Synthetic Studies of Vitamin D Analogs. XXII. 1) Synthesis and Antiproliferation Activity of Putative Metabolites of 1α,25-Dihydroxy-22-oxavitamin D₃ 2)

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As putative metabolites of 1α,25-dihydroxy-22-oxavitamin D₃ (OCT), 24-hydroxylated OCT in 24(R) and 24(S) forms, 24-ketoOCT, 26-hydroxylated OCT in 25(S) and 25(R) forms, pentanorOCT and pentanor-ketoOCT were synthesized from the steroidal 20(S)-alcohol. Their antiproliferation activities towards human promyelocytic leukemia cells (HL-60 cells) are also reported. Oxidized derivatives at the C-24 position, 24-ketoOCT, 24(R)-hydroxylated OCT and 24(S)-hydroxylated OCT, showed activities comparable to or slightly weaker than that of OCT, while 26-hydroxylated OCT and 24(S)-hydroxylated OCT was less active than OCT. Truncated OCT, pentanor OCT and pentanor-ketoOCT, were inactive at 10⁻⁷–10⁻¹⁰ M.

Key words vitamin D₃ analog; 1α,25-dihydroxyvitamin D₃; 1α,25-dihydroxy-22-oxavitamin D₃; OCT; metabolite; antiproliferation activity

1α,25-Dihydroxy-22-oxavitamin D₃ (OCT, 1), the 22-oxygenated analog of 1α,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃, 2], has potent in vitro differentiation-induction and antiproliferation activities with low in vivo calcemic liability. 4–6) Compound 1 is being clinically investigated as a candidate for antihyperparathyroidism injection 7) and antipsoriatic ointment. 8)

During the course of our development of 1, it was necessary to synthesize possible metabolites of 1 for pharmacokinetic and metabolic studies. It is well known that the active vitamin D₃, 2, is hydroxylated at C-23, C-24 or C-26 as the first step in its metabolism. The hydroxylated metabolites of 2 are further oxidized to ketoalcohol, lactone (calcitriol lactone) or carboxylic acid (calcitric acid). 9–13) On the assumption that oxidation pathway of 1 to 2 would be similar, we undertook the synthesis of OCT derivatives oxidized at C-23, C-24 or C-26 as putative metabolites of 1. In this paper we wish to describe the synthesis of 24-hydroxylated OCT (3 and 4) in 24(R) and 24(S) forms, 4') 24-ketoOCT (5), 5' 26-hydroxylated OCT (6 and 7) in 25(S) and 25(R) forms and truncated OCT, pentanorOCT (8) and pentanor-ketoOCT (9), which might be derived from the 23-hydroxylated hemiacetal (10). Their antiproliferation activities towards human promyelocytic leukemia cells (HL-60 cells), measured in a preliminary biological evaluation of these compound, are also reported.

The common starting material for the synthesis of each oxidized OCT was the 20(S)-alcohol (11), which was prepared from dehydroepiandrosterone via microbiological 1α-hydroxylation as described previously. 4') First, we synthesized 3 and 4. The 20(S)-alcohol (11) was alkylated with the (R)-epoxide (12a) and the (S)-epoxide (12b) prepared from d-mannitol and l-serine, 17) in the presence

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of dibenzo-18-crown-6 and potassium tert-butoxide to give the alcohol (13a or 13b) in 24% and 10% yields, respectively. The alcohols (13a and 13b) were then separately deprotected with tetrabutylammonium fluoride (TBAF) in N,N'-dimethylpropyleneurea (DMPU) at 80°C to give the tetraols (14a and 14b) in 77% and 70% yields, respectively. Subsequent irradiation of 14a and 14b in ethanol at 0°C using a high-pressure mercury lamp through a Vycor filter followed by thermal isomerization under reflux in ethanol gave rise to 24(R)-hydroxylated OCT (3) and 24(S)-hydroxylated OCT (4) in 17% and 13% yields, respectively. For the synthesis of 5, the tert-butylidemethylsilyl (TBS) group used for protection of the 3-hydroxy part in 11 was changed to a methoxymethyl (MOM) group in 15 after extensive examination of deprotection conditions. Thus, the alcohol (15) was alkylated with the racemic epoxide (12c)\textsuperscript{18} to give the ether (16) in 73% yield. The silyl ether moiety in 16 was cleaved by TBAF to afford the triol (17). To protect allylic positions of the 5,7-diene in 17 from the next oxidation step, 17 was converted to the 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) adduct (18). The Swern oxidation of 18 gave the 24-ketone (19) in 44% yield, and this was converted to the 5,7-diene (21) by retro Diels–Alder reaction\textsuperscript{19} (65%) of the triol (20) obtained by the deprotection (68%) of 19.

The 5,7-diene (21) was then transformed to 5 by irradiation and thermal isomerization.

Next, the synthesis of 6 and 7 was examined. After many fruitless attempts, we focused our attention on a route using the Katsuki–Sharpless epoxidation.\textsuperscript{20} Thus, the bromide (29) was prepared from the allyl alcohol (22) as follows: a) silylation giving 23, b) ozonolysis giving 24, c) Horner–Emmons reaction giving 25, d) reduction giving 26, e) tetrahydropyranyl (THP) ether formation.
Table 1. Biological Properties of OCT and its Putative Metabolites

<table>
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<tr>
<th>Compd.</th>
<th>B/B\text{max} (pg/tube)</th>
<th>Relative to OCT</th>
<th>ED\text{50} (x 10^{-10} mol dm^{-3})</th>
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<tr>
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<td>7650</td>
<td>1/364</td>
<td>&gt;1000</td>
<td>&lt;1/217</td>
</tr>
</tbody>
</table>

Experimental

General Methods Optical rotations were measured with JASCO DIP-370 and Horiba SEPA-200 polarimeters. Ultraviolet (UV) spectra were recorded with a Shimadzu UV-240 in EtOH. Infrared (IR) spectra were obtained using Hitachi 270-30 and JASCO IR-700 spectrometers. 1H-Nuclear magnetic resonance (NMR) spectra were recorded on JEOL JNM-FX-90A, JEOL FX-200, JEOL JNM-GX-500 and Hitachi R-3000 spectrometers in CDCl3, with tetramethylsilane as an internal standard. Coupling constants (J) are given in Hz. Mass spectra (MS) were obtained on Shimadzu GCMS-QP 1000 and JEOL JMS-DX303. High-resolution mass spectra (HRMS) were obtained using VG Auto Spec Q and JEOL JMX-AX500 instruments. All air-sensitive reactions were carried out under an atmosphere of dry argon or nitrogen. Preparative TLC was performed on 20 x 20 cm plates coated with 0.5 mm thickness of Merck Kieselgel 60 containing F254 indicator. The phrase "residue upon work-up" refers to the residue obtained when the organic layer was separated and dried over MgSO4, and the solvent was evaporated under reduced pressure.

(20S,24R)-1s,3s-Bis(tert-butyldimethylsilyloxy)-24-hydroxy-25-[2-(trimethylsilyl)ethoxy)methyloxy]-22-oxacholesta-5,7-diene (13a) A mixture of the 20(S)-alcohol (11) (874 mg, 1.56 mmol), tert-BuOK (90%; 213 g, 17.1 mmol), dibenzo-18-crown-6 (405 g, 1.12 mmol) and 12a
(809 mg, 3.48 mmol) in toluene (51 ml) was stirred at 80 °C for 3.5 h, then poured into H₂O and extracted with AcOEt. The extract was washed with brine, dried with Na₂SO₄, filtered and concentrated in vacuo. The residue upon work-up was purified by flash column chromatography with AcOEt-hexane (1:1) as the eluent to give 13a (297 mg, 24%) as a yellow oil.

1H NMR, δ (400 MHz, CDCl₃): 7.68 (d, 2H, J = 8.4 Hz), 7.51 - 7.46 (m, 4H), 7.42 - 7.37 (m, 2H), 7.34 - 7.29 (m, 2H), 7.28 - 7.23 (m, 2H), 7.22 - 7.18 (m, 2H), 4.39 - 4.33 (m, 2H), 3.34 - 3.29 (m, 4H), 2.93 - 2.87 (m, 2H), 2.86 - 2.81 (m, 2H), 2.71 - 2.66 (m, 2H), 2.41 - 2.36 (m, 2H), 2.33 - 2.29 (m, 2H), 1.53 - 1.48 (m, 4H), 1.36 - 1.31 (m, 4H), 1.23 - 1.18 (m, 4H), 0.94 - 0.89 (m, 6H), 0.82 - 0.77 (m, 2H), 0.74 - 0.70 (m, 2H).

MS m/z: 478 (M⁺), 43 (100%).

Chloromethyl methyl ether (3.9 ml, 51.3 mmol) was added dropwise to a stirred solution of the above-mentioned alcohol (688 mg, 1.41 mmol) and disopropylethylamine (2.6 mm, 6.89 mmol) in THF (20 ml) at 0 °C. The mixture was stirred at room temperature for 20 h, then poured into 10% HCl, extracted with AcOEt and washed with saturated NaHCO₃ and H₂O. The residue upon work-up was purified by flash column chromatography with AcOEt-hexane (1:1) as the eluent to give 20S) -20-acetoxy-1z,13b-(1r,3r,13d,15b)-15(1H)-pregna-1,4,6-trien-3β-(1H,7H)-dien-17β-3S, 11β,18β-triol (25 mg, 81%) as a colorless oil.

1H NMR, δ (400 MHz, CDCl₃): 7.67 (d, 2H, J = 8.4 Hz), 7.48 - 7.43 (m, 4H), 7.42 - 7.37 (m, 2H), 7.36 - 7.31 (m, 2H), 7.28 - 7.24 (m, 2H), 7.22 - 7.17 (m, 2H), 4.40 - 4.34 (m, 2H), 3.34 - 3.30 (m, 4H), 2.89 - 2.83 (m, 2H), 2.82 - 2.76 (m, 2H), 2.70 - 2.65 (m, 2H), 2.38 - 2.33 (m, 2H), 2.30 - 2.25 (m, 2H), 1.54 - 1.49 (m, 4H), 1.44 - 1.39 (m, 4H), 1.34 - 1.30 (m, 4H), 1.25 - 1.20 (m, 4H), 0.94 - 0.89 (m, 6H), 0.80 - 0.75 (m, 2H), 0.72 - 0.68 (m, 2H).

MS m/z: 700 (M⁺), 405 (100%).
brs, i-1(CH), 4.62—4.87 (1H, m, 3-CH), 4.70 and 4.80 (each 1H, d, J = 6.5, OCH3), 6.26 and 6.40 (each 1H, d, J = 8.1, 6-CH, 7-CH), 7.23—
7.46 (5H, m, PhH). MS m/z: 653 (M+), 45 (100%).

PTAD Adduct of (20S)-1z,2z,25-Dihydroxy-3z,24-methoxymethyl-24-
20-22-22-oxocholest-5-7-diene (19) DMSO (0.11 ml, 1.50 mmol) was added to a colorless solution of triphenylg (79 mg, 0.27 mmol) in CH2Cl2 (0.3 ml) at —65 °C. The mixture was stirred at the same temperature for 10 min, then a solution of IB (95 mg, 0.15 mmol) in CH2Cl2 (0.5 ml) was added dropwise. Stirring was continued at the same temperature for 15 min. Then triethylamine (0.26 ml, 1.90 mmol) was added and the mixture was stirred at the same temperature for 10 min and at room temperature for 20 min. The mixture was diluted with CH2Cl2 and washed with H2O and saturated NaCl. The residue upon work-up was purified by preparative TLC developed with AcOEt to give 19 (42 mg, 44%) as a colorless powder. UV Vmax nm: 226, 291, 292, 295, 1725, 1800, 1410, 1400 cm-1. NMR δ: 0.83 (3H, s, 18-CH3), 0.95 (3H, s, 19-CH3), 1.22 (3H, d, J = 6.1, 21-CH3), 1.38 (6H, s, 26-CH2, 27-CH3), 3.38 (3H, s, OCH3), 3.90 (1H, brs, 1-CH), 4.22 and 4.43 (each 1H, d, J = 16.7, 23-CH3), 4.65—4.83 (1H, m, 3-CH3), 4.71 and 4.82 (each 1H, d, J = 6.7, OCH3), 6.26 (1H, d, J = 8.3, 7-CH3), 6.42 (1H, d, J = 8.5, 6-CH3), 7.27—7.41 (5H, m, PhH). MS m/z: 476 (M+ — PTAD), 45 (100%).

PTAD Adduct of (20S)-1z,3z,25-Trihydroxy-24-oxo-22-oxocholest-5-7-diene (20) A mixture of 19 (38 mg, 0.06 mmol) and HCl (6 ml solution, 0.5 mol/L) in MeOH (14 ml) was stirred at room temperature for 17.5 h. The mixture was poured into saturated NaHCO3, and extracted with CH2Cl2. The residue upon work-up was purified by preparative TLC developed with AcOEt to give 20 (24 mg, 68%) as a colorless solid. The mixture was stirred at room temperature for 20 h, then diluted with Et2O and washed with H2O, 10% HCl, saturated NaHCO3, and saturated NaCl. The residue upon work-up was purified by preparative TLC developed with AcOEt to give 20 (11 mg, 65%) as a colorless powder. UV Vmax nm: 271, 282, 293. IR (KBr): 3410, 2940, 2925, 1720, 1655, 1045 cm-1. NMR δ: 0.83 (3H, s, 18-CH3), 0.94 (3H, s, 19-CH3), 1.22 (3H, d, J = 6.1, 21-CH3), 1.39 (6H, s, 26-CH2, 27-CH3), 3.38 (3H, brs, 1-CH), 4.22 and 4.44 (each 1H, d, J = 16.7, 23-CH3), 4.79—4.95 (1H, m, 3-CH3), 6.27 (1H, d, J = 8.4, 7-CH3), 6.41 (1H, d, J = 8.4, 6-CH3), 7.27—7.45 (5H, m, PhH). MS m/z: 472 (M+) — PTAD, 59 (100%).

(20S)-1z,3z,25-Trihydroxy-24-oxo-22-oxocholest-5-7-diene (21) A solution of 20 (35 mg, 0.04 mmol) in DMSO (0.4 ml) was stirred at 80 °C for 2.5 h. The mixture was diluted with AcOEt and washed with saturated NaCl. The residue upon work-up was purified by preparative TLC developed with AcOEt to give 21 (11 mg, 65%) as a colorless powder. UV Vmax nm: 271, 282, 293. IR (KBr): 3410, 2940, 2925, 1720, 1655, 1045 cm-1. NMR δ: 0.62 (3H, s, 18-CH3), 0.94 (3H, s, 19-CH3), 1.23 (3H, d, J = 6.0, 21-CH3), 1.39 (6H, s, 26-CH2, 27-CH3), 3.76 (1H, brs, 1-CH), 4.26 and 4.45 (each 1H, d, J = 16.8, 23-CH3), 5.37—5.43 (1H, m, 3-CH), 5.72 (1H, brd, J = 4.0, 6-CH). MS m/z: 432 (M+) — PTAD, 59 (100%).

3-tert-Butylidimethylsiloxyl-1-propene (23) A mixture of 22 (8.16 mmol, 20 mmol), TBSCI (150.9 g, 100 mmol), triethylamine (50.2 ml, 360 mmol) and 4-dimethylaminopyridine (1.47 g, 12.0 mmol) in CH2Cl2 (254 ml) was stirred at room temperature for 20 h, then diluted with Et2O, and washed with H2O, 10% HCl, saturated NaHCO3, and saturated NaCl. The residue upon work-up was distilled under reduced pressure to give 23 (13.8, 80%) as a colorless oil, bp 49—50 °C (16 mmHg). IR (neat): 1254, 1007, 918 cm-1. NMR δ: 0.07 (6H, s, 2 x SiCH3), 0.91 (9H, s, Si(CH3)3), 4.17 (2H, dt, J = 1.7, 4.4, OCH3), 5.01—5.38 (2H, m, CH2=CH3), 5.73—6.09 (1H, m, CH3—CH=CH2). HRMS m/z: 172.1258 (Calcd for C4H7OSi: 172.1283). 3-tert-Butylidimethylsiloxyl-2-methyl-2-butene (25) Ozonolysis was a mixture of 23 (100.0 g, 5.81 mmol) and NaHCO3 (1.15 g, 13.7 mmol) in CH2Cl2 (60 ml) at —82 °C for 45 min. Excess ozone was removed by bubbling nitrogen for 30 min. Ph3P (2.30 g, 8.72 mmol) was added and stirring was continued at room temperature for 1 h. The obtained aldehyde 24 was used without isolation. (Carbethoxymethyldiene)triphenylphosphorane (4.88 g, 12.8 mmol) was added to the above mixture and stirring was continued at room temperature for 14 h. The mixture was concentrated in vacuo, and the residue was extracted with hexane. The insoluble material was removed by filtration. The filtrate was concentrated in vacuo. The crude product was purified by chromatography with Et2O-hexane (1:2) as the eluent to give 25 (1.27 g, 64% from 23) as a colorless oil. IR (neat): 1715, 1243 cm-1. NMR δ: 0.08 (6H, s, 2 x SiCH3), 0.90 (9H, s, Si(CH3)3), 1.28 (3H, t, J = 7.1, 1-CH3), 1.79 (3H, brs, 2-CH3), 4.19 (2H, q, J = 7.1, CH3-CH2), 4.33 (2H, brd, J = 5.6, 4-CH2), 6.76 (1H, brt, J = 5.6, 3-CH). HRMS m/z: 258.1661 (Calcd for C12H16O2Si: 258.1651). 4-(Tetrahydroxy-2-oxo)-3-methyl-2-butenol (28) DIBAH (2.53
chromatography with EtO$_2$-hexane (5:1) as the eluent to give 32a (156 mg, 89%) as a colorless oil. [x]$_D^{20}$ +1.76° (c = 1.45 in CHCl$_3$). IR (neat): 3404, 1525, 1147, 1087, 1066, 868, 812, 770 cm$^{-1}$. NMR δ: 0.07 (3H, s, Si(CH$_3$)$_3$), 0.11 (3H, s, Si(CH$_3$)$_3$), 0.61 (3H, s, CH$_3$-18), 0.63—1.77 (9H, m), 0.88 (9H, s, Si(CH$_3$)$_3$), 1.21 (9H, s, CH$_3$-18), 1.31 (9H, s, CH$_3$-19), 1.59 (9H, s, CH$_3$-25), 1.86—2.09 (4H, m), 2.29 (9H, br t, J = 13.6, 23-CH$_3$), 2.49 (9H, br d, J = 13.6, 23-CH$_3$), 2.80 (1H, brs, 24-CH$_3$), 3.19—3.81 (8H, m), 4.07 (1H, brs, 1-CH$_3$), 5.33 (1H, brd, J = 6.8, 7-CH$_3$), 5.61 (1H, brd, J = 6.8, 6-CH$_3$). HRMS m/z: 456.3734 (Calcd for C$_{32}$H$_{43}$O$_3$Si: 456.3741).

(20S,24S,25R)-1a,25S,26,27,28,29,30-Hexahydropyrano[2,3-e]oxacridine-5,7-diene (32b) This (151 mg, 86%) was obtained as a colorless oil from 31 (170 mg, 0.32 mmol) in the same manner as described for the preparation of 32a. [x]$_D^{20}$ +16.72° (c = 1.92 in CHCl$_3$). IR (neat): 3400, 1254, 1147, 1086, 1064, 867, 833 cm$^{-1}$. NMR δ: 0.07 (3H, s, Si(CH$_3$)$_3$), 0.12 (3H, s, Si(CH$_3$)$_3$), 0.63 (3H, s, CH$_3$-18), 0.88 (9H, s, Si(CH$_3$)$_3$), 0.96—1.79 (9H, m), 1.19 (9H, d, J = 5.9, 21-CH$_3$), 1.31 (9H, s, CH$_3$-19), 1.60 (9H, s, CH$_3$-25), 1.87—2.09 (4H, m), 2.31 (9H, br t, J = 13.6, 23-CH$_3$), 2.50 (1H, br d, J = 13.6, 23-CH$_3$), 2.80 (1H, brs, 24-CH$_3$), 3.22—3.77 (8H, m), 4.06 (1H, brs, 1-CH$_3$), 5.33 (1H, brd, J = 6.8, 7-CH$_3$), 5.63 (1H, brd, J = 6.8, 6-CH$_3$). HRMS m/z: 456.3720 (Calcd for C$_{32}$H$_{43}$O$_3$Si: 456.3741).
free forms of [3H]-1,25(OH)2D3 were separated by addition of
dextran-charcoal suspension and centrifugation. The radioactivity
was measured with an Aloka LSC-700.

Assessment of HL-60 Cell Growth HL-60 cells were kindly provided
by Dr. Inaba, Osaka City University, Medical School. Cells were cul-
tured at 37 °C in RPMI 1640 medium (Nissui Pharmaceutical, Japan)
supplemented with 10% heat-inactivated fetal calf serum and 60 µg/ml
of kanamycin in a humidified atmosphere of 5% CO2 in air. Under
these conditions, the doubling time of HL-60 cells was 24 h. Vitamin
D-induced cells were obtained by seeding HL-60 at 1 x 105/ml in growth
medium and culturing for 72 h in the presence of 10-10–10-7 M OCT
I or its putative metabolites 3–9 dissolved in EtOH. Control cultures
contained the EtOH vehicle at 0.1% (v/v). After the incubation period,
cells were harvested and the cell number was determined using a
hemacytometer. Cell viability was determined in terms of trypan blue
exclusion. The number of cells counted in triplicate experiments was
expressed as a percentage of the control. Data are expressed as the mean
of triplicate counts±standard error.

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