

Synthesis of 26,26,26,27,27,27-Hexafluoro-25-hydroxyvitamin D₃

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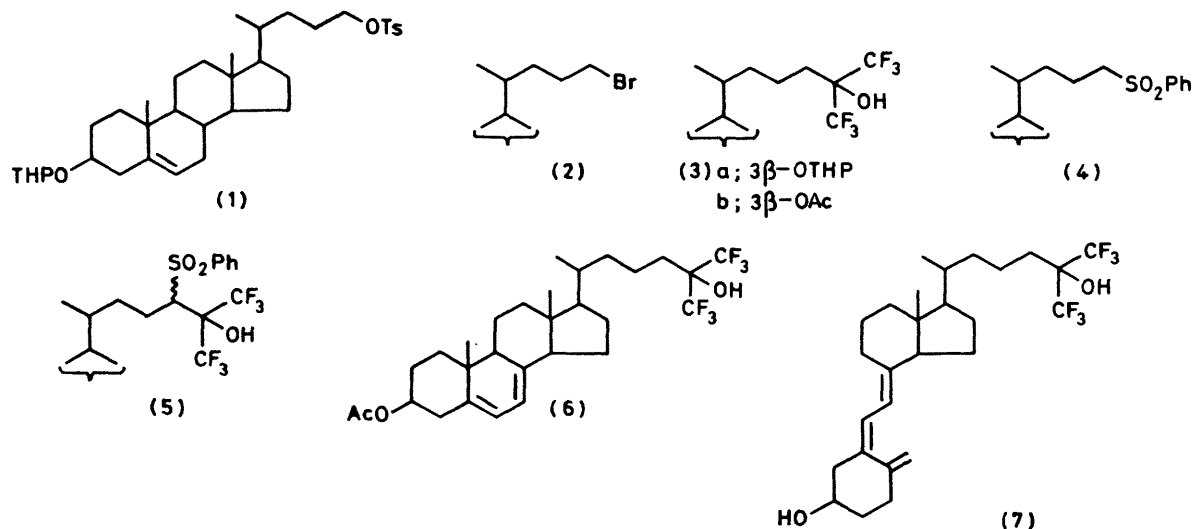
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Summary In order to investigate the biological significance of 26-hydroxylation of vitamin D₃, 26,26,26,27,27,27-hexafluoro-25-hydroxyvitamin D₃ was prepared from 24-tosyloxy-25,26,27-trinorcholest-5-en-3 β -yl tetrahydropyranyl ether.

It is well known that vitamin D₃ undergoes sequential 25-hydroxylation and 1 α -hydroxylation to be converted into a physiologically active hormone.¹ It has also been demonstrated that 25-hydroxyvitamin D₃ undergoes 24*R*-hydroxylation and 26-hydroxylation as alternatives to 1 α -hydroxylation.¹ To study the functional importance of 24-

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 (CDCl₃) 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 (CDCl₃) 2.02 (s, Ac), 4.56 (m, 3-H), and 5.34 (m, 6-H).



THP = tetrahydropyran-2-yl

hydroxylation of vitamin D₃, 25-hydroxyvitamin D₃, blocked at the 24 position with fluorine atoms (24,24-difluoro-25-hydroxyvitamin D₃), has been synthesized² and its biological activity reported.³

Although 25,26-dihydroxyvitamin D₃ is one of the major metabolites of vitamin D₃,⁴ the biological significance of 26-hydroxylation remained to be clarified. The evidence for side-chain oxidation of vitamin D₃ metabolites⁵ and the isolation of a new metabolite, 25-hydroxyvitamin D₃ 26,23-lactone (calciol lactone)⁶ by DeLuca *et al.* suggested an important role for the 26-hydroxylation. 25-Hydroxyvitamin D₃ 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 D₃.

When the 24-bromide (**2**)[†], prepared from 3 β -tetrahydropyranyloxychole-5-en-24-ol tosylate (**1**)² with lithium bromide, was treated with activated magnesium (prepared from

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 (CDCl₃) 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 Na₂HPO₄, methanol, and THF, at room temperature for 1 h⁸ 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, $\lambda_{\text{max}}(\text{EtOH})$, 262 nm (ϵ 7900), 271 nm (ϵ 11,000), 282 nm (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; $\lambda_{\text{min}}(\text{EtOH})$, 227.5 nm (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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