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SYNTHETIC STUDIES OF VITAMIN D₃ ANALOGUES. VIII.¹⁾
SYNTHESIS OF 22-OXAVITAMIN D₃ ANALOGUES

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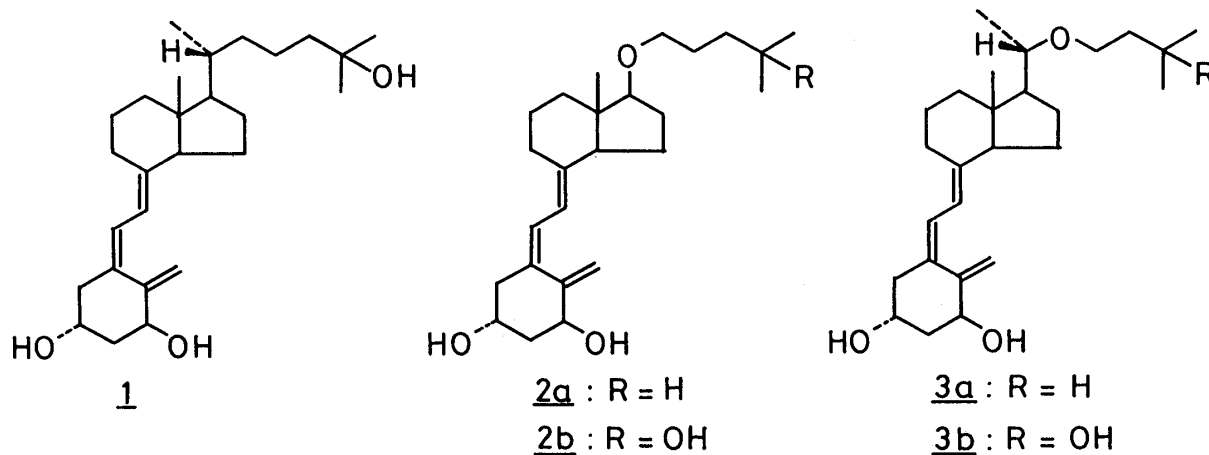
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The synthesis of two vitamin D₃ analogues, 1 α -hydroxy-22-oxavitamin D₃ (3a) and 1 α ,25-dihydroxy-22-oxavitamin D₃ (3b) from dehydroepiandrosterone (4) is described.

KEYWORDS — dehydroepiandrosterone; vitamin D₃ analogue; 1 α -hydroxy-22-oxavitamin D₃; 1 α ,25-dihydroxy-22-oxavitamin D₃; 1 α ,3 β -bis(tert-butyldimethylsilyloxy)-5,7-androstadien-17-one; 1 α ,3 β -bis(tert-butyldimethylsilyloxy)-5,7-pregnadien-20(S)-ol

Since 1 α ,25-dihydroxyvitamin D₃ (1) [1 α ,25-(OH)₂-D₃] 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 D₃ 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 1 α -hydroxy-22-oxavitamin D₃ (3a) [1 α -OH-22-oxa-D₃] and 1 α ,25-dihydroxy-22-oxavitamin D₃ (3b) [1 α ,25-(OH)₂-22-oxa-D₃] from dehydroepiandrosterone by a novel reaction sequence involving 1 α - and 3 β -tert-butyldimethylsilyloxy derivatives as key intermediates.

The ketodiols (5), prepared by microbiological 1 α -hydroxylation³⁾ of dehydroepiandrosterone (4), was converted into the bis-tert-butyldimethylsilyl ether (6) in 94% yield upon treatment with tert-butyldimethylsilyl chloride and imidazole in



DMF in the presence of catalytic amounts of 1-hydroxybenzotriazole⁴⁾ 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 reaction⁶⁾ 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-BBN⁷⁾ to 8 in THF at room temperature for 16 h followed by the oxidation with NaOH and H₂O₂ gave the 20(S)-alcohol (9)^{5b)} in 84% yield.

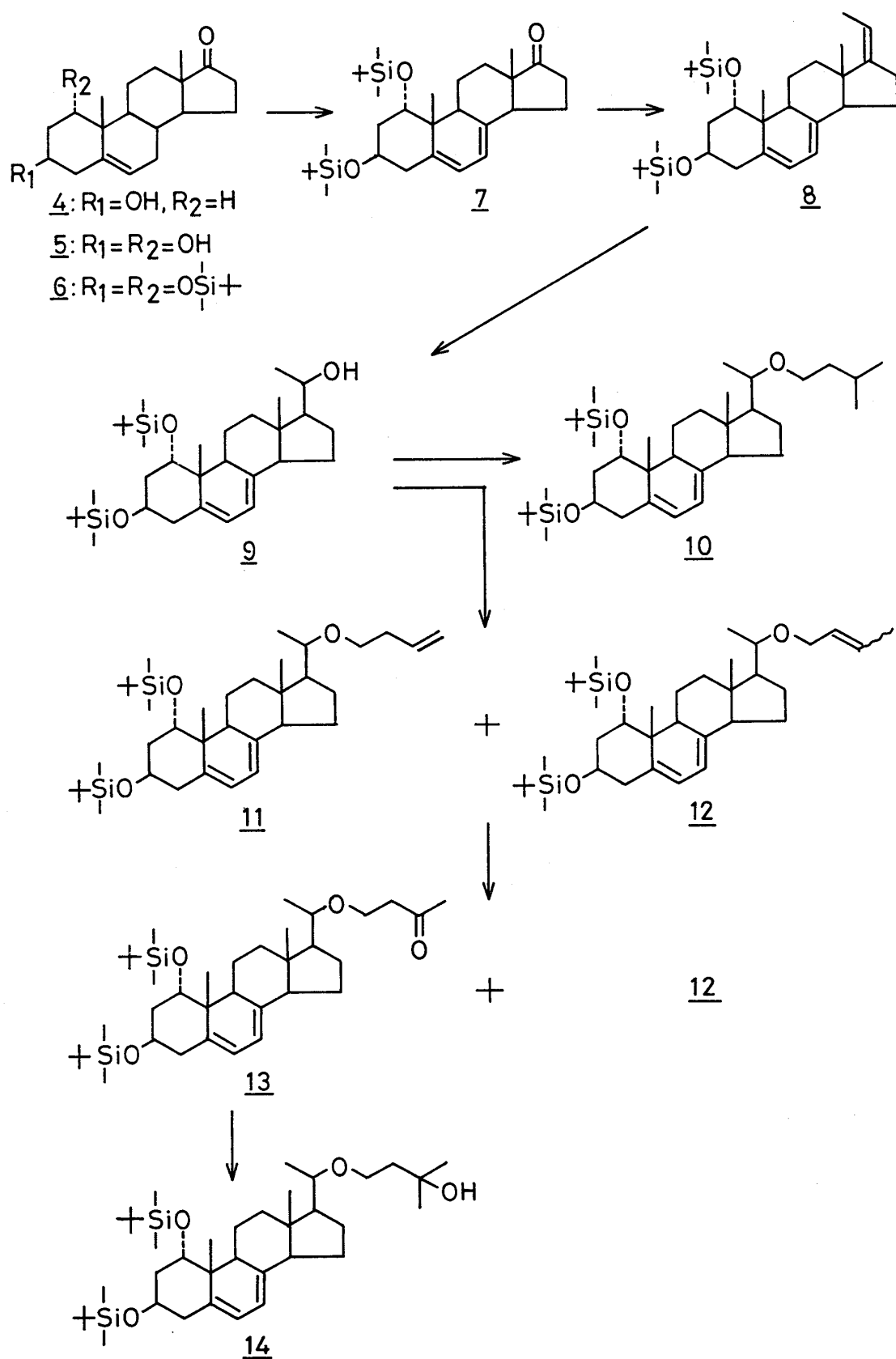
Treatment⁸⁾ of 9 with NaH and 1-bromo-3-methylbutane in refluxing xylene for 22 h gave the pro-D₃ derivative (10) in 86% yield. Irradiation⁹⁾ of 10 in hexane under argon atmosphere using a high pressure mercury lamp (400 W, Vycor filter), followed by the thermal isomerization of the so-formed pre-D₃ in boiling hexane and subsequent elimination of the silyl groups with tetrabutylammonium fluoride in THF for 16 h furnished 1 α -OH-22-oxavitamin D₃ 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 failed.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 PdCl₂ and excess CuCl in DMF-H₂O, O₂ 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-D₃ 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 1 α ,25-(OH)₂-22-oxa-D₃ 3b^{5d)} in 9% yield.

While the tert-butyldimethylsilylation of the 1 α -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 1 α - and 3 β -positions were remarkably stable under all conditions used in our synthetic procedures, and had no influence on the photoreaction of pro-D₃ 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 1 α -hydroxyvitamin D₃ analogues.

The inducing effects of 3a, 3b and the related D₃ 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 1 α ,25-(OH)₂-D₃ (1), and 3a and 3b were about 50 times as effective as 20-oxa-21-nor-D₃ 2a and 2b, respectively.¹³⁾ On the other hand, *in vitro* measurement of the binding affinity with chick intestinal cytosolic receptor¹⁴⁾ 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 D₃ showed no effect on bone calcium mobilization at a dosage of 125 μ g/kg (*iv*). Further pharmacological studies are now in progress.

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- 5) a) **7**: white powder; IR $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\lambda_{\text{max}}^{\text{EtOH}}$ 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=1.4Hz, 1H), 6.02(d, J=11.4Hz, 1H), and 6.36(d, J=11.4Hz, 1H); MS m/z: 418 (M^+), 69(100%); UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 262.
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- 10) The alkylation of 1 α ,3 β -bis(tetrahydropyranyloxy)-5-androsten-17 β -ol with 1-chloro-4,4-ethylenedioxybutane 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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- 13) While the inducing effect of **2b** was reported to be as effective as **1**,¹⁾ repeated experiments showed **2b** was about 1/5 times as effective as **1**.
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