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PREPARATION OF FLUORINE-MODIFIED 25-HYDROXYVITAMIN D_2 28,28,28-TRIFLUORO-, 26,26,26,27,27,27-HEXAFLUORO- AND 28-NOR-26,26,26,27,27,27-HEXAFLUORO-25-HYDROXYVITAMIN D_2

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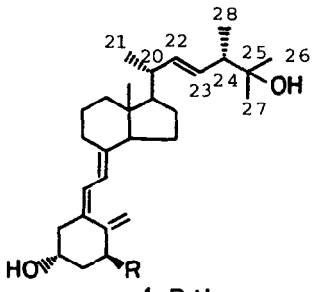
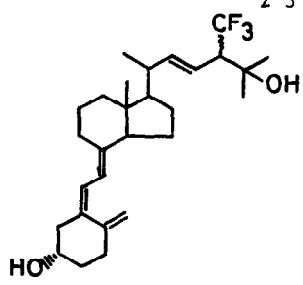
Summary Preparations of the titled fluorinated vitamin D_2 analogs (3, 4 and 5) were efficiently achieved through reactions of the C_{22}-aldehyde (6) with phenylsulfone derivatives (7, 8 and 9).

As in the case of vitamin D_3,[1] it was demonstrated that vitamin D_2 must be metabolically hydroxylated at C-25 followed by C-1 to yield the active form, 1,25-dihydroxyvitamin D_2 (2, 1,25-$(OH)_2D_2$).[2] Hydroxylation at C-24 and C-26 of 25-OH-D_2 (1) is an alternative metabolic pathway.[3,4] Recently, DeLuca and Ikekawa reported a unique methyl migration on the side chain of 24-epi-25-OH-D_2 to form biologically potent 22-dehydro-1,25-dihydroxy-26-homovitamin D_3 (1,25$(OH)_2$-Δ^{22}-26-homo-D_3), although the mechanism of this biotransformation is the present subject.[5] Biological potencies of vitamin D_2 and/or its metabolites are equal to those of the corresponding vitamin D_3 forms in rat and human, but about one-tenth as active in bird.[2,6] It is suggested that the differential biological activity of vitamin D_2 in bird is due to the presence of 24-methyl rather than an unsaturated side chain,[7] the functional importance of 24-methyl of vitamin D_2 has still remained to be clarified.

On the basis of metabolism and mode of function of vitamin D_3, and the characteristic properties of fluorinated molecules with respect to biological response, fluorinated vitamin D_3 analogs were designed, synthesized and their biological response was investigated to clarify the physiological significance of metabolic hydroxylation.[1d,8] The hexafluoro- and 24,24-difluoro analogs of 1,25$(OH)_2D_3$ showed higher activities than those of 1,25$(OH)_2D_3$, presumably due to the metabolic stability of these fluoro analogs.[9,10] Moreover, these fluorinated analogs[11] as well as 24- or 26-homologs of 1,25$(OH)_2D_3$[12] were reported to show preferential



1 R=H
2 R=OH



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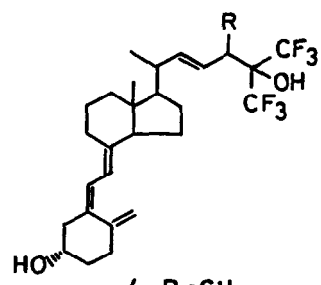


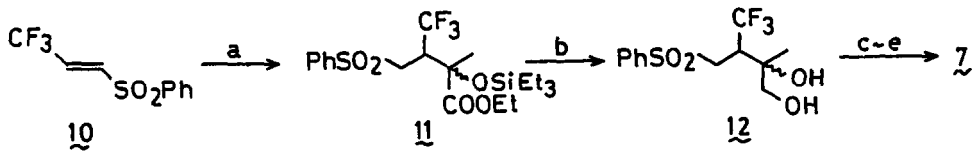
4 R=CH_3
5 R=H

activity in inducing differentiation of human leukemia cells HL-60. These results prompted us to carry out the preparation of the fluorinated vitamin D_2 analogs replaced the hydrogens at C-28 or C-26,27 by fluorines to clarify the biological significance of methyl group at C-24 of vitamin D_2 and to investigate the importance of the modification of the side chain in such biological responses. In this paper we report the synthesis of the titled flurinated vitamin D_2 analogs (3, 4 and 5).

Synthetic strategy for these fluorinated analogs is as follows [13] 1) Addition of the sulfone derivatives (7-9) to the C_{22}-aldehyde (6), and 2) reductive desulfonylation leading to trans-olefin. Since the presence of fluorine substituents in 7 or 8 caused to decrease in reactivity in the reaction with the aldehyde (6) and to facilitate retro-reaction of the β-hydroxysulfone intermediates (13, 16, 19) at the desulfonylation step, several modifications were required for these reactions.

Preparation of 28,28,28-F_3-25-OH-D_2 (3)

The phenylsulfone (7) was prepared using the trifluoropropene derivative (10)[14] as follows Reaction of lithium enolate derived from the lactate with 10 gave the adduct (11), which was, in turn, reduced to the diol (12), followed by coversion to the tertiary alcohol via the epoxide, then protected the hydroxyl group as THP ether (7).



10 11 12

a, $CH_3CH(OSiEt_3)COOEt$, LDA/THF (92%); b, i) DIBAL/Et_2O ii) 10% HCl, MeOH (98%); c, i) MsCl, Et_3N ii) DBU/CH_2Cl_2 (82%); d, $LiAlH_4/Et_2O$ (98%); e, DHP, p-TsOH/ 1,4-dioxane (74%)

Reaction of the lithio derivative of 7 with the C_{22}-aldehyde (6)[13a,15] gave the desired adduct (13) in low yield (7%), probably due to steric effect.[16] Addition of etheral solution of $MgBr_2 \cdot Et_2O$ prepared by reaction of 1,2-dibromoethane with Mg in ether was found quite effective. Thus, lithiation of 7 (LDA, THF, 0°C, 30 min) followed by the addition of 2.2 equiv. of etheral solution of $MgBr_2$ (-78°C, 5 min), and then the aldehyde (0.7 equiv. of 6, -78°C, 1.5 h) gave 13 as an unseparable mixture of diastereomers in 89% yield. Desulfonylation of 13 with freshly prepared 3% Na-Hg[17](THF-MeOH, Na_2HPO_4, 0°C) gave the THP ether (14) in 67% yield, which was deprotected (MeOH, p-TsOH, rt) to give the trifluorergosterol (15, 98%).[18] Photoirradiation of 15 (200 W medium-pressure Hg lamp, Vycor filter, EtOH-benzene, 5 min) followed by thermal isomerization (reflux, 1h) afforded 3 in 32% yield after chromatografic purification [3 λ_{max}(EtOH) 265, 228 nm, m/e· 466, 433, 271, 253, 136, 118, 59].

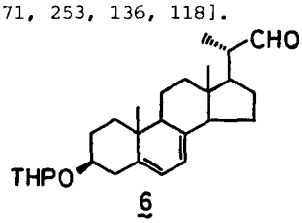
Preparation of Hexafluoro Analogs (4, 5)

For the preparation of the hexafluoro analogs (4, 5) the sulfone intermediates (8, 9) were synthesized through the reaction of lithium enolate of ethyl propionate or Reformatsky reagent from ethyl bromoacetate with hexafluoroacetone. Protection of the hydroxyl group as methoxymethyl(MOM) ether was the only one choice for these hexafluorocarbinols due to the

difficulty of introducing other protecting groups such as THP or silyl group. Without protection no adduct was obtained by the reaction of the dianion with the aldehyde (6).

Reaction of the anion of 8 (LDA, -78°C, 30 min, then $MgBr_2 \cdot Et_2O$, 5 min) with 6 (THF-Et_2O, -78°C, 1h) gave the adduct (16, 98%) as chromatographically separable four diastereomers (16a-d) in a ratio, 23.28 27 21(16a.16b 16c 16d) according to the order of elution on flash column chromatography (hexane-AcOEt). Desulfonylation of each isomer by freshly prepared Na-Hg afforded the trans-olefinic compound in each case (35-71% yield). Removal of THP group (MeOH-p-TsOH, rt, 17, 93-96%) and then MOM group (MeOH-CH_2Cl_2, p-TsOH, reflux) gave 25-hydroxy-ergosterol derivatives (18). On comparing the nmr spectrum and chromatographic behavior of each isomer corresponding to 17 and 18, two (16a, 16d) of the four isomers of 16 were converted to one of 18 (18a) and the other two (16b, 16c) to the other isomer (18b).[19] As with the conversion of 15 to 3, each isomer of 18 was coverted to the vitamin D_2 form (4a from 18a and 4b from 18b, respectively).[20]

Preparation of the 28-nor-hexafluoro analog (5) was also carried out.[21] The absense of a branched methyl group in 9 facilitated the reaction with 6. Thus, reaction of the lithio derivative of 9 with 6 (THF, -78°C, 1.5h) gave the adduct (19) in 82% yield. Acetylation of 19 proceeded smoothly to give 20 (Ac_2O, Py, DMAP, 90%) and subsequent desulfonylation with Na-Hg gave the trans-olefinic compound [21, ($CDCl_3$)δ: 5.50(dd, J=15.2 and 8.7 Hz, 22-H)] in 73% yield. Deprotection of the THP and MOM groups and subsequent conversion to the vitamin D_2 form (5) were carried out by the similar method as above [5 λ_{max}(EtOH) 264, 228 nm; m/e 506, 473, 271, 253, 136, 118].



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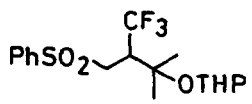

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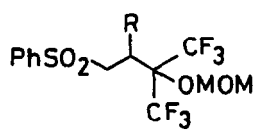
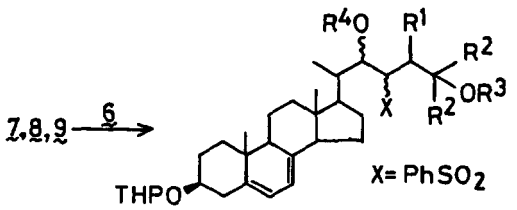
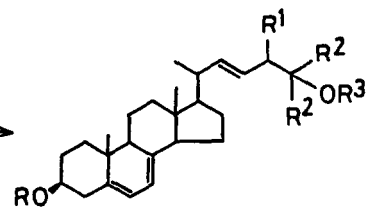


8 R=CH_3
9 R=H





13 R^1=CF_3, R^2=CH_3, R^3=THP, R^4=H

16 R^1=CH_3, R^2=CF_3, R^3=MOM, R^4=H

19 R^1=R^4=H, R^2=CF_3, R^3=MOM

20 R^1=H, R^2=CF_3, R^3=MOM, R^4=Ac

14 R^1=CF_3, R^2=CH_3, R^3=R=THP

15 R^1=CF_3, R^2=CH_3, R^3=R=H

17 R^1=CH_3, R^2=CF_3, R^3=MOM, R=H

18 R^1=CH_3, R^2=CF_3, R^3=R=H

21 R^1=H, R^2=CF_3, R^3=MOM, R=THP

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16. Similar reaction of lithio derivative of 7 with benzaldehyde and cyclohexanecarboxaldehyde gave the adduct in 56% and 74% yield, respectively.
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18. On the basis of ^{1}H-nmr(400 MHz) and ^{19}F-nmr(188 MHz) spectrum, 15 may be a 1:1 mixture of stereoisomers at C-24. ^{1}H-nmr($CDCl_3$)δ: 0.638, 0.644(3H, both s, 18-H_3), 2.720, 2.726(1H, both quintet, J=9.7 Hz, 24-H); ^{19}F-nmr($CDCl_3$, relative to benzotrifluoride) -0.87 ppm(d, J=9.7 Hz), -1.04 ppm(d, J=9.7 Hz).
19. Although the ^{1}H-nmr spectrum of 18a was quite similar to that of 18b, the chemical shifts of two unequivalent trifluoromethyl groups in 18a clearly differed from those of 18b. 18a ^{1}H-nmr($CDCl_3$)δ 5.59(dd, J=15.2, 9.0 Hz, 22-H); ^{19}F-nmr($CDCl_3$) -8.78 ppm(q, J=9 Hz), -9.75 ppm(q, J=9 Hz), 18b: ^{1}H-nmr($CDCl_3$)δ. 5.60(dd, J=15.4, 8.7 Hz); ^{19}F-nmr($CDCl_3$) -8.56 ppm(q, J=9 Hz), -9.82 ppm(q, J=9 Hz).
20. Each isomer of 4 showed a retention time on HPLC (Zorbax Sil column, 4.6x25 cm; 5% i-PrOH in hexane, flow rate 2 ml/min) different from that of the other; 5.1 min for one isomer(4a) and 5.4 min for another one(4b). Although both compounds showed biological activity in calcium mobilization from bone in rat, 4a was more active than 4b. These results as well as the nmr data indicate 4b to possibly be an epimer at C-24 of 4a.
21. 1α-Hydroxy derivative of 5 was reported by Hoffmann-La Roche group. E. Baggiolini, G. Pizzolato, M. Uskokovic, and G. Truitt, Eur. Pat. Appl. EP 182,298(1986).

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