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SYNTHESIS OF 26,26,26-TRIFLUORO-25-HYDROXY AND 27-NOR-26,26,26-TRIFLUORO-25-HYDROXYVITAMIN D_3

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SUMMARY: Two new fluorinated 25-hydroxyvitamin D_3 analogs, 26,26,26-trifluoro-25-hydroxy (1) and 27-nor-26,26,26-trifluoro-25-hydroxyvitamin D_3 (2), were prepared from 24-phenylsulfonyl 25,26,27-triorcholest-5-en-3β-yl tetrahydropyranyl ether (3).

It is well known that vitamin D_3 must be sequentially hydroxylated at 25 and 1 position before it can carry out the biological activities. It has also demonstrated that 25-hydroxyvitamin D_3 (25-OH-D_3) undergoes 24R-hydroxylation, 26-hydroxylation and 26,23-lactonization as alternatives to 1α-hydroxylation.[1,2] To investigate the biological significance of the 26-hydroxylation of vitamin D_3, 25-hydroxyvitamin D_3 blocked at the 26 and 27 positions with fluorine atoms (26,26,26,27,27,27-hexafluoro-25-hydroxyvitamin D_3) has been synthesized[3] and its biological activity reported.[4] The hexafluoro analog was found to be approximately 40 times more potent than 25-OH-D_3 in bone-resorbing activity on fetal rat forelimb bones in vitro. Although this result may suggest some effects of the presence of the fluorine atoms at terminal carbon atoms of 25-OH-D_3 on augmentation and/or alteration of the biological activity, it is unclear whether this result was caused by the electronic effect of the fluorine atoms, metabolic stability of C-F bond, structural change or other effect. It is expected that similar analogs possessing trifluoromethyl group around 25-hydroxyl group would give some informations on this points. In this report we wish to describe the syntheses of 26,26,26-trifluoro-25-hydroxy (1) and 27-nor-26,26,26-trifluoro-25-hydroxyvitamin D_3 (2).

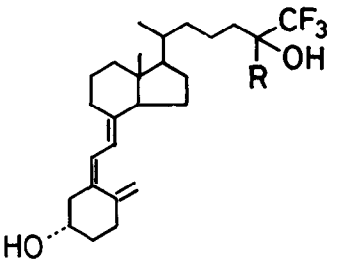
For the synthesis of 1, a similar method for the preparation of the hexafluoro analog via the reaction of the sulfone derivative (3) with hexafluoroacetone followed by the desulfonylation by Na-Hg[3] was not so effective, because of the formation of olefinic product at the desulfonylation reaction

of the trifluoroacetone adduct (4), similar as in the case of hydrogen substituent instead of fluorine atoms.[5] Thus, the treatment of lithio derivative of the sulfone (3) with an excess amount of trifluoroacetone gas (THF, -78°C, 15 min) gave the adduct (4) [quant., m/e 596 (M^+-84)] and the subsequent reaction of 4 with 4% Na-Hg (Na_2HPO_4, THF-MeOH, r.t., 1.5 h) afforded the Δ^{24}-trifluoride (7) [52%; E,Z mixture, mp 140-143°; m/e 438 (M^+-84); $\delta(CDCl_3)$ 1.78 (s, C-27), 5.64 and 6.02 (total 1H, each m, C-24)] and the desired trifluoromethyl carbinol (5) [14%; glass; m/e 456 (M^+-84), 438, 423; $\delta(CDCl_3)$ 1.33 (s, C-27)]. Deprotection (p-TsOH, CH_2Cl_2-MeOH, r.t., 2h) of 5 and acetylation (Ac_2O-Py, r.t., 15h) afforded the 3β-monoacetate (6) [89%; mp 124-127.5°; m/e 438 (M^+-60); $\delta(CDCl_3$ 1.36 (s, C-27), 2.04 (s, OAc); i.r.(KBr) 3360, 1720 cm^{-1}].

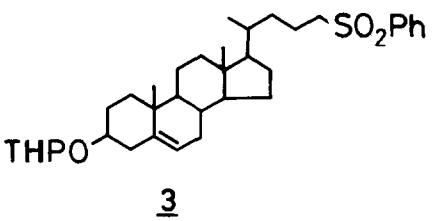
An alternative synthesis of compound (1) used an intermediary trifluoromethylketo sulfone derivative (8). Treatment of the lithio derivative of 3 with 5 equiv. of ethyl trifluoroacetate (THF, -78°, 1.5 h) afforded the keto sulfone (8) [78%; mp 159-163°; m/e 580 (M^+-84); $\delta(CDCl_3)$ 4.50 (1H, m, C-24), 7.20-7.82 (5H, m, aromatic)]. Reductive desulfonylation of the keto sulfone (8) with Al-Hg (10% aqueous THF, reflux, 30 min)[6] followed by the subsequent reaction of the reaction mixture with MeMgI [1.2 equiv. to 8, THF-ether (1:3), 0°C, 20 min) gave the desired trifluoride (5; 66%), the difluoride (9) [6.2%; mp 133-135°; m/e 438 (M^+-84); $\delta(CDCl_3)$ 1.24 (bs, C-27), 5.53 (1H, t, J_{HF}=56 Hz, C-26)] and the trifluoromethyl ketone (10) [13%; mp 136-139°; m/e 440 (M^+-84), 329; $\nu_{C=O}$(KBr) 1765 cm^{-1}; $\delta(CDCl_3)$ 2.70 (2H, t, J=7 Hz , C-24)], respectively.[7] Although the reductive desulfonylation of 8 with Al-Hg accompanied the further reduction of fluorine substituent resulted in the unseparable reaction mixture, the hydroxyl derivatives (5 and 9) were easily separated by silica gel chromatography.

In a similar manner, desulfonylation of 8 (reflux, 45 min) followed by the reaction with $NaBH_4$ (THF-EtOH, r.t., 20 min) afforded the trifluoro carbinol (11) [80%; mp 149-152°; m/e 442 (M^+-84); $\delta(CDCl_3)$ 3.72-4.02 (2H, m, C-3 and C-25)], the difluoro carbinol (12) [11%; mp 133-135°; m/e 424 (M^+-84); $\delta(CDCl_3)$ 5.62 (1H, dt, J_{HH}=4 and J_{HF}=56 Hz, C-26)] and the monofluoro carbinol (13)[8] [6.5%; mp 97-99°; m/e 406 (M^+-84)], respectively.[7] Deprotection and acetylation of 12 by usual manner afforded the corresponding diacetate (14; mp 92-94°).

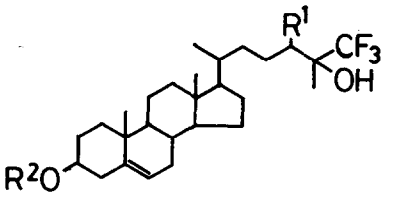
Transformation of 6 and 14 into the corresponding vitamin D_3 form (1 and 2) was carried out by the standard vitamin D_3 synthesis from cholesterol. Thus, bromination of 6 with NBS (CCl_4, reflux, 15 min) followed by dehydrobromination with s-collidine (xylene, reflux, 10 min) afforded a mixture of the 5,7-diene and 4,6-diene which on acid treatment (p-TsOH, acetone, overnight), the 4,6-diene converted into much less polar material to allow for effective isolation



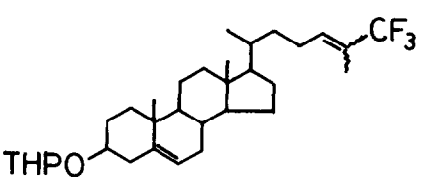
1 R=CH_3
2 R=H



3



4 R^1=SO_2Ph R^2=THP
5 R^1=H R^2=THP
6 R^1=H R^2=Ac



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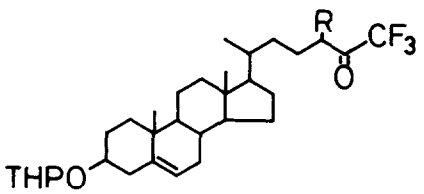
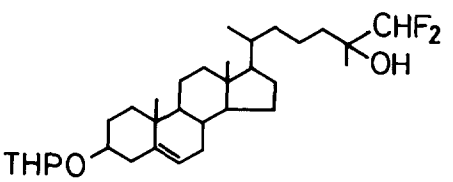
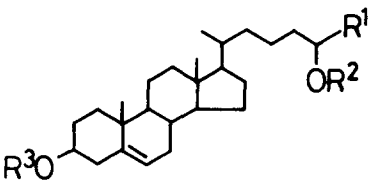


8 R=SO_2Ph
10 R=H



9



11 R^1=CF_3 R^2=H R^3=THP
12 R^1=CHF_2 R^2=H R^3=THP
13 R^1=CH_2F R^2=H R^3=THP
14 R^1=CF_3 R^2=R^3=Ac

of the desired 5,7-diene (λ_{max} 262,271,282,293.5 nm) by preparative TLC (benzene ethyl acetate 100:1 v/v). This was irradiated with a medium pressure mercury lamp (Hanovia 654A 36; 200W) in a mixture of benzene-EtOH (2:1) for 2.5 min and then refluxed for 1 hr to give the vitamin D monoacetate in 18% yield. Subsequent saponification [5% KOH, MeOH-THF (1:1), r.t., 16 hr] and then purification

by HPLC [Zorbax Sil, 4.6 mm x 15 cm, CH_2Cl_2-hexane (3:1), 90 Kg/cm^2] afforded 26,26,26-trifluoro-25-hydroxyvitamin D_3 (1) [λ_{min} 227, λ_{max} 265 nm; m/e 454 (M^+), 493, 436, 421, 271, 253, 136, 118]. Similarly, 14 was converted into 27-nor-26,26,26-trifluoro-25-hydroxyvitamin D_3 (2) [λ_{min} 228, λ_{max} 264 nm; m/e 440 (M^+), 425, 422, 408, 271, 253, 136, 118].

References and Notes

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7. Yields of 5 and 11 were not optimized. When desulfonylation reaction of 8 was carried for 1.5 hr under reflux, the yield of 11 decreased to 55%, but 12 and 13 was obtained in 28% and 12% yield, respectively.
8. Removal of the THP group of monofluoro carbinol (13) gave 27-nor-26-fluoro-25-hydroxycholesterol [mp 163-165°; m/e 406 (M^+), 391, 388, 255], which showed a characteristic H-F coupling pattern in n.m.r. spectrum: δ($CDCl_3$-DMSO-d_6) 4.41 (2H, dd, J_{HH}=5.5 and J_{HF}=69 Hz, C-26).

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