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# SYNTHESIS OF 24,24-DIFLUORO-25-HYDROXYVITAMIN $D_3$

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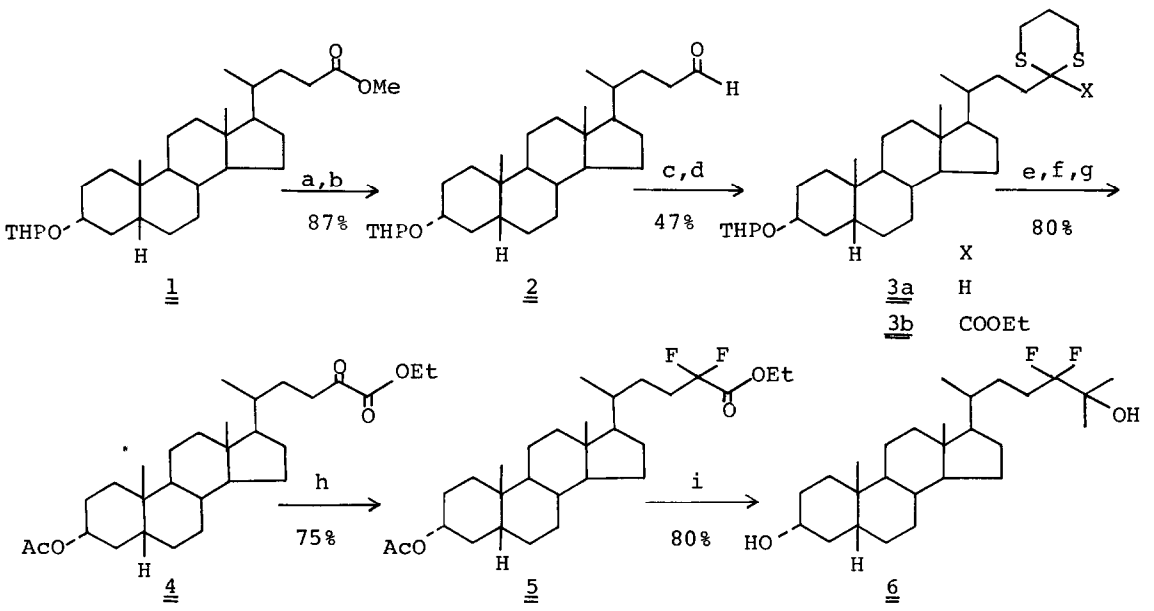
Summary: 24,24-Difluoro-25-hydroxyvitamin $D_3$ (13) has been prepared from commercially available lithocholic acid derivative to study the role of 24-hydroxylation in the metabolism of vitamin $D_3$.

By extensive studies on the metabolism of vitamin $D_3$, a number of metabolites have been isolated and identified.[1] Besides the active metabolite (i.e. 1α,25-dihydroxyvitamin $D_3$) and the precursor (i.e. 25-hydroxyvitamin $D_3$) leading to it, the metabolites hydroxylated at 24-position [i.e. (24R)-24,25-dihydroxyvitamin $D_3$ and (24R)-1α,24,25-trihydroxyvitamin $D_3$] have been directed much attention because of their reduced but still considerably high activity compared with the corresponding non-hydroxylated vitamin.[2] However, the role of 24-hydroxylated vitamin D in the metabolism of the vitamin has still been remained to be clarified.

Due to similar steric bulk and dissimilar chemical behavior, fluorinated biological compounds have been known to act as antimetabolites with respect to the corresponding fluorine-free natural products.[3] Based on this reason, we have chosen the title compound (13) in which 24-position is blocked for metabolic hydroxylation by substitution with fluorine atoms as an analog of 25-hydroxyvitamin $D_3$ to study the role of 24-hydroxylation in the metabolism of the vitamin.

Using commercially available lithocholic acid, construction of the side chain was achieved as shown in Scheme 1 in which the desired α,α-difluoro-t-carbinol function was derived efficiently from the α-keto ester, and the key intermediate, 24,24-difluoro-5β-cholestane-3α,25-diol (6), was obtained in 20% overall yield. Reduction of the ester 1 with $LiAlH_4$ followed by Collins oxidation gave the aldehyde 2: IR ($CHCl_3$) 1715 $cm^{-1}$; NMR ($CDCl_3$) δ 0.65 (3H, s), 0.97 (3H, s), 4.75 (1H, m), 9.82 (1H, t, J = 2 Hz). The 1,3-dithiane 3a derived from the aldehyde 2 was transformed into the ester 3b [IR ($CHCl_3$) 1720 $cm^{-1}$; NMR ($CDCl_3$) δ 0.63 (3H, s), 0.91 (3H, s), 1.34 (3H, t, J = 6.5 Hz), 4.27 (2H, q, J = 6.5 Hz), 4.74 (1H, m)] via its lithium salt by reaction with ethyl chloroformate.[4] The α-keto ester 4 [IR ($CHCl_3$) 1720 $cm^{-1}$; m/e 474, 414] obtained by exchanging the protecting group of the alcohol from THP to acetyl followed by removal of the dithiane group[5] was treated with diethylaminosulfur trifluoride (DAST)[6] to provide the difluoro ester 5 [IR ($CHCl_3$) 1755, 1720 $cm^{-1}$; NMR ($CDCl_3$) δ 0.65 (3H, s), 0.93 (3H, s), 1.36 (3H, t, J =

7 Hz), 2.03 (3H, s), 4.35 (2H, q, J = 7 Hz), 4.73 (1H, m)] , which upon treatment with methyl magnesium bromide afforded the t-carbinol 6: 142-143°; NMR ($CDCl_3$) δ 0.66 (3H, s), 0.92 (3H, s), 1.31 (6H, s), 3.65 (1H, m); m/e 440, 422.




1 2 3a H 3b COOEt 4 5 6

(a) $LiAlH_4$, THF. (b) $CrO_3$.pyridine.HCl, $CH_2Cl_2$. (c) 1,3-propanedithiol, $BF_3.Et_2O$, $CH_2Cl_2$, then dihydropyrane, p-TsOH.pyridine. (d) n-BuLi, THF, then ClCOOEt. (e) p-TsOH.pyridine, EtOH. (f) $Ac_2O$, pyridine. (g) NBS, aq. acetone. (h) DAST, $CH_2Cl_2$. (i) $CH_3MgBr$, THF.

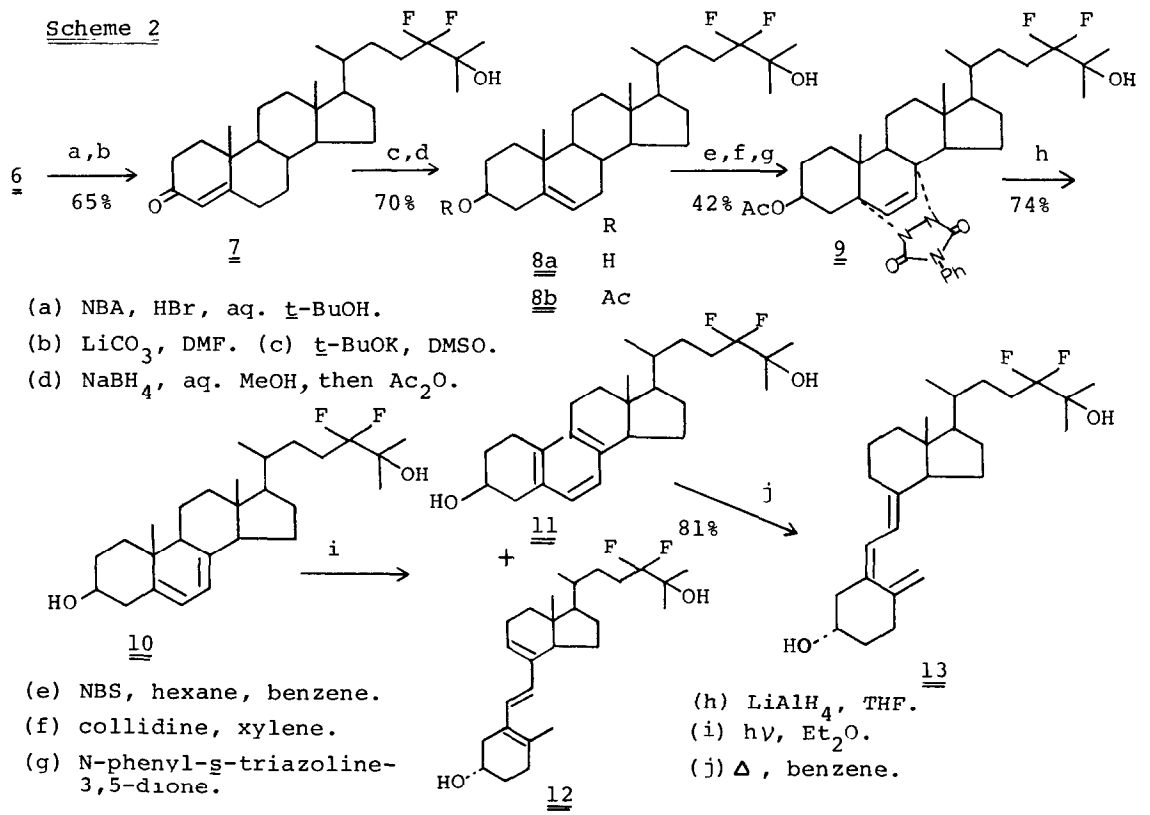
Scheme 1

Having thus established the construction of the side chain, the stage was set to effect the transformation of the saturated steroid skelton to the vitamin D ring system. Conversion to the 3β-hydroxy-$\Delta^5$-sterol 8a [mp 168- 170°; m/e 438, 420; NMR ($CDCl_3$) δ 0.70 (3H, s), 0.95 (3H, d, J = 6 Hz), 1.02 (3H, s), 1.32 (6H, s), 3.55 (1H, m, w/2 = 24 Hz), 5.40 (1H, d, J = 4 Hz)] was achieved by deconjugation[7] of the enone 7 (mp 177-178°; m/e 436 ), which was obtained by simultaneous oxidation bromination reaction[8] of 6 followed by dehydrobromination, and subsequent reduction with $NaBH_4$. The acetate 8b derived from 8a was transformed to the corresponding vitamin in the usual manner.[9] Allylic bromination followed by dehydrobromination gave a mixture of the 5,7- and the 4,6-diene from which the former was isolated as the triazoline adduct 9 mp 194-195°; NMR ($CDCl_3$) δ 0.82 (3H, s), 1.00 (3H, s), 1.32 (6H, s), 2.04 (3H, s), 3.25 (1H, dd, J = 14, 5 Hz), 5.50 (1H, tt, J = 10, 5 Hz), 6.36 (2H, ABq, J = 8 Hz) , which by reduction with $LiAlH_4$ afforded the provitamin 10: mp 177-179°; m/e 436, 403, 377; NMR ($CDCl_3$) δ 0.63 (3H, s), 0.94 (3H, s), 1.31 (6H, s), 3.60 (1H, m, w/2 = 26 Hz), 5.40 (1H, m), 5.60 (1H, dd, J = 6, 2 Hz). Irradiation

of the provitamin 10 in ether by high pressure mercury lamp through Vycor filter and chromatography of the products on Sephadex LH20 yielded the previtamin 11 (38.5%) [$\lambda_{max}$ (95% EtOH) 262 nm], the tachysterol analog[10] 12 (25.5%) [$\lambda_{max}$ (95% EtOH) 271(sh), 281, 291 (sh) nm; NMR ($CDCl_3$) $\delta$ 0.72 (3H, s), 1.00 (3H, d, J = 6 Hz), 1.34 (6H, s), 1.82 (3H, s), 4.00 (1H, m), 5.75 (1H, bs) 6.40 (2H, ABq, J = 16 Hz)], and unchanged 10 (7.5%). Refluxing in benzene (2 hr) and subsequent storage at room temperature (5 days) converted the previtamin 11 exclusively to the vitamin 13 (81%). The vitamin thus obtained showed typical UV spectrum [$\lambda_{max}$ (95% EtOH) 265 nm ($\log \varepsilon$ = 4.24)] and mass fragmentation pattern (m/e 436, 136, 118) of vitamin D derivatives supporting the assigned structure. The $^1$H NMR spectrum of 13 afforded further supporting evidence for the structure showing the signals of methyl groups at $\delta$ 0.56 (3H, s), 0.95 (3H, d, J = 6 Hz), and 1.32 (6H, s), the 3$\alpha$ proton at $\delta$ 3.95 as multiplet with w/2 = 20 Hz, the C-19 olefinic protons at $\delta$ 4.85 and 5.08 as broad singlets, and the protons on C-6 and C-7 at $\delta$ 6.16 as AB quartet with J = 11 Hz. (Scheme 2).

The fluorovitamin obtained in the present work was now subjected to the biological testing. The results will be reported elsewhere.

Scheme 2



Synthesis of 24,24-difluoro-1α,25-dihydroxyvitamin $D_3$ is progressing using the same synthetic intermediate 6.

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