Synthesis of 26,26,26,27,27,27-Hexafluoro-25-hydroxyvitamin D_3

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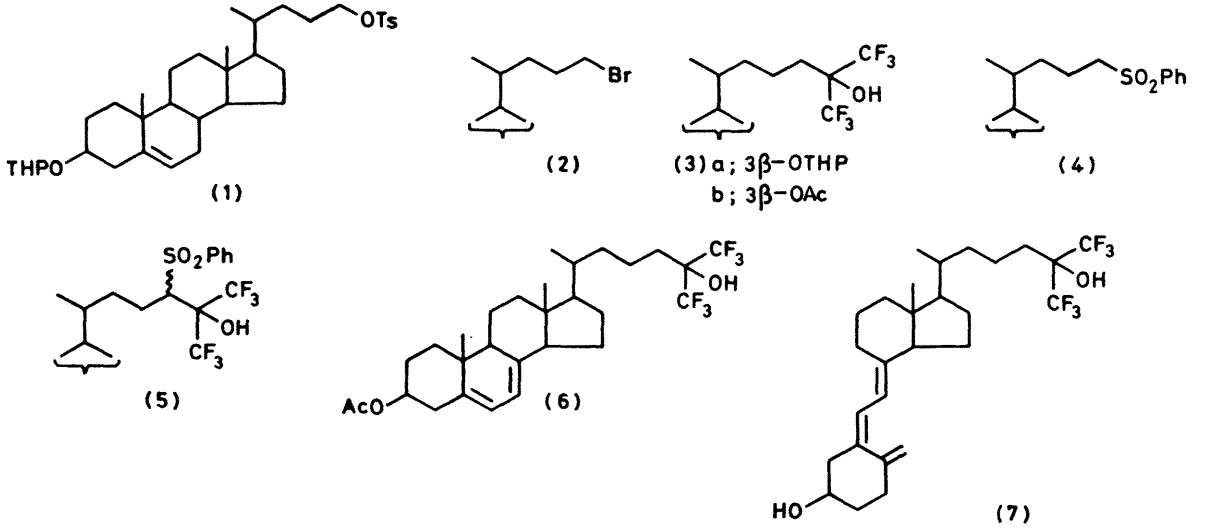
Summary In order to investigate the biological significance of 26-hydroxylation of vitamin D_3, 26,26,26,27,27,27-hexafluoro-25-hydroxyvitamin D_3 was prepared from 24-tosyloxy-25,26,27-trinorcholest-5-en-3β-yl tetrahydropyranyl ether.

IT is well known that vitamin D_3 undergoes sequential 25-hydroxylation and 1α-hydroxylation to be converted into a physiologically active hormone.[1] It has also been demonstrated that 25-hydroxyvitamin D_3 undergoes 24*R*-hydroxylation and 26-hydroxylation as alternatives to 1α-hydroxylation.[1] To study the functional importance of 24-hydroxylation of vitamin D_3, 25-hydroxyvitamin D_3, blocked at the 24 position with fluorine atoms (24,24-difluoro-25-hydroxyvitamin D_3), has been synthesized[2] and its biological activity reported.[3]

Although 25,26-dihydroxyvitamin D_3 is one of the major metabolites of vitamin D_3,[4] the biological significance of 26-hydroxylation remained to be clarified. The evidence for side-chain oxidation of vitamin D_3 metabolites[5] and the isolation of a new metabolite, 25-hydroxyvitamin D_3 26,23-lactone (calcidiol lactone)[6] by DeLuca *et al.* suggested an important role for the 26-hydroxylation. 25-Hydroxyvitamin D_3 blocked at the 26 and 27 positions with fluorine atoms to prevent the hydroxylation may be of importance in elucidating this role. We report herein the synthesis of 26,26,26,27,27,27-hexafluoro-25-hydroxyvitamin D_3.

When the 24-bromide (**2**)†, prepared from 3β-tetrahydropyranyloxychol-5-en-24-ol tosylate (**1**)[2] with lithium bromide, was treated with activated magnesium (prepared from potassium and magnesium chloride)[7] in tetrahydrofuran (THF) at room temperature for 2 h followed by introduction of an excess of hexafluoroacetone gas with cooling with solid carbon dioxide–acetone, the hexafluoro-25-hydroxy-compound (**3a**) was obtained in 16% yield; *m/e* 510 (M^+ — THP), 492, 477, and 255; δ ($CDCl_3$) 0·68 (s, 18-H), 0·94 (d, *J* 6 Hz, 21-H), 1·00 (s. 19-H), 3·48 (m), 3·88 (m, 3-H), 4·72 (m), and 5·32 (m, 6-H). Removal of the THP group and subsequent acetylation gave the acetate (**3b**) in 60% yield; m.p. 165—166 °C (from cyclohexane); *m/e* 492 (M^+ — AcOH), 477, 384, 371, and 255; δ ($CDCl_3$) 2·02 (s, Ac), 4·56 (m, 3-H), and 5·34 (m, 6-H).



THP = tetrahydropyran-2-yl

An alternative simple synthesis of compound (**3**) used an intermediary steroidal sulphone derivative. Treatment of the bromide (**2**) with sodium benzenesulphinate (3·5 equiv.) in dimethylformamide at 65—70 °C for 6 h afforded the sulphone (**4**), m.p. 155—161 °C, in 84% yield. Lithiation of the sulphone (**4**) with 1·2 equiv. of lithium di-isopropylamide in THF at 0 °C for 15 min, followed by introduction of hexafluoroacetone gas gave the adduct (**5**) in 84% yield; *m/e* 650 (M^+ — THP), 632, and 617; δ ($CDCl_3$) 0·59 (s, 18-H), 0·74 (d, *J* 6 Hz, 21-H), 1·01 (s, 19-H), 3·48 (m), 3·88 (m, 3-H), 4·68 (m), 5·30 (m, 6-H), and 7·56—7·98 (m). Desulphonylation of (**5**) with 4% Na–Hg in the presence of Na_2HPO_4, methanol, and THF, at room temperature for 1 h[8] gave (**3a**), in 64% yield, which was converted into the acetate (**3b**) in 51% yield from (**4**).

Conversion of (**3b**) into the corresponding vitamin D form was carried out by the standard procedure as follows. Allylic bromination of (**3a**) with *N*-bromosuccinimide in

† All new compounds gave the expected microanalytical and spectral data.

CCl_4 followed by dehydrobromination with 2,4,6-trimethylpyridine in xylene gave the 5,7-diene acetate (**6**) in 26% yield, λ_{max}(EtOH), 262 sh (ϵ 7900), 271 (ϵ 11,000), 282 (ϵ 11,600), and 293 nm (ϵ 6500). This was irradiated with a medium-pressure mercury lamp in ethanol–benzene, refluxed for 1 h, and saponified with 5% KOH–methanol. Purification by h.p.l.c. [Zorbax SIL, methylene chloride–hexane (2 : 1)] gave 26,26,26,27,27,27-hexafluoro-25-hydroxyvitamin D_3 (**7**) in 25% yield; λ_{min}(EtOH), 227·5 (ϵ 8600), λ_{max} 264 nm (ϵ 18,000); *m/e* 508 (M^+), 493, 490, 476, 271, 253, 136, and 118.

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[1] H. F. DeLuca and H. K. Schnoes, *Annu. Rev. Biochem.*, 1976, **45**, 631.
[2] Y. Kobayashi, T. Taguchi, T. Terada, J. Oshida, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 1979, 2023.
[3] Y. Tanaka, H. F. DeLuca, Y. Kobayashi, T. Taguchi, N. Ikekawa, and M. Morisaki, *J. Biol. Chem.*, 1979, **254**, 7163.
[4] T. Suda, H. F. DeLuca, H. K. Schnoes, Y. Tanaka, and M. F. Holick, *Biochemistry*, 1970, **9**, 4776.
[5] R. Kumar, D. Harnden, and H. F. DeLuca, *Biochemistry*, 1976, **15**, 2420; D. Harnden, R. Kumar, M. F. Holick, and H. F. DeLuca, *Science*, 1976, **193**, 493.
[6] H. F. DeLuca and H. K. Schnoes, 'Vitamin D: Basic Research and its Clinical Application,' eds. A. W. Norman, K. Schaefer, D. V. Herrath, H. G. Grigolet, J. W. Coburn, H. F. DeLuca, E. B. Mawer, and T. Suda, Walter de Gryter, Berlin, 1979, p. 445.
[7] R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, 1974, **96**, 1775.
[8] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1978, **100**, 3435.