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SYNTHESIS OF 24,24-DIFLUORO- AND 24ξ-FLUORO-25-HYDROXYVITAMIN D_3

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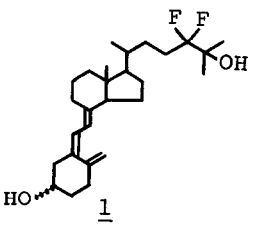
SUMMARY From cholenic acid 24,24-difluoro-25-hydroxyvitamin D_3 and 24ξ-fluoro-25-hydroxyvitamin D_3 were prepared.

Although it is established that hydroxylation of vitamin D_3 at C-1 and C-25 positions is essential for eliciting biological activity, the functional role of C-24 hydroxylation has not yet been fully clarified.[1] Blocking of 24-hydroxylation by substitution with fluorine atom[2] at this position would give an important information on this problem. Herein we describe synthesis of 24,24-difluoro-25-hydroxyvitamin D_3 1 and 24ξ-fluoro-25-hydroxyvitamin D_3 2, starting from Δ^5-cholenic acid 3.[3]



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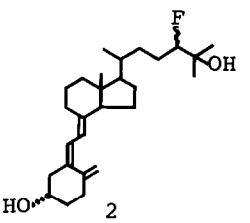

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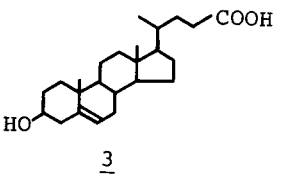

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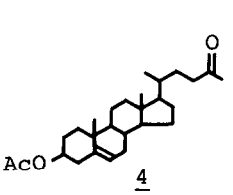
Treatment of cholenic acid (3) tetrahydropyranyl ether with an excess of CH_3Li in tetrahydrofuran(THF)-ethyl ether(0°, 4 hr) followed by deprotection [p-toluenesulfonic acid(p-TsOH) in CH_2Cl_2-methanol, 20°, 24 hr] and acetylation gave the methylketone 4 [mp 148-151°, δ 2.12(3H, s, C-25), m/e 354(M-60] in 67% overall yield from 3. Enolacetylation of 4 was effected by refluxing for 7 hr in acetic anhydride in the presence of p-TsOH to give, in 72% yield, the diacetate 5 [mp 109-110°, δ 5.02(1H, m, C-23), 1.90(3H, s, C-25), m/e 396(M-60)]. Reaction of 5 with difluorocarbene generated from sodium chlorodifluoroacetate in diglyme(170°, 0.5 hr)[4] furnished the cyclopropane 6 [34% yield, mp 112-115°, δ 1.60(3H, C-26),2.02 and 2.05(6H, acetyl), m/e 446(M-60)]. Treatment of 6 with LiOH in THF-methanol-water at 20° for 2 hr followed by acetylation gave, after chromatography on silica gel, the difluoroketone 7 [9.3% yield, mp 135-136.5°,

δ 2.26(3H, t, J_{HF}=1 Hz, C-26), m/e 404 (M-60)] and a mixture of the 23(E)- and 23(Z)-conjugated ketone 8 [the 24(E)-olefin : 7.7% yield, mp 142-143°, δ 5.62 (1H, dt, J_{HF}=22 Hz, J_{HH}=8 Hz, C-23), 2.23 (3H, d, J_{HF}=5 Hz, C-26), m/e 384 (M-60); the 23(Z)-olefin : 53% yield,mp 169-170°, δ 6.03(1H, dt, J_{HF}=34 Hz, J_{HH}=8 Hz, C-23), 2.27(3H, d, J_{HF}=3 Hz, C-26), m/e 384 (M-60)]. Grignard reaction of the fluoroketone 7 with an excess of CH_3MgI in ethyl ether (0°, 15 min) and subsequent acetylation furnished, in 85% yield, the 25-carbinol 9 [mp 163-164.5°, δ 1.28 (6H, s, C-26,27), m/e 420 (M-60)]. Allylic bromination of 9 (N-bromosuccinimide in refluxing CCl_4, 25 min) and then dehydrobromination (s-collidine in refluxing xylene, 15 min) afforded a mixture of the 4,6-diene and the 5,7-diene from which the desired 5,7-diene [λ_{max} 263, 272, 282, and 292 nm; m/e 419 (M-59)] was isolated, in 28% yield, by treatment with p-TsOH in acetone, 20°, 15 hr followed by preparative thin layer chromatography [benzene-ethyl acetate (15:1), 3 times]. The 24,24-difluoro-5,7-diene was saponified (5% KOH-methanol, 20°, 15 hr) and then irradiated (Hanovia 654A36; 200W) in a mixture of ethanol and benzene for 2.5 min at 0°. After refluxing for 1 hr, the products were fractionated with thin layer chromatography [silica gel, benzene-ethyl acetate (5:1), 3 times] and high pressure liquid chromatography (Zorbax SIL, CH_2Cl_2) to give the vitamin D_3 1[λ_{max} 264 nm, λ_{min} 228 nm, m/e 436 (M^+), 421, 418, 403, 377, 271, 253, 136, 118].

For the synthesis of 24-fluoro analog 2, cholenic acid (3) was successively treated with dihydropyran-p-TsOH, $LiAlH_4$-THF, and p-TsCl-pyridine to afford the tosylate 10, which in turn was reacted with KCN/18-crown-6 in dimethylformamide at 70°, 3 hr to give the cyanide 11 (48% yield, mp 142-143°). Hydrolysis of 11 with KOH in aqueous ethanol (140°, 48 hr) yielded the carboxylic acid 12 (63% yield, mp 171-172°), which on treatment with CH_2N_2 gave the methyl ester 13 (79% yield, mp 159-161°). The enolate of 13 (generated by treatment with lithium dicyclohexylamide at -78°) was treated with iodine in THF at -78° to yield the iodide 14. Substitution of iodine of 14 with hydroxyl was accomplished by reaction with CF_3COOAg-Ag_2O in CH_3CN-ethyl ether (20°, 20 hr) followed by saponification (KOH-methanol-THF, 20°, 16 hr). Reesterification with CH_2N_2 gave the hydroxyester 15 [mp 114-117°, δ 4.16 (1H, m, C-24), m/e 418 (M-84)] in 63% overall yield from 13.[5] The tosylate derived from 15 was treated with KF/18-crown-6 in dimethylformamide (70°, 15 hr) to give the fluoride 17, which on deprotection (p-TsOH in methanol-CH_2Cl_2, 0°, 4 hr) afforded the fluoro ester 18 [73% yield, mp 104-105°, δ 4.86 (1H, dm, J_{HF}=48 Hz, C-24), m/e 420 (M^+)]. Treatment of 18 with an excess of CH_3MgI in ethyl ether (20°, 20 min) followed by acetylation furnished, in 80% yield, the fluorohydrin 19 [mp 153-154°, δ 4.14 (1H, dm, J_{HF}=48 Hz, C-24), 1.20 (6H, s, C-26,27), m/e 402 (M-60)]. Conversion of 19 to the corresponding vitamin D_3 2 was carried out essentially as described for the difluoro analog 9. Compound 2 showed the expected spectral properties [λ_{max} 263 nm, λ_{min} 228 nm, m/e 418 (M^+), 403 (M-15), 400 (M-18), 385 (M-15-18), 359, 271, 253, 136, 118].



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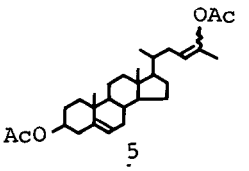

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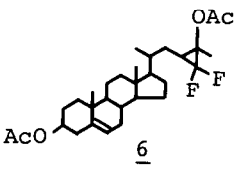

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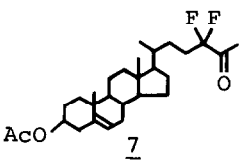

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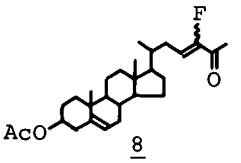

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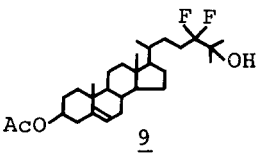

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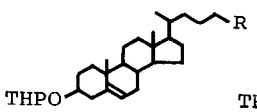

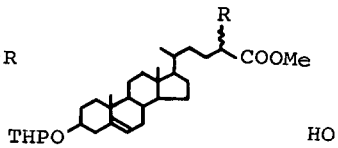

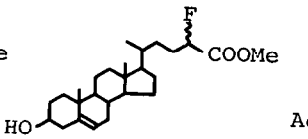

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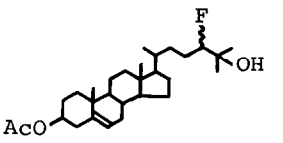

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10	R = OTs	14	R = I
11	R = CN	15	R = OH
12	R = COOH	16	R = OTs
13	R = COOMe	17	R = F

Biological activities of 1 and 2 are now being examined by Prof. H. F. DeLuca, University of Wisconsin.

References and Notes

1. The potential importance of the 24-hydroxyl has been suggested from the remarkable selectivity for the 24R isomer for expression of vitamin D activity: Y. Tanaka, H. Frank, H.F. DeLuca, N. Koizumi and N. Ikekawa, Biochem., 14, 3293 (1975) (24-hydroxyvitamin D_3); Y. Tanaka, H.F. Deluca, N. Ikekawa, M. Morisaki, and N. Koizumi, Arch. Biochem. Biophys., 170, 620 (1975) (24,25-dihydroxyvitamin D_3). H. Kawashima, K. Hoshina, Y. Hashimoto, T. Takeshita, S. Ishimoto, T. Noguchi, N. Ikekawa, M. Morisaki, and H. Orimo, FEBS-Letters, 76, 177 (1977) (1,24-dihydroxyvitamin D_3). In contrast, (24S)- and (24R)-1,24,25-trihydroxyvitamin D_3 are approximately equal in activity: L. Castillo, Y. Tanaka, H.F. DeLuca, and N. Ikekawa, Mineral Electrol. Met., 1, 198 (1978), and the fact that 25-hydroxy- and 1,25-dihydroxyvitamin D_3 are more active than the corresponding 24-hydroxylated compounds seems to support the idea that 24-hydroxylation may be an inactivation rather than activation step in vitamin D metabolism. However, the recent reports suggest some positive biological function for the 24-hydroxyl : M.L. Sunde, C.M. Turk and H.F. DeLuca, Science, 200, 1067 (1978); H.L. Henry and A.W. Norman, ibid, 201, 835 (1978); P. Bordier, H. Rasmussen, P. Marie, L.

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2. It is well known that carbon-fluorine bonds are biologically seldom cleaved and bulkiness of fluorine atom approximates that of hydrogen : C. Heidelberger, L. Griesbach, B.J. Montag, D. Mooren, and O. Cruz, Cancer Res., 18, 305 (1958); L. Pauling, "The Nature of the Chemical Bond", 3rd ed, Ithaca N.Y., Cornell University Press, 1960, p. 88.
3. For synthesis of another fluorinated vitamin D_3 analogs see : R.I. Yakhimovich, V.M. Klimashevsky and G.M. Segal, Khim. Farm. Zhur., 10, 58 (1976); B.L. Onisko, H.K. Schnoes, and H.F. DeLuca, Tetrahedron Letters, 1107 (1977); S.S. Yang, C.P. Dorn, and H. Jones, ibid., 2315 (1977); M. Sheves, B. Sialom, and Y. Mazur, J.C.S. Chem. Comm., 1978, 554; J.L. Napoli, M.A. Fivizzani, A.H. Hamstra, H.K. Schnoes, H.F.DeLuca and P.H. Stern, Steroids, 32, 458 (1978).
4. P. Crabbé, A. Cervantes, A. Cruz, E. Gleazzi, J. Iriarte, and E. Velarde, J. Am. Chem. Soc., 95, 6655 (1973).
5. The 3,24-dibenzoyl ester derived from 15 showed a twin peak on high pressure liquid chromatography (HPLC) (Zorbax SIL, 10% CH_2Cl_2 in n-hexane), indicating that 15 is a 1:1 epimeric mixture at C-24 position. This was further corroborated by transformation of 15 into a 1:1 mixture of (24R)- and (24S)-3,24-dibenzoyloxycholest-5-en-25-ol trimethylsilyl ether which was cochromatographed on HPLC with authentic samples [M. Seki, N. Koizumi, M. Morisaki, and N. Ikekawa, Tetrahedron Letters, 15 (1975)].

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