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SYNTHESIS OF 2β-FLUORO-1α-HYDROXYVITAMIN D_3

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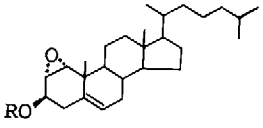
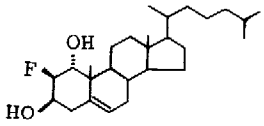
Summary 2β-Fluoro-1α-hydroxyvitamin D_3(3) was prepared from 1,2α-epoxycholest-5-en-3β-yl tetrahydropyranyl ether(1a) via 2β-fluorocholest-5-ene-1α, 3β-diol(2).

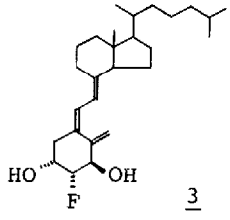
The crucial importance of 1α-hydroxyl function of 1α,25-dihydroxyvitamin D_3, a hormonal active form of vitamin D_3 for eliciting its biological activity, is well established,[1] and 1α-hydroxyvitamin D_3 is the most frequently prepared compound[2] among various analogs of vitamin D_3 and its metabolites. In search for agents with augmented or differential activity, we thought that an analog fluorinated around 1α-hydroxyl group should possess interesting biological activity.[3] Thus, in view of the similar atomic dimensions of fluorine to hydrogen, the steric effect on disrupting hormone-receptor interaction(presumably through the conjugate base of 1α-hydroxyl) would be small, but the binding properties of 1α-hydroxyl group may be greatly influenced by the strong electronegative substituent. Described here is the synthesis of 2β-fluoro-1α-hydroxyvitamin D_3(3) from 1,2α-epoxycholest-5-en-3β-yl tetrahydropyranyl ether(1a) which was previously prepared as the intermediate of our synthesis of 1α-hydroxyvitamin D_3.[4]



1a, R=THP
1b, R=H



2



3

Treatment of 1a with pyridinium p-toluenesulfonate (0.1 mol equiv) in a 1 : 1 mixture of CH_2Cl_2 and MeOH at 55° for 5 hr gave the epoxyalcohol 1b [75 % yield, mp 105-107°, δ 0.72(3H, s, 18-Me), 1.15(3H, s, 19-Me), 3.08 and 3.20(2H, a pair of d, J=4 Hz, 1- and 2-H), 3.90(1H, m, 3-H), 5.5(1H, m, 6-H), m/e 400(M^+), 382, 342, 287, 269]. Attempts to introduce fluorine at C-2 of 1b by Et_4NF or KF/dicyclohexyl-18-crown-6 were fruitless. However, heating of 1b with potassium hydrogen difluoride (Merck KF cont. KHF_2) in ethylene glycol at 170° for 1.5 hr[5] furnished the fluorohydrin 2 [48 % yield, mp 167-170°, δ 0.68(3H, s, 18-Me), 1.13 (3H, s, 19-Me), 3.7(1H, m, 3-H), 3.96(1H, m, 1-H), 4.78(1H, td, J_{HF}=50 Hz, J_{HH}=3 Hz, 2-H), 5.6(1H, m, 6-H), m/e 420(M^+), 405, 402, 400, 382, 307, 289, 265, 247]. The β orientation of the fluorine at C-2 was predicted from diaxial opening of

epoxide and evidenced with the coupling constant (3 Hz) of the triplet of doublets in 2 which is consistent with dihedral angles of $\theta(H_2-H_1)=\theta(H_2-H_3)=60^{\circ}$. Transformation of 2 into 2β-fluoro-1α-hydroxyvitamin D_3(3) was carried out by the standard vitamin D methodology. Thus, acetylation of 2 with acetic anhydride-pyridine at 90° for 4 hr gave the diacetate which on bromination (N-bromosuccinimide in refluxing CCl_4 for 1.3 hr) followed by dehydrobromination (s-collidine in refluxing xylene for 15 min) was converted to a mixture of the 5,7-diene and 4,6-diene. Acid treatment (p-toluenesulfonic acid in acetone, overnight) of the crude product converted the 4,6-diene into a much less polar material to allow for effective isolation by chromatography of the desired 5,7-diene [30 % yield from 2, λ_{max} 262, 271, 281.5 and 293 nm]. This was irradiated with a medium pressure mercury lamp (Hanovia 654A 36; 200W) in a mixture of benzene-EtOH(2 : 1) at 0° for 2.5 min and then refluxed for 1 hr to give, after purification by silica gel TLC developed 2 times with benzene-AcOEt(14 : 1), the vitamin D diacetate in 36 % yield. Subsequent saponification with 2.5 % KOH in a mixture of MeOH-THF(1 : 1) at 15° overnight and then purification by HPLC [Zorbax SiL, 15 cm x 4.1 mm, CH_2Cl_2-hexane(4 : 1), 90 kg/cm^2] afforded 2β-fluoro-1α-hydroxyvitamin D_3(3) [λ_{min} 226, λ_{max} 265 nm, m/e 418(M^+), 403, 400, 398, 380, 365, 305, 287, 150, 135, δ 0.49(3H, s, 18-Me), 0.82(6H, d, J=7 Hz, 26,27-Me), 0.87(3H, d, J=6 Hz, 21-Me), 4.3 and 4.5 (3H, a pair of m, 1-, 2- and 3-H), 5.14 and 5.54(2H, a pair of m, 19-H), 5.99(1H, d, J=12 Hz, 7-H), 6.36(1H, d, J=12 Hz, 6-H)].[6]

Biological activity of 3 is being tested at the laboratories of Prof. H.F. DeLuca, University of Wisconsin. We are indebted to Dr. S. Urano, Tokyo Metropolitan Institute of Gerontology for taking 200 MHz nmr of 3.

References and Notes

1. M.F.Holick, E.J.Semmler, H.K.Schnoes and H.F.DeLuca, Science, 180, 190(1973); H.F.DeLuca and H.K.Schnoes, Ann. Rev. Biochem., 45, 631(1976).
2. N.Ikekawa and T.Takeshita, J.Org. Synth. Chem., 37, 755; 809(1979).
3. It is well known that introduction of 6α- or 9α-fluoro function in the corticosteroid skeleton remarkably potentiates biological activity : A.Wettstein, "A Ciba Foundation Symp., Carbon-Fluorine Compounds", Elsevier(1972).
4. M.Morisaki, A.Saika, K.Bannai, M.Sawamura, J.R-Lightbourn and N.Ikekawa, Chem. Pharm. Bull., 23, 3272(1975).
5. P.A.Grieco, T.Sugahara, Y.Yokoyama and E.Williams, J. Org. Chem., 44, 2189 (1979).
6. The mass spectrum of 3 revealed only weak ion due to cleavage of C-7,8 bond (m/e 170) and instead, m/e 380 derived from M-H_2O-HF predominated. It should also be noted that the fluorine atom has a remarkable effect of decreasing polarity and the retention time of 3 on HPLC (vide supra) was 4.1 min, when those of 1α-hydroxyvitamin D_3 and vitamin D_3 were 11.0 and 1.5 min, respectively.

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