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SYNTHESIS OF 25-FLUOROVITAMIN D_3

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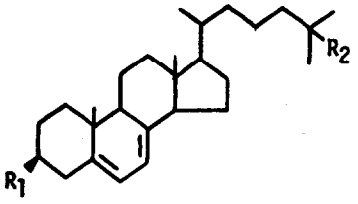
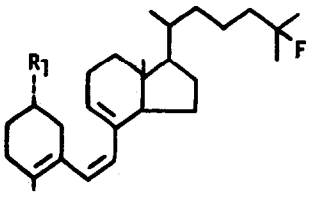
Recent studies concerning the pharmacology of vitamin D have indicated that metabolic conversion of the parent compound to hydroxylated derivative is a necessary requirement for biological activity.[1] In order to further delineate structure activity relationships and also to study the effect of blocking the known metabolic sites of compounds in this series, the synthesis of 25-blocked vitamin D_3 would be of great interest. The recent publication[2] of the synthesis of 25-fluorovitamin D_3, 24-dehydrovitamin D_3 and 25-dehydrovitamin D_3 from 25-hydroxyvitamin D_3 prompts us to report the alternate synthesis of 25-fluorovitamin D_3 from 7-dehydro-25-hydroxycholesterol.[3,4]

The diol 1a was selectively acetylated to monoacetate 1b [mp 142-144° (acetone); uv (EtOH) λ_{max} 262 (7,600), 271 (10,800), 282 (11,400), 293 nm (6,500)]. Fluorination of 1b with diethylaminosulfur trifluoride[5] gave 1c [76% yield; mp 130-133°; uv (EtOH) λ_{max} 262 (7,700), 271 (11,000), 282 (11,500), 293 nm (6,500); nmr ($CDCl_3$) δ 0.62 (s, 3H, 18-Me), 0.95 (s, 3H, 19-Me), 1.34 (d, 6H $J_{H,F}$ = 22 Hz, 26,27-Me's), 2.03 (s, 3H, CH_3CO), 4.7 (m, 1H, C-3-H), 5.35 and 5.65 ppm (ABq, 2H, J = 6 Hz, C-6,7-H's)]. Conversion of 1c into the corresponding vitamin D was carried out using established procedures.[6]

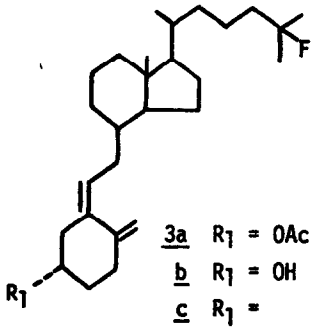
Irradiation of an ether solution of 1c under nitrogen in a quartz cell at 0 to 5° for 15 min with a 450-W Hanovia lamp resulted in ca 70% conversion. Addition of 9-fluorenone[7] as a triplet sensitizer to this photolysis mixture, followed by a second 10 min irradiation gave 2a as the major product. The previtamin 2a was isolated by preparative tlc in 45% yield.[8] Thermal equilibration of 2a in isooctane at 100 to 110° for 2 hr under nitrogen gave a 2:3 mixture of 2a and 3a from which 3a[9] could be isolated in low yield. Saponification of the mixture gave alcohols 2b and 3b from which the desired 3b was isolated as a glass by low temperature preparative tlx [35% from 2a; uv (Et_2O) λ_{max} 266, λ_{min} 229 nm; ir (nujol) ν_{max} 3340 cm^{-1}; nmr ($CDCl_3$) δ 0.57 (s, 3H, 18-Me), 0.93 (d, 3H, J = 4 Hz, 21-Me), 1.33 (d, 6H, $J_{H,F}$ = 22 Hz, 26,27-Me's), 3.9 (m, 1H, C-3-H), 4.80 (m, 1H, 19-CH_2), 5.02 (m, 1H, 19-CH_2), 5.99 and 6.26 ppm (ABq, J = 11 Hz, C-6, 7-H's); m/e (rel. intensity) 402 (M^+, 100), 382 (M-HF, 25), 369 (M-H_2O-CH_3, 60). Compound 3b was further characterized by conversion to its 3,5-dinitrobenzoate 3c [50% yield; mp 132-135° (aq. EtOH); m/e (rel. intensity) 596 (M^+, 1), 576 (M-HF, 100); Anal. Calcd for $C_{34}H_{35}FNO_2$: C, 68.43; H, 7.60; N, 4.70. Found: C, 68.08; H, 7.52; N, 4.44].



1a $R_1 = R_2 = OH$
b $R_1 = OAc$; $R_2 = OH$
c $R_1 = OAc$; $R_2 = F$



2a $R_1 = OAc$
b $R_1 = OH$



3a $R_1 = OAc$
b $R_1 = OH$
c $R_1 = OCOC_6H_3(NO_2)_2$

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3. J. W. Blunt and H. F. DeLuca, Biochem., 8, 671 (1969).
4. The diol 1a was synthesized from 25-hydroxycholesterol[10] according to the established procedures; *i.e.*, dibenzoylation, bromination,[11] dehydrobromination,[11] purification through triazoline adduct,[12] and LAH reduction.
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8. 2a: nmr ($CDCl_3$) δ 0.68 (s, 3H, 18-Me), 0.98 (d, 3H, J = 4 Hz, 21-Me), 1.34 (d, 6H, $J_{H,F}$ = 22 Hz, 26,27-Me's), 2.03 (s, 3H, CH_3CO), 4.9 (m, 1H, C-3-H), 5.48 (m, 1H, C-9-H), 5.60 and 5.91 ppm (ABq, 2H, J = 12 Hz, C-6,7-H's).
9. 3a: uv (EtOH) λ_{max} 265 nm; nmr ($CDCl_3$) δ 0.55 (s, 3H, 18-Me), 0.93 (d, 3H, J = 4 Hz, 21-Me), 1.35 (d, 6H, $J_{H,F}$ = 22 Hz, 26,27-Me's), 2.02 (s, 3H, CH_3CO), 4.82 (m, 1H, 19-CH_2) 4.95 (m, 1H, C-3-H), 5.04 (m, 1H, 19-CH_2), 5.99 and 6.22 ppm (ABq, 2H, J = 11 Hz, C-6,7-H's); m/e rel. intensity) 444 (M^+, 25), 424 (M-HF, 8), 384 (M-AcOH, 100), 364 (M-AcOH-HF, 21).
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