

Communications to the Editor

[Chem. Pharm. Bull.]
34(5)2286—2289(1986)

SYNTHETIC STUDIES OF VITAMIN D ANALOGUES. VII.¹⁾
SYNTHESIS OF 20-OXA-21-NORVITAMIN D₃ ANALOGUES

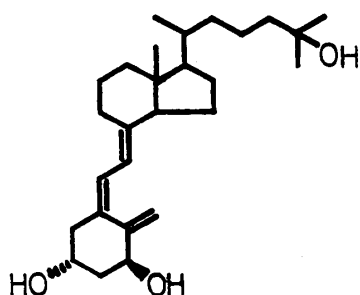
Noboru Kubodera,* Katsuhito Miyamoto, Kiyoshige Ochi
and Isao Matsunaga

New Drug Research Laboratories, Chugai Pharmaceutical Co., Ltd.,
41-8, Takada 3 chome, Toshima-ku, Tokyo 171, Japan

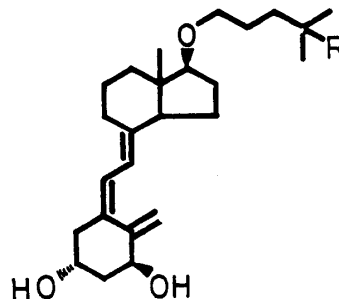
The synthesis of two vitamin D₃ analogues, 1 α ,25-dihydroxy-20-oxa-21-norvitamin D₃ (**2**) and 1 α -hydroxy-20-oxa-21-norvitamin D₃ (**3**) from dehydroepiandrosterone (**4**) is described.

KEYWORDS—dehydroepiandrosterone; vitamin D₃ analogue; 1 α ,25-dihydroxy-20-oxa-21-norvitamin D₃; 1 α -hydroxy-20-oxa-21-norvitamin D₃; 1-chloro-4,4-ethylenedioxy-pentane; vitamin D₃ synthesis

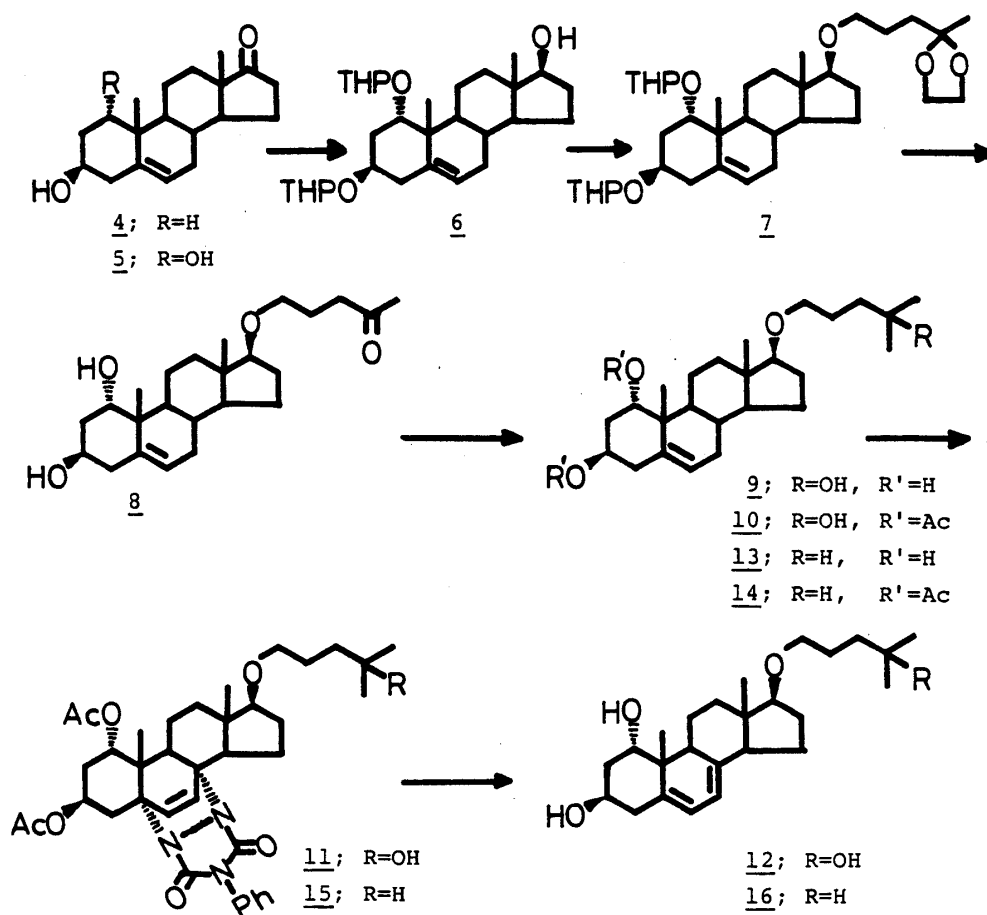
There has been increasing interest in the synthesis of vitamin D₃ analogues since 1 α ,25-dihydroxyvitamin D₃ (**1**) [1 α ,25-(OH)₂-D₃] was shown to have a differentiation-inducing effect on myeloid leukemia cells in addition to its regulatory effect on calcium and phosphorus metabolism.²⁾ In an attempt to separate these types of physiological action, we have undertaken the synthesis of vitamin D₃ analogues having an oxygen atom in the side chain skeleton. Only a few vitamin D₃ analogues containing heteroatoms in the side chain were prepared,^{3,4)} and the details of their biological activities are not available. This paper deals with the synthesis of 1 α ,25-dihydroxy-20-oxa-21-norvitamin D₃ (**2**) and 1 α -hydroxy-20-oxa-21-norvitamin D₃ (**3**) from dehydroepiandrosterone (**4**), and with the preliminary studies of their biological activities.



1 : 1 α ,25-OH-D₃



2 ; R = OH
3 ; R = H



The ketodiols (5), prepared from 4 by microbiological 1α -hydroxylation,⁵⁾ was converted to the 17β -alcohol (6)^{6a)} in 42% yield via bis-tetrahydropyranyl ether formation followed by reduction with NaBH_4 in EtOH at room temperature for 2 h. Alkylation⁷⁾ of 6 with 1-chloro-4,4-ethylenedioxy-pentane⁸⁾ in the presence of NaH in boiling xylene for 20 h gave the ether (7)^{6b)} in 66% yield. Then 7 was hydrolyzed to the 24-keto-diol (8)^{6c)} in 78% yield upon treatment with Amberlyst-15 in MeOH at room temperature for 15 h. Addition of 8 to excess MeMgBr in THF at -10°C during 0.5 h afforded the triol (9)^{6d)} in 66% yield. The secondary hydroxyl groups in 9 were acetylated and the resulting diacetate (10)^{6e)} was transformed into the 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) adduct (11)^{6f)} in 32% overall yield by the usual 3-step procedure: i) bromination at the 7-position (NBS , NaHCO_3 , hexane, reflux, 1 h); ii) dehydrobromination (γ -collidine, xylene, reflux, 1.5 h); and iii) addition of PTAD⁹⁾ (CH_2Cl_2 , room temperature, 1 h). Treatment⁹⁾ of 11 with LiAlH_4 in refluxing THF for 1 h afforded the 5,7-diene (12)^{6g)} in 48% yield. Subsequent irradiation¹⁰⁾ of 12 in EtOH at 0°C under argon atmosphere using a high pressure mercury lamp (200 W, Vycor filter), followed by thermal isomerization in boiling THF for 1.5 h gave $1\alpha,25$ -dihydroxy-20-oxa-21-norvitamin D_3 (2)^{6h)} in 12% yield after purification by means of Sephadex LH-20 column chromatography with CHCl_3 -hexane (13:7).

Another analogue, 1 α -hydroxy-20-oxa-21-norvitamin D₃ (3), was prepared in a similar manner. The alcohol 6 was converted to the diol ether (13)⁶ⁱ⁾ via alkylation with 1-bromo-4-methylpentane (72% yield) followed by hydrolysis of the tetrahydropyranyl ether groups (73% yield). The diacetate (14)^{6j)} was transformed into the PTAD adduct (15)^{6k)}, in 41% yield by the same procedure as in the preparation of 11. Treatment of 15 with LiAlH₄ afforded the 5,7-diene (16)^{6l)} in 41% yield, which was subjected to the irradiation-thermal isomerization sequence to give 3^{6m)} in 12% overall yield.

Some preliminary studies showed that 2 and 3 have interesting biological properties. In *in vitro* experiments exploring the inducing effect of differentiation of human myeloid leukemia cells (HL-60) into macrophages,¹¹⁾ 2 and 3 were respectively proved to be as effective as 1 α ,25-(OH)₂-D₃ and 3 1 α -hydroxyvitamin D₃ (1 α -OH-D₃). On the other hand, *in vitro* measurement of binding affinity with chick intestinal cytosolic receptor¹²⁾ disclosed that 2 and 3 have only one 1,000th as much affinity as 1 α ,25-(OH)₂-D₃ and 1 α -OH-D₃ and application of 2 to rats deficient in vitamin D showed no effect on intestinal calcium transportation and bone calcium mobilization at a dose of 125 μ g/kg (iv). Pharmacological studies are now under investigation.

ACKNOWLEDGEMENT We are grateful to Emeritus Professor Masatomo Hamana for his encouragement. Thanks are also due Dr. M. Fukushima, E. Kamijo and Y. Takita for biological experiments.

REFERENCES AND NOTES

- 1) Part VI: K. Miyamoto, N. Kubodera, E. Murayama, K. Ochi, T. Mori, and I. Matsunaga, *Syn. Commun.*, in press.
- 2) E. Abe, C. Miyaura, H. Sakagami, M. Takeda, K. Konno, T. Yamazaki, S. Yoshiki, and T. Suda, *Proc. Natl. Acad. Sci. U.S.A.*, **78**, 4990 (1981).
- 3) K. Matoba, K. Kondo, and T. Yamazaki, *Chem. Pharm. Bull.*, **32**, 1416 (1984) and references cited therein.
- 4) R. H. Hesse, Japan Patent 126861 (1983) (Chem. Abstr., **99**, 176164 (1983)).
- 5) R. M. Dodson, A. H. Goldkamp, and R. D. Muir, *J. Am. Chem. Soc.*, **82**, 4026 (1960).
- 6) a) 6: colorless foam softening at 86-93°C; IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3460, 1025; NMR (CDCl₃) δ : 0.76(3H,s), 1.00(1.3H,s), 1.01(1.7H,s), 4.5-4.8(2H,br), 5.3-5.5(1H,br).
 b) 7: pale yellow oil; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1030; NMR(CDCl₃) δ : 0.77(3H,s), 1.00(1.3H,s), 1.02(1.7H,s), 1.31(3H,s), 3.45(2H,brt, J=6Hz), 3.91(4H,s), 4.5-4.9(2H,s), 5.4-5.6(1H,br); MS m/e: 602(M⁺), 85(100%).
 c) 8: colorless prisms; mp 96-97°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3350, 1710; NMR(CDCl₃) δ : 0.75(3H,s), 1.02(3H,s), 2.00 (2H,s, exchanged with D₂O), 2.13(3H,s), 3.1-4.0(3H,br), 3.42(2H,t, J=6Hz), 5.45-5.65(1H,br); MS m/e: 390(M⁺), 85(100%).
 d) 9: colorless powder; mp 70-72°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3400; NMR(CDCl₃) δ : 0.78(3H,s), 1.03(3H,s), 3.47(2H,br t, J=6Hz), 5.4-5.6(1H,br); MS m/e: 406(M⁺), 83(100%).

- e) 10: colorless oil; IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3450, 1730, 1240; NMR(CDCl_3) δ : 0.75(3H,s), 1.08(3H,s), 1.20(6H,s), 1.98(3H,s), 2.01(3H,s), 2.70(1H,s, exchanged with D_2O), 3.1-3.6(3H,br), 4.7-5.1(2H,br), 5.4-5.6(1H,br); MS m/e: 472($\text{M}^+ - \text{H}_2\text{O}$), 118(100%).
- f) 11: colorless powder; mp 115-117°C; IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3475, 1740, 1690, 1240; NMR(CDCl_3) δ : 0.91(3H,s), 1.06(3H,s), 1.21(6H,s), 2.00(3H,s), 2.01(3H,s), 3.1-3.7(3H,br), 5.0-5.2(1H,br), 5.6-6.0(1H,m), 6.29(1H,d, J=8Hz), 6.49(1H,d, J=8Hz), 7.2-7.6(5H,m); MS m/e: 488($\text{M}^+ - \text{PTAD}$), 177(100%).
- g) 12: colorless foam; IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3375; NMR(CDCl_3) δ : 0.71(3H,s), 0.93(3H,s), 1.20(6H,s), 3.3-3.9(5H,br), 5.2-5.5(1H,br), 5.69(1H, br d, J=6Hz); UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 292.5, 281, 270.
- h) 2: colorless crystals; NMR (CDCl_3) δ : 0.63(3H,s), 1.23 (6H,s), 3.51(3H,m), 4.17-4.29(1H,m), 4.34-4.49(1H,m), 4.98(1H,t, J=1.6Hz), 5.31(1H,t, J=1.6Hz), 5.99(1H,d, J=12.0Hz), 6.36(1H,d, J=12.0Hz); MS m/e: 404(M^+), 83(100%); UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 262, $\lambda_{\text{min}}^{\text{EtOH}}$ nm: 227; $[\alpha]_{\text{D}}^{24}$ -44.6° (c=0.56, EtOH).
- i) 13: colorless prisms; mp 129-131°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3350; NMR(CDCl_3) δ : 0.77(3H,s), 0.87(6H,d, J=6Hz), 1.03(3H,s), 2.55(2H,br, exchanged with D_2O), 3.41(2H,t, J=6Hz), 3.6-4.3(3H,br), 5.4-5.7(1H,br); MS m/e: 390(M^+), 372(100%).
- j) 14: colorless foam; IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1740, 1240; NMR(CDCl_3) δ : 0.76(3H,s), 0.87(6H,d, J=6Hz), 1.09(3H,s), 2.03(3H,s), 2.06(3H,s), 3.2-3.6(1H,br), 3.42(2H,t, J=6Hz), 4.6-5.2(2H,m), 5.4-5.7(1H,br); MS m/e: 474(M^+), 118(100%).
- k) 15: colorless powder; mp 94-97°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1740, 1690, 1230; NMR(CDCl_3) δ : 0.87(6H,d, J=6Hz), 0.90(3H,s), 1.06(3H,s), 2.00(3H,s), 2.02(3H,s), 3.1-3.5(1H,br), 3.51(2H,t, J=6Hz), 5.0-5.2(1H,br), 5.6-6.0(1H,m), 6.27(1H,d, J=8Hz), 6.47(1H,d, J=8Hz), 7.2-7.6(5H,m); MS m/e: 472($\text{M}^+ - \text{PTAD}$), 352(100%).
- l) 16: colorless powder; mp 87-90°C; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3375; NMR(CDCl_3) δ : 0.70(3H,s), 0.89(6H,d, J=6Hz), 0.92(3H,s), 3.45(2H,t, J=6Hz), 3.7-4.2(3H,br), 5.2-5.5(1H,br), 5.68(1H,br d, J=6Hz); MS m/e: 388(M^+), 134(100%); UV $\lambda_{\text{min}}^{\text{EtOH}}$ nm: 292.5, 281, 270.
- m) 3: colorless crystals; NMR(CDCl_3) δ : 0.62(3H,s), 0.86(3H,d, J=0.8Hz), 0.89(3H,d, J=0.8Hz), 3.35-3.56(3H,m), 4.15-4.32(1H,m), 4.38-4.51(1H,m), 5.00(1H,t, J=1.6Hz), 5.32(1H,t, J=1.6Hz), 6.00(1H,d, J=12.0Hz), 6.38(1H,d, J=12.0Hz); MS m/e: 388(M^+), 134(100%); UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 262, $\lambda_{\text{min}}^{\text{EtOH}}$ nm: 227, $[\alpha]_{\text{D}}^{24}$ -30.2° (c=0.86, EtOH).
- 7) J. H. Dygos, and B. N. Desai, *J. Org. Chem.*, **44**, 1590 (1979).
- 8) G. A. Grob and R. Moesh, *Helv. Chim. Acta*, **42**, 728 (1959).
- 9) D. H. Barton, T. Shioiri, and D. H. Widdowson, *J. Chem. Soc.*, (C), **1979**, 1968.
- 10) K. Ochi, I. Matsunaga, H. Nagano, M. Fukushima, M. Shindo, C. Kaneko, M. Ishikawa, and H. F. DeLuca, *J. Chem. Soc. Perkin Trans. 1*, **1979**, 165.
- 11) C. Miyaura, E. Abe, T. Kuribayashi, H. Tanaka, K. Konno, Y. Nishii and T. Suda, *Biochem. Biophys. Res. Commun.*, **102**, 937 (1981).
- 12) S. Ishizuka, K. Bannai, T. Naruchi, and Y. Hashimoto, *Steroids*, **37**, 33 (1981).

(Received March 10, 1986)