Communications to the Editor

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SYNTHETIC STUDIES OF VITAMIN D_3 ANALOGUES. VIII.[1] SYNTHESIS OF 22-OXAVITAMIN D_3 ANALOGUES

Eigoro Murayama,* Katsuhito Miyamoto, Noboru Kubodera, Takashi Mori, and Isao Matsunaga

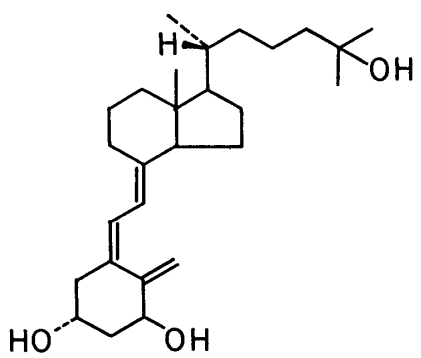
New Drug Research Laboratories, Chugai Pharmaceutical Co., Ltd., 41-8, Takada 3 chome, Toshima-ku, Tokyo 171, Japan

The synthesis of two vitamin D_3 analogues, 1α-hydroxy-22-oxavitamin D_3 (3a) and 1α,25-dihydroxy-22-oxavitamin D_3 (3b) from dehydroepiandrosterone (4) is described.

KEYWORDS —— dehydroepiandrosterone; vitamin D_3 analogue; 1α-hydroxy-22-oxavitamin D_3; 1α,25-dihydroxy-22-oxavitamin D_3; 1α,3β-bis(tert-butyldimethylsilyloxy)-5,7-androstadien-17-one; 1α,3β-bis(tert-butyldimethylsilyloxy)-5,7-pregnadien-20(S)-ol

Since 1α,25-dihydroxyvitamin D_3 (1) [1α,25-$(OH)_2$-D_3] was shown to induce differentiation in myeloid leukemia cells in addition to its regulation of calcium and phosphorus metabolism,[2] our efforts have been concentrated on the separation of these types of physiological action. The preceding paper described the synthesis of 20-oxa-21-norvitamin D_3 analogues (2a and 2b) and showed that they have a differentiation-inducing effect but no calcium regulating effect.[1] As a continuation of this work, we synthesized 1α-hydroxy-22-oxavitamin D_3 (3a) [1α-OH-22-oxa-D_3] and 1α,25-dihydroxy-22-oxavitamin D_3 (3b) [1α,25-$(OH)_2$-22-oxa-D_3] from dehydroepiandrosterone by a novel reaction sequence involving 1α- and 3β-tert-butyldimethylsilyloxy derivatives as key intermediates.

The ketodiol (5), prepared by microbiological 1α-hydroxylation[3] of dehydroepiandrosterone (4), was converted into the bis-tert-butyldimethylsilyl ether (6) in 94% yield upon treatment with tert-butyldimethylsilyl chloride and imidazole in



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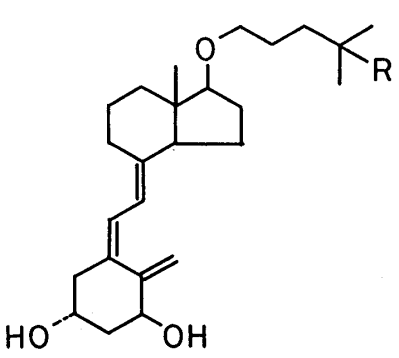
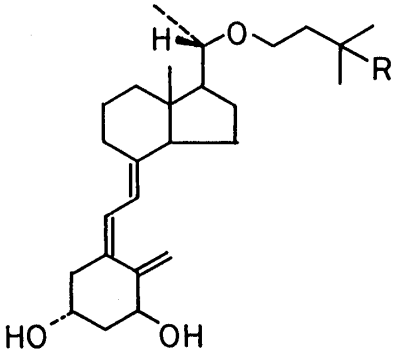


2a : R = H

2b : R = OH



3a : R = H

3b : R = OH

DMF in the presence of catalytic amounts of 1-hydroxybenzotriazole[4] at 50-60°C for 3 d. The ether 6 was treated with NBS in boiling hexane for 1 h,[1] followed by refluxing in a mixture of γ-collidine and xylene for 1 h to give the 5,7-diene (7)[5a] in 65% yield. The Wittig reaction[6] of 7 with ethylidene triphenylphosphorane in a mixture of DMSO and THF at room temperature afforded the triene (8) in 64% yield. The addition of 9-BBN[7] to 8 in THF at room temperature for 16 h followed by the oxidation with NaOH and H_2O_2 gave the 20(S)-alcohol (9)[5b] in 84% yield.

Treatment[8] of 9 with NaH and 1-bromo-3-methylbutane in refluxing xylene for 22 h gave the pro-D_3 derivative (10) in 86% yield. Irradiation[9] of 10 in hexane under argon atmosphere using a high pressure mercury lamp (400 W, Vycor filter), followed by the thermal isomerization of the so-formed pre-D_3 in boiling hexane and subsequent elimination of the silyl groups with tetrabutylammonium fluoride in THF for 16 h furnished 1α-OH-22-oxavitamin D_3 3a[5c] in 24% yield.

In contrast to the formation of 10, attempted alkylation of 9 with 1-bromo-3,3-ethylenedioxybutane or 3,3-ethylenedioxy-1-iodobutane faild.[10] However, the desired 25-keto derivative (13) was obtained by the following two-step procedure; the alcohol 9 was treated with 4-bromo-1-butene and a large excess of NaH in refluxing xylene for 18 h, then the resulting 1:1 mixture of the double bond isomers (11 and 12) was oxidized by the Wacker process (catalytic amounts of $PdCl_2$ and excess CuCl in DMF-H_2O, O_2 atmosphere, room temperature, 19 h)[11] to give the ketone 13 in 44% yield based on the consumed 9, together with the unchanged isomer 12. The reaction of 13 with MeMgBr in THF at 0°C for 1 h gave the pro-D_3 derivative (14) in 79% yield. 14 was successively subjected to the irradiation, thermal isomerization and deprotection in the same manner as mentioned above to give 1α,25-$(OH)_2$-22-oxa-D_3 3b[5d] in 9% yield.

While the tert-butyldimethylsilylation of the 1α-hydroxy group of the diol 5 required somewhat higher temperature (50-60°C) and prolonged period (3 days), the removal of the silyl group to give 3a and 3b was easily effected by treatment with fluoride ion. Both of the silyl ethers at 1α- and 3β-positions were remarkably stable under all conditions used in our synthetic procedures, and had no influence on the photoreaction of pro-D_3 derivatives and the subsequent thermal isomerization. Furthermore, the 5,7-diene function was shown to be stable enough through the reaction sequences. These findings demonstrate that the 17-ketone 7 is a general and useful key compound for the synthesis of 1α-hydroxyvitamin D_3 analogues.

The inducing effects of 3a, 3b and the related D_3 analogues on differentiation of the human myeloid leukemia cells (HL-60) into macrophages were examined *in vitro*.[12] The most remarkable result was the high inducing efficacy of 3a and 3b. 3b was about 10 times as effective as 1α,25-$(OH)_2$-D_3 (1), and 3a and 3b were about 50 times as effective as 20-oxa-21-nor-D_3 2a and 2b, respectively.[13] On the other hand, *in vitro* measurement of the binding affinity with chick intestinal cytosolic receptor[14] disclosed that 3a and 3b have only one 100th and one 14th as much affinity as 1, respectively, and their application to rats deficient in vitamin D_3 showed no effect on bone calcium mobilization at a dosage of 125 μg/kg (iv). Further pharmacological studies are now in progress.

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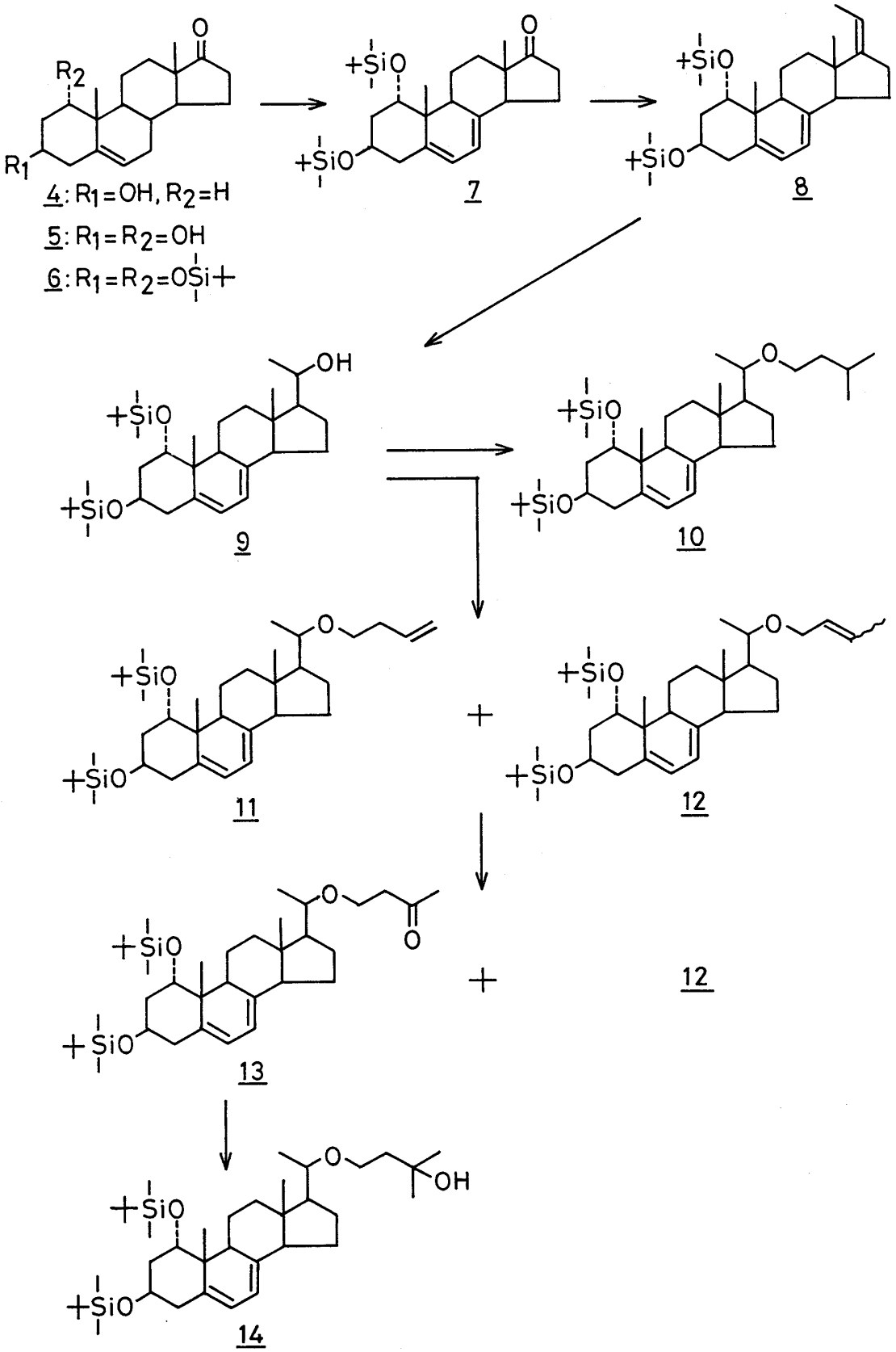

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5) a) 7: white powder; IR ν_{max}^{KBr} cm^{-1}: 3040, 2960, 1742, 1478, 1465, 1225, 1100, 1080, 838, and 775; NMR ($CDCl_3$) δ : 0.06(s,6H), 0.07(s,3H), 0.11(s,3H), 0.82 (s,3H), 0.88(s,9H), 0.90(s,9H), 0.93(s,3H), 2.85(t,J=8.5Hz,1H), 3.69(t,J=2Hz, 1H), 3.88-4.14(m,1H), 5.40-5.47(m,1H), and 5.59(d,J=5.7Hz,1H); MS m/z : 530 (M^+), 73(100%).

b) 9: colorless needles; mp 169°C; IR ν_{max}^{KBr} cm^{-1}: 3410, 3040, 2960, 1478, 1470, 1255, 1102, 1084, 836, and 775; NMR ($CDCl_3$) δ : 0.05(s,3H), 0.06(s,6H), 0.11 (s,3H), 0.62(s,3H), 0.88(s,18H), 0.90(s,3H), 1.24(d,J=5.7Hz,3H), 2.71-2.85(m, 1H), 3.62-3.79(m,2H), 3.92-4.11(m,1H), 5.32(dt,J=5.7 and 2.9Hz,1H), and 5.58 (d,J=5.7Hz,1H); MS m/z : 560(M^+), 73(100%).

c) 3a: colorless glass; NMR ($CDCl_3$) δ : 0.53(s,3H), 0.89(d,J=6.7Hz,3H), 0.90 (d,J=6.7Hz,3H), 1.16(d,J=6.2Hz,3H), 2.32(dd,J=13.6 and 6.8Hz,1H), 2.60(dd,J= 13.6 and 3.4Hz,1H), 2.84(dd,J=12.2 and 3.4Hz,1H), 3.10-3.30(m,2H), 3.48-3.62 (m,1H), 4.14-4.28(m,1H), 4.38-4.50(m,1H), 4.99(t,J=1.6Hz,1H), 5.32(t,J=1.6Hz, 1H), 6.02(d,J=11.4Hz,1H), and 6.37(d,J=11.4Hz,1H); MS m/z : 402(M^+), 71(100%); UV λ_{max}^{EtOH} nm : 262.

d) 3b: colorless glass; NMR ($CDCl_3$) δ : 0.54(s,3H), 1.18(d,J=6.3Hz,3H), 1.23 (s,6H), 2.31(dd,J=13.7 and 6.6Hz,1H), 2.60(dd,J=13.7 and 3.4Hz,1H), 2.82(dd,J= 12.0 and 1.7Hz,1H), 3.25(quint,J=6.3Hz,1H), 3.47(dt,J=9.1 and 5.4Hz,1H), 3.75-3.91(m,2H), 4.16-4.30(m,1H), 4.36-4.50(m,1H), 4.98(t,J=1.4Hz,1H), 5.32(t,J=1.4 Hz,1H), 6.02(d,J=11.4Hz,1H), and 6.36(d,J=11.4Hz,1H); MS m/z : 418(M^+), 69 (100%); UV λ_{max}^{EtOH} nm : 262.

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10) The alkylation of 1α,3β-bis(tetrahydropyranyloxy)-5-androsten-17β-ol with 1-chloro-4,4-ethylenedioxypentane in the presence of NaH in boiling xylene gave the desired ether in good yield.[1] The failure in this work might be due to the bulkiness of 1-halo-3,3-ethylenedioxybutane compared with the former one.

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