

SYNTHESIS OF 24-HOMO-26,26,26,27,27,27-HEXAFLUORO-1 α ,22,25-TRIHIDROXYVITAMIN D₃

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The novel fluorinated vitamin D₃ analog, 24-homo-26,26,26,27,27,27-hexafluoro-1 α ,22,25-trihydroxyvitamin D₃, was prepared utilizing the ene reaction of hexafluoroacetone for the construction of the side chain.

KEYWORDS vitamin D₃; fluorinated vitamin D₃ analog; cell differentiation; calcium regulation

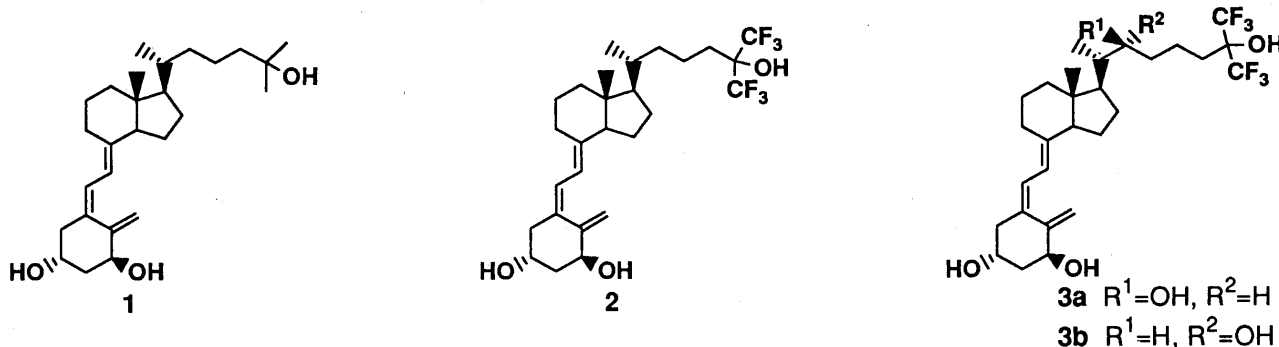
The recognition of the important role that the physiologically active form of vitamin D₃, 1 α ,25-dihydroxycholecalciferol (**1**), plays in the regulation of calcium metabolism in animals and its therapeutic use as a drug for bone diseases, e.g., osteoporosis, has stimulated the synthesis of vitamin D₃ analogs in efforts to increase and also modify the activity of vitamin D₃. Kobayashi and Ikekawa reported the synthesis of a fluorinated analog (**2**), which is more potent than 1 α ,25-dihydroxycholecalciferol in various bioassays including the ability to increase serum calcium concentration.¹⁾

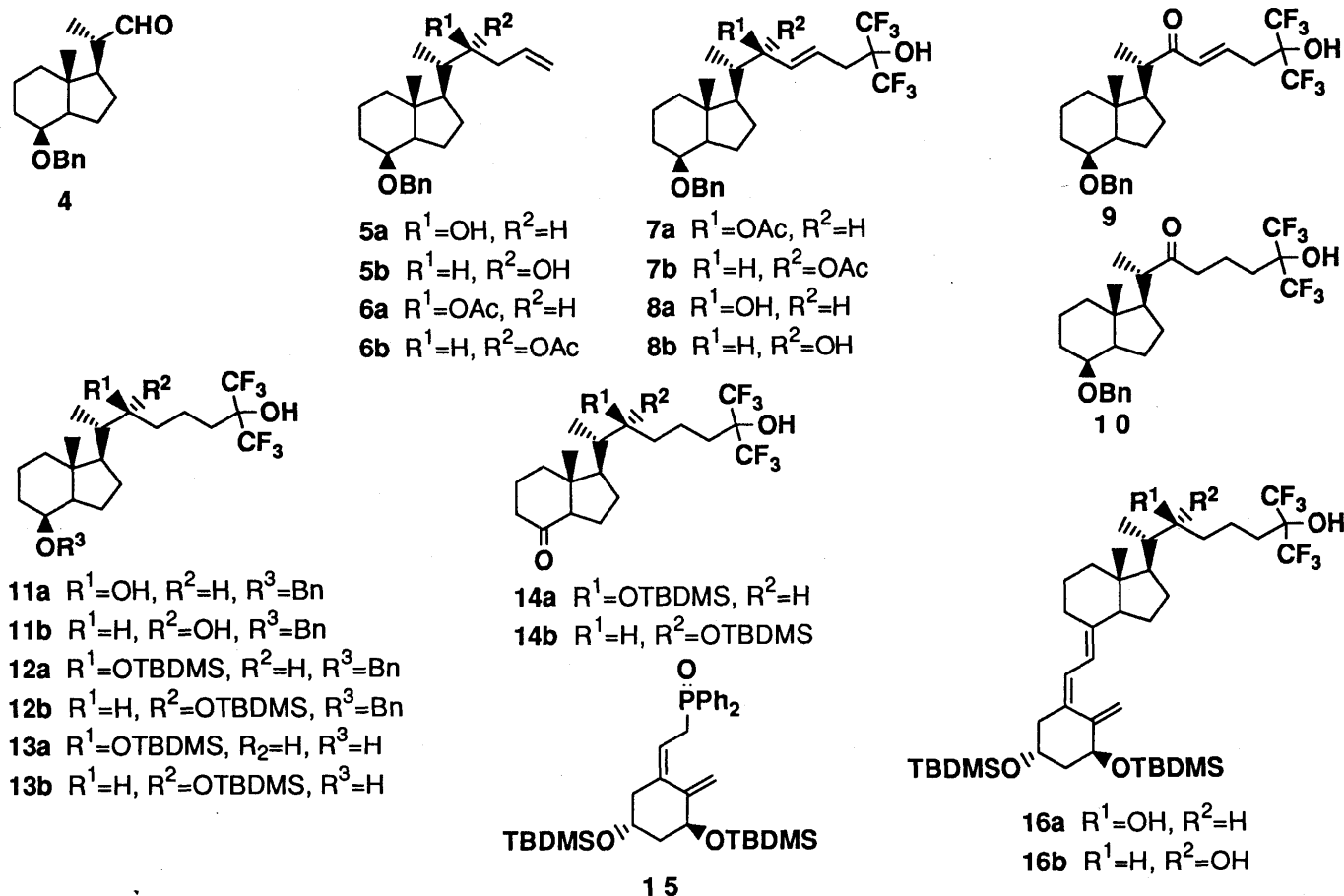
Recently, in addition to the regulation of calcium metabolism, **1** has also been found to suppress proliferation and to induce differentiation in human cancer cells.²⁾ Our synthetic efforts for fluorinated analogs have been made with the aim of separating activities in cell differentiation and calcium 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 D₃ 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 D₂ 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** (Ac₂O-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** (K₂CO₃ in CH₃OH, 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** (H₂(1 atm), 5% Pd-C in CH₃OH, r.t., 1h, 96%), followed by reduction of the resultant ketone **10** with NaBH₄ 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 (H₂(1 atm) in benzene-EtOH, r.t.).

Silylation of **11a** (TBDMSTf, 2,6-lutidine in CH₂Cl₂, r.t.), hydrogenolysis (5% Pd-C, H₂(1 atm) in CH₃OH, 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 deprotection⁷⁾ with n-Bu₄N⁺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⁾





Preliminary biological results obtained with **3a** and **3b** indicate that **3a** is approximately 30 times more potent than $1\alpha,25$ -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 exchange 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 crystallography.
- Analytical Data:**
- 5 a colorless oil; $^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 0.92(d, $J=5.9\text{Hz}$, 3H), 0.97(s, 3H), 1.10-2.40(m, 16H), 3.64-3.80(m, 2H), 4.36(d, $J=12.3\text{Hz}$, 1H), 4.63(d, $J=12.3\text{Hz}$, 1H), 5.02-5.21(m, 2H), 5.64-5.87(m, 1H), 7.17-7.50(m, 5H) ppm; IR(neat) 3421, 2938, 2865 cm^{-1} ; MS(EI) m/z : 301(M-41), 233.
- 5 b colorless oil; $^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 0.93(d, $J=6.8\text{Hz}$, 3H), 0.99(s, 3H), 1.00-2.29(m, 16H), 3.64-3.78(m, 2H), 4.36(d, $J=12.4\text{Hz}$, 1H), 4.63(d, $J=12.4\text{Hz}$, 1H), 5.03-5.21(m, 2H), 5.66-6.00(m, 1H), 7.18-7.42(m, 5H) ppm; IR(neat) 3406, 2937, 2864 cm^{-1} ; MS(EI) m/z : 301(M-41), 233.
- 7 a mp 134.8-135.9°C(n-hexane, needle); $^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 0.96(d, $J=6.7\text{Hz}$, 3H), 0.96(s, 3H), 1.08-2.11(m, 13H), 2.08(s, 3H), 2.71(d, $J=7.2\text{Hz}$, 2H), 3.41(s, 1H), 3.65-3.80(m, 1H), 4.35(d, $J=12.3\text{Hz}$, 1H), 4.61(d, $J=12.3\text{Hz}$, 1H), 5.25-5.35(m, 1H), 5.50(dt, $J=15.6, 5.1\text{Hz}$, 1H), 5.71(dd, $J=15.6, 5.2\text{Hz}$, 1H), 7.19-7.40(m, 5H) ppm; $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3) -76.94(q, $J=7.8\text{Hz}$), -77.07(q, $J=7.8\text{Hz}$) ppm; IR(KBr) 3364, 2932, 1720 cm^{-1} ; MS(EI) m/z : 550(M^+).
- 7 b mp 120.7-121.8°C(n-hexane, needle); $^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 0.90-2.20(m, 13H), 0.96(d, $J=6.4\text{Hz}$, 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, $J=12.3\text{Hz}$, 1H), 4.61(d, $J=12.3\text{Hz}$, 1H), 5.16-5.28(m, 1H), 5.55-5.81(m, 2H), 7.17-7.38(m, 5H) ppm; $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3) -76.81(bs) ppm; IR(KBr) 3422, 2941, 1707 cm^{-1} ; MS(EI) m/z : 550(M^+), 490.
- 8 a mp 130.0-130.5°C(n-hexane-EtOAc, needle); $^1\text{H-NMR}$ (CDCl_3) δ : 0.87(d, $J=6.4\text{Hz}$, 3H), 0.97(s, 3H), 1.06-2.10(m, 14H), 2.73(d, $J=7.5\text{Hz}$, 2H), 3.26(bs, 1H), 3.69-3.78(m, 1H), 4.33(bs, 1H), 4.36(d, $J=12.3\text{Hz}$, 1H), 4.63(d, $J=12.3\text{Hz}$, 1H), 5.66(dt, $J=15.5, 7.5\text{Hz}$, 1H), 5.79(dd, $J=15.5, 3.7\text{Hz}$, 1H), 7.18-7.44(m, 5H) ppm; $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3) -77.03~-77.15(m) ppm; IR(KBr) 3535, 3114, 2945 cm^{-1} ; MS(EI) m/z : 508(M^+).
- 8 b colorless oil; $^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 0.92(d, $J=6.7\text{Hz}$, 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, $J=12.3\text{Hz}$, 1H), 4.61(d, $J=12.3\text{Hz}$, 1H), 5.54-5.82(m, 2H), 7.17-7.41(m, 5H) ppm; $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3) -76.42(q, $J=9.3\text{Hz}$), -77.22(q, $J=9.3\text{Hz}$) ppm; IR(neat) 3374, 2939, 2866 cm^{-1} ; MS(EI) m/z : 508(M^+).
- 9 colorless oil; $^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 1.00(s, 3H), 1.00-2.10(m, 12H), 1.11(d, $J=6.9\text{Hz}$, 3H), 2.73(dq, $J=9.9, 6.9\text{Hz}$, 1H), 2.86(d, $J=7.6\text{Hz}$, 2H), 3.68-3.78(m, 1H), 4.35(d, $J=12.3\text{Hz}$, 1H), 4.48(bs, 1H), 4.61(d, $J=12.3\text{Hz}$, 1H), 6.31(d, $J=15.6\text{Hz}$, 1H), 6.89(dt, $J=15.6, 7.6\text{Hz}$, 1H), 7.20-7.43(m, 5H) ppm; $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3) -76.88~-77.14(m) ppm; IR(neat) 3299, 2936, 1686, 1660 cm^{-1} ; MS(EI) m/z : 506(M^+).
- 10 colorless oil; $^1\text{H-NMR}$ (200MHz, CDCl_3) δ : 0.98(s, 3H), 1.09(d, $J=6.8\text{Hz}$, 3H), 1.05-2.12(m, 16H), 2.40-2.78(m, 4H), 3.68-3.77(m, 1H), 4.35(d, $J=12.3\text{Hz}$, 1H), 4.62(d, $J=12.3\text{Hz}$, 1H), 7.20-7.45(m, 5H) ppm; $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3) -77.66(q, $J=7.1\text{Hz}$), -77.82(q, $J=7.1\text{Hz}$) ppm; IR(neat) 3283, 2936, 1694 cm^{-1} ; MS(EI) m/z : 508(M^+).
- 11 a mp 156.9-157.6°C(n-hexane-EtOAc, needle); $^1\text{H-NMR}$ (CD_3COCD_3) δ : 0.91(d, $J=6.5\text{Hz}$, 3H), 0.97(s, 3H), 1.10-2.13(m, 18H), 2.93(s, 1H), 3.24(d, $J=5.6\text{Hz}$, 1H), 3.60-3.80(m, 2H), 4.35(d, $J=12.3\text{Hz}$, 1H), 4.60(d, $J=12.3\text{Hz}$, 1H), 6.54(s, 1H), 7.14-7.45(m, 5H) ppm; $^{19}\text{F-NMR}$ (CD_3COCD_3 , CFCl_3) -76.04(q, $J=9.6\text{Hz}$), -76.50(q, $J=9.6\text{Hz}$) ppm; IR(KBr) 3536, 942 cm^{-1} ; MS(EI) m/z : 510(M^+).
- 11 b mp 142.3-144.0°C(n-hexane-EtOAc, needle); $^1\text{H-NMR}$ (200MHz, CD_3CN) δ : 0.87(d, $J=6.7\text{Hz}$, 3H), 0.94(s, 3H), 1.00-2.10(m, 19H), 2.87(d, $J=4.4\text{Hz}$, 1H), 3.50-3.68(m, 1H), 3.68-3.80(m, 1H), 4.32(d, $J=12.1\text{Hz}$, 1H), 4.59(d, $J=12.1\text{Hz}$, 1H), 5.95(bs, 1H), 7.10-7.44(m, 5H) ppm; $^{19}\text{F-NMR}$ (CD_3CN , CFCl_3) -75.60(q, $J=9.5\text{Hz}$), -76.08(q, $J=9.5\text{Hz}$) ppm; IR(KBr) 3512, 3156, 2932 cm^{-1} ; MS(EI) m/z : 510(M^+).
- 3 a mp 186.4-187.2°C(CH_3OH , needle); $^1\text{H-NMR}$ (200MHz, CD_3OD) δ : 0.58(s, 3H), 0.92(d, $J=6.7\text{Hz}$, 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, $J=11.2\text{Hz}$, 1H), 6.33(d, $J=11.2\text{Hz}$, 1H) ppm; $^{19}\text{F-NMR}$ (CD_3OD , CFCl_3) -75.94(q, $J=9.2\text{Hz}$), -76.14(q, $J=9.2\text{Hz}$) ppm; IR(KBr) 3438, 2929, 1212 cm^{-1} ; MS(EI) m/z : 554(M^+), 536; HR-MS: Calcd. for $\text{C}_{28}\text{H}_{38}\text{F}_6\text{O}_3$: 536.273. Found: 536.273; UV(EtOH) λ_{max} : 264 nm (ϵ 15488); $[\alpha]_D^{24}$: +28.4° ($c=0.06$, CH_3OH).
- 3 b mp 112.7-114.3°C(CH_3OH , needle); $^1\text{H-NMR}$ (200MHz, CD_3OD) δ : 0.59(s, 3H), 0.93(d, $J=6.8\text{Hz}$, 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, $J=11.4\text{Hz}$, 1H), 6.32(d, $J=11.4\text{Hz}$, 1H) ppm; $^{19}\text{F-NMR}$ (CD_3OD , CFCl_3) -75.75~-76.10(m) ppm; IR(KBr) 3438, 2947, 1214 cm^{-1} ; MS(EI) m/z : 554(M^+); HR-MS: Calcd. for $\text{C}_{28}\text{H}_{40}\text{F}_6\text{O}_4$: 554.283. Found: 554.283; UV(EtOH) λ_{max} : 264 nm (ϵ 15501); $[\alpha]_D^{24}$: +38.2° ($c=0.1$, CH_3OH).

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