5·90 (2H, ABq, J 11·5 Hz, 7- and 8-H), 5·26 and 4·95 (2H, m, 19-H), 4·91 and 4·73 (1H, J_{HF} 50 Hz, septet, J 7·0 and 4·0 Hz, 3-H), and 4·33 (1H, dd, J 7·5 and 4·3 Hz, 1-H); *m/e* 402 (8%), 163 (10), 157 (13), 155 (20), 154 (37), 136 (10), 134 (12), 133 (16), and 56 (100)] was synthesized in the same fashion as (**2a**). The sevenstep synthesis of (**7b**) starting from the known 5,7-diene diacetate (**4a**) is shown in the Scheme.

The fluoro-analogue (**7b**) was found to be active in inducing the formation of a calcium binding protein and in the stimulation of intestinal calcium absorption in rachitic chicks.[9]

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‡ The large excess of the *trans*-vitamin may be due to a partial isomerization of (**2d**) to (**3d**) caused by traces of iodine.

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