SYNTHESIS OF 24-HOMO-26,26,26,27,27,27-HEXAFLUORO-1α,22,25-TRIHYDROXYVITAMIN D_3

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The novel fluorinated vitamin D_3 analog, 24-homo-26,26,26,27,27,27-hexafluoro-1α,22,25-trihydroxyvitamin D_3, was prepared utilizing the ene reaction of hexafluoroacetone for the construction of the side chain.

KEYWORDS vitamin D_3; fluorinated vitamin D_3 analog; cell differentiation; calcium regulation

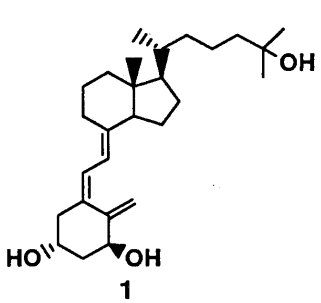
The recognition of the important role that the physiologically active form of vitamin D_3, 1α,25-dihydroxycholecalciferol (**1**), plays in the regulation of calcium metabolism in animals and its therapeutic use as a drug for bone diseases, e.g., osteoporosis, has stimulated the synthesis of vitamin D_3 analogs in efforts to increase and also modify the activity of vitamin D_3. Kobayashi and Ikekawa reported the synthesis of a fluorinated analog (**2**), which is more potent than 1α,25-dihydroxycholecalciferol in various bioassays including the ability to increase serum calcium concentration.[1)]

Recently, in addition to the regulation of calcium metabolism, **1** has also been found to suppress proliferation and to induce differentiation in human cancer cells.[2)] Our synthetic efforts for fluorinated analogs have been made with the aim of separating activities in cell differentiation and calcium regulation. Its separation may be necessary for the therapy of malignancy and psoriasis. In this communication, we wish to report the first synthesis of a novel vitamin D_3 analog **3** utilizing the ene reaction of hexafluoroacetone for the construction of the side chain.

As a result of retrosynthetic analysis, we chose as our starting material the aldehyde **4**, which is readily available from vitamin D_2 via the oxidation procedure of Okamura.[3)] The aldehyde **4** was reacted with allylmagnesium chloride in ether-THF at 0°C to give the allyl alcohol **5a** (47%) together with its isomer **5b** (39%). Acetylation of **5a** (Ac_2O-Py, r.t.) provided the acetate **6a** (95%) which was treated with hexafluoroacetone in a sealed tube at 150°C for 35h to afford **7a** in 74% yield.[4)] Deacetylation of **7a** (K_2CO_3 in CH_3OH, r.t., 92%), followed by oxidation of the resultant alcohol **8a** with Collins reagent, gave the enone **9** in 96% yield. In the same manner, **5b** was converted to **9** in 61% yield in four steps.

Hydrogenation of **9** (H_2(1 atm), 5% Pd-C in CH_3OH, r.t., 1h, 96%), followed by reduction of the resultant ketone **10** with $NaBH_4$ in ethanol at room temperature, gave the more polar alcohol **11a** (67%) and the less polar alcohol **11b** (23%). Alternatively, **11a** was directly obtained from **8a** in 71% yield by hydrogenation with Wilkinson's catalyst (H_2(1 atm) in benzene-EtOH, r.t.).

Silylation of **11a** (TBDMSOTf, 2,6-lutidine in CH_2Cl_2, r.t.), hydogenolysis (5% Pd-C, H_2(1 atm) in CH_3OH, r.t.), and PCC oxidation furnished the ketone **14a** in 90% overall yield. According to the general approach pioneered by Lythgoe,[5)] Horner-Wittig reaction of **14a** with the phosphinoyl carbanion prepared from **15**[6)] (n-BuLi in THF, -78°C→r.t.) gave **16a**, and, after deprotection[7)] with n-$Bu_4N^+F^-$(in THF, 60°C), **3a** was obtained in 43% yield in two steps. In the same manner, **3b** was obtained from **11b** in 36% overall yield. The configuration at C22 was confirmed by X-ray crystallography of the ketone **14a**.[8)]



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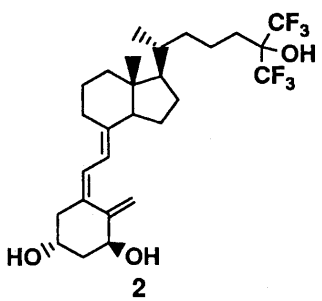

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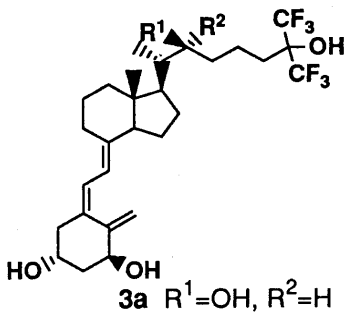
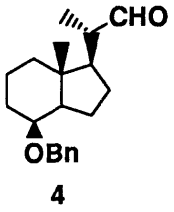


3a R^1=OH, R^2=H

3b R^1=H, R^2=OH



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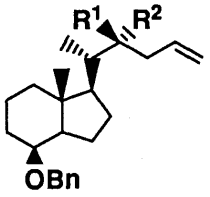
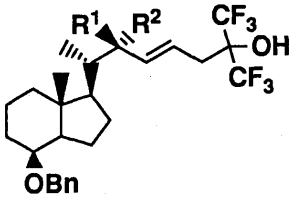
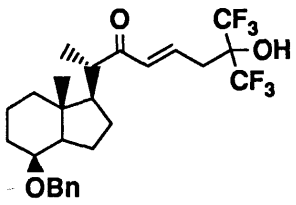


5a R^1=OH, R^2=H
5b R^1=H, R^2=OH
6a R^1=OAc, R^2=H
6b R^1=H, R^2=OAc



7a R^1=OAc, R^2=H
7b R^1=H, R^2=OAc
8a R^1=OH, R^2=H
8b R^1=H, R^2=OH



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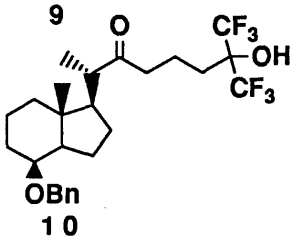

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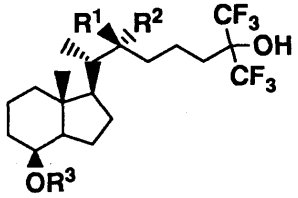
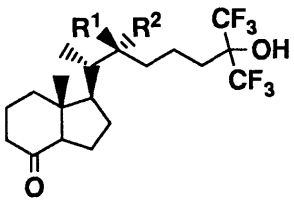
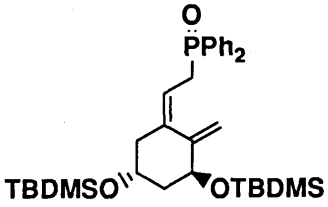


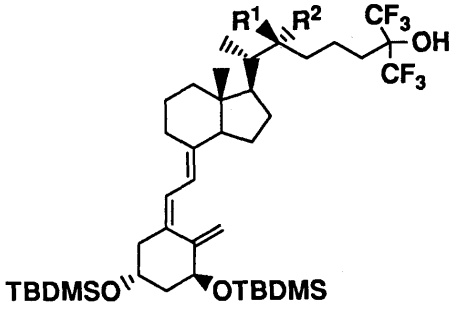
11a R^1=OH, R^2=H, R^3=Bn
11b R^1=H, R^2=OH, R^3=Bn
12a R^1=OTBDMS, R^2=H, R^3=Bn
12b R^1=H, R^2=OTBDMS, R^3=Bn
13a R^1=OTBDMS, R_2=H, R^3=H
13b R^1=H, R^2=OTBDMS, R^3=H



14a R^1=OTBDMS, R^2=H
14b R^1=H, R^2=OTBDMS



15



16a R^1=OH, R^2=H
16b R^1=H, R^2=OH

Preliminary biological results obtained with **3a** and **3b** indicate that **3a** is approximately 30 times more potent than 1α,25-dihydroxycholecalciferol (**1**) and 10 times more potent than **3b** in induction of differentiation in human colon tumor cells. However, neither **3a** nor **3b** increases serum calcium concentration in rats. Most importantly, **3a** has much greater separation of cell differentiation from calcium regulation than **1**. A more detailed description of the biological properties will be submitted for publication.

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6) The phosphine oxide **15** was obtained by the procedure of Takano et al.; S. Hatakeyama, H. Numata, K. Osanai, and S. Takano, *J. Org. Chem.*, **54**, 3515 (1989).

7) Alternatively, the deprotection was carried out by the treatment with cation exchage resin in methanol; E. G. Baggiolini, J. A. Iacobelli, B. M. Hennessy, A. D. Batcho, J. F. Sereno, and M. R. Uskokovic, *J. Org. Chem.*, **51**, 3098 (1986).

8) We are grateful to Dr. M. Shiro, Rigaku Corporation, for the measurement of the X-ray chrystallography.

Analytical Data:

5 a colorless oil; ^{1}H-NMR(200MHz,$CDCl_3$) δ: 0.92(d,J=5.9Hz,3H),0.97(s,3H),1.10-2.40(m,16H),3.64-3.80 (m,2H),4.36(d,J=12.3Hz,1H),4.63(d,J=12.3Hz,1H),5.02-5.21(m,2H),5.64-5.87(m,1H),7.17-7.50(m,5H) ppm; IR(neat) 3421,2938,2865cm^{-1}; MS(EI) m/z:301(M-41),233.

5 b colorless oil; ^{1}H-NMR(200MHz,$CDCl_3$) δ: 0.93(d,J=6.8Hz,3H),0.99(s,3H),1.00-2.29(m,16H),3.64-3.78 (m,2H),4.36(d,J=12.4Hz,1H),4.63(d,J=12.4Hz,1H),5.03-5.21(m,2H),5.66-6.00(m,1H),7.18-7.42(m,5H) ppm; IR(neat) 3406,2937,2864cm^{-1}; MS(EI) m/z:301(M-41),233.

7 a mp 134.8-135.9°C(n-hexane, needle); ^{1}H-NMR(200MHz,$CDCl_3$) δ: 0.96(d,J=6.7Hz,3H),0.96(s,3H), 1.08-2.11(m,13H),2.08(s,3H),2.71(d,J=7.2Hz,2H),3.41(s,1H),3.65-3.80(m,1H),4.35(d,J=12.3Hz,1H), 4.61(d,J=12.3Hz,1H),5.25-5.35(m,1H),5.50(dt,J=15.6,5.1Hz,1H),5.71(dd,J=15.6,5.2Hz,1H),7.19-7.40 (m,5H)ppm; ^{19}F-NMR($CDCl_3$,$CFCl_3$) -76.94(q,J=7.8Hz),-77.07(q,J=7.8Hz)ppm; IR(KBr) 3364,2932, 1720cm^{-1}; MS(EI) m/z:550(M^+).

7 b mp 120.7-121.8°C(n-hexane, needle); ^{1}H-NMR(200MHz,$CDCl_3$) δ: 0.90-2.20(m,13H),0.96(d,J=6.4 Hz,3H),0.98(s,3H),2.04(s,3H),2.60-2.85(m,2H),3.65-3.76(m,1H),4.00(bs,1H),4.35(d,J=12.3Hz,1H), 4.61(d,J=12.3Hz,1H),5.16-5.28(m,1H),5.55-5.81(m,2H),7.17-7.38(m,5H)ppm; ^{19}F-NMR($CDCl_3$,$CFCl_3$) -76.81(bs)ppm; IR(KBr) 3422,2941,1707cm^{-1}; MS(EI) m/z:550(M^+),490.

8 a mp 130.0-130.5°C(n-hexane-EtOAc, needle); ^{1}H-NMR($CDCl_3$) δ: 0.87(d,J=6.4Hz,3H),0.97(s,3H), 1.06-2.10(m,14H),2.73(d,J=7.5Hz,2H),3.26(bs,1H),3.69-3.78(m,1H),4.33(bs,1H),4.36(d,J=12.3Hz, 1H),4.63(d,J=12.3Hz,1H),5.66(dt,J=15.5,7.5Hz,1H),5.79(dd,J=15.5,3.7Hz,1H),7.18-7.44(m,5H)ppm; ^{19}F-NMR($CDCl_3$,$CFCl_3$) -77.03~-77.15(m)ppm; IR(KBr) 3535,3114,2945cm^{-1}; MS(EI) m/z:508(M^+).

8 b colorless oil; ^{1}H-NMR(200MHz,$CDCl_3$) δ: 0.92(d,J=6.7Hz,3H),0.98(s,3H),1.00-2.18(m,14H),2.59-2.83 (m,2H),3.65-3.76(m,1H),4.13-4.32(m,1H),4.26(bs,1H),4.35(d,J=12.3Hz,1H),4.61(d,J=12.3Hz,1H), 5.54-5.82(m,2H),7.17-7.41(m,5H)ppm; ^{19}F-NMR($CDCl_3$,$CFCl_3$) -76.42(q,J=9.3Hz),-77.22(q,J=9.3Hz) ppm; IR(neat) 3374,2939,2866cm^{-1}; MS(EI) m/z:508(M^+).

9 colorless oil; ^{1}H-NMR(200MHz,$CDCl_3$) δ: 1.00(s,3H),1.00-2.10(m,12H),1.11(d,J=6.9Hz,3H),2.73(dq, J=9.9,6.9Hz,1H),2.86(d,J=7.6Hz,2H),3.68-3.78(m,1H),4.35(d,J=12.3Hz,1H),4.48(bs,1H),4.61(d,J=12.3 Hz,1H),6.31(d,J=15.6Hz,1H),6.89(dt,J=15.6,7.6Hz,1H),7.20-7.43(m,5H)ppm; ^{19}F-NMR($CDCl_3$,$CFCl_3$) -76.88~-77.14(m)ppm; IR(neat) 3299,2936,1686,1660cm^{-1}; MS(EI) m/z:506(M^+).

10 colorless oil; ^{1}H-NMR(200MHz,$CDCl_3$) δ: 0.98(s,3H),1.09(d,J=6.8Hz,3H),1.05-2.12(m,16H),2.40-2.78 (m,4H),3.68-3.77(m,1H),4.35(d,J=12.3Hz,1H),4.62(d,J=12.3Hz,1H),7.20-7.45(m,5H)ppm; ^{19}F-NMR ($CDCl_3$,$CFCl_3$) -77.66(q,J=7.1Hz),-77.82(q,J=7.1Hz)ppm; IR(neat) 3283,2936,1694cm^{-1}; MS(EI) m/z: 508(M^+).

11 a mp 156.9-157.6°C(n-hexane-EtOAc, needle); ^{1}H-NMR(CD_3COCD_3) δ: 0.91(d,J=6.5Hz,3H),0.97(s,3H), 1.10-2.13(m,18H),2.93(s,1H),3.24(d,J=5.6Hz,1H),3.60-3.80(m,2H),4.35(d,J=12.3Hz,1H),4.60(d,J=12.3 Hz,1H),6.54(s,1H),7.14-7.45(m,5H)ppm; ^{19}F-NMR(CD_3COCD_3,$CFCl_3$) -76.04(q,J=9.6Hz),-76.50(q,J=9.6 Hz)ppm; IR(KBr) 3536,942cm^{-1}; MS(EI) m/z:510(M^+).

11 b mp 142.3-144.0°C(n-hexane-EtOAc, needle); ^{1}H-NMR(200MHz,CD_3CN) δ: 0.87(d,J=6.7Hz,3H),0.94 (s,3H),1.00-2.10(m,19H),2.87(d,J=4.4Hz,1H),3.50-3.68(m,1H),3.68-3.80(m,1H),4.32(d,J=12.1Hz,1H), 4.59(d,J=12.1Hz,1H),5.95(bs,1H),7.10-7.44(m,5H)ppm; ^{19}F-NMR(CD_3CN,$CFCl_3$) -75.60(q,J=9.5Hz), -76.08(q,J=9.5Hz)ppm; IR(KBr) 3512,3156,2932cm^{-1}; MS(EI) m/z:510(M^+).

3 a mp 186.4-187.2°C(CH_3OH,needle); ^{1}H-NMR(200MHz,CD_3OD) δ: 0.58(s,3H),0.92(d,J=6.7Hz,3H),1.10-2.63(m,20H),2.20-2.36(m,1H),2.47-2.62(m,1H),2.80-2.95(m,1H),3.59-3.71(m,1H),4.09-4.23(m,1H), 4.32-4.42(m,1H),4.80-5.00(m,1H),5.27-5.35(m,1H),6.10(d,J=11.2Hz,1H),6.33(d,J=11.2Hz,1H)ppm; ^{19}F-NMR(CD_3OD,$CFCl_3$) -75.94(q,J=9.2Hz),-76.14(q,J=9.2Hz)ppm; IR(KBr) 3438,2929,1212cm^{-1}; MS(EI) m/z:554(M^+),536; HR-MS: Calcd.for $C_{28}H_{38}F_6O_3$: 536.273. Found:536.273; UV(EtOH) λ_{max}:264nm (ε15488); $[\alpha]_D^{24}$=+28.4°(c=0.06,CH_3OH).

3 b mp 112.7-114.3°C(CH_3OH, needle); ^{1}H-NMR(200MHz,CD_3OD) δ: 0.59(s,3H),0.93(d,J=6.8Hz,3H),1.15-2.10(m,20H),2.20-2.33(m,1H),2.45-2.60(m,1H),2.80-2.93(m,1H),3.57-3.70(m,1H),4.07-4.22(m,1H), 4.32-4.41(m,1H),4.85-5.00(m,1H),5.27-5.35(m,1H),6.10(d,J=11.4Hz,1H),6.32(d,J=11.4Hz,1H)ppm; ^{19}F-NMR(CD_3OD,$CFCl_3$) -75.75~-76.10(m)ppm; IR(KBr) 3438,2947,1214cm^{-1}; MS(EI) m/z:554(M^+); HR-MS: Calcd.for $C_{28}H_40F_6O_4$:554.283. Found:554.283; UV(EtOH)λ_{max}: 264nm(ε15501); $[\alpha]_D^{24}$=+38.2°(c=0.1,CH_3OH)

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