HETEROCYCLES, Vol. 62, 2004, pp. 423 - 436
Received, 28th July, 2003, Accepted, 22nd August, 2003, Published online, 14th October, 2003

# SYNTHESIS OF NOVEL 1α,25-DIHYDROXY-19-NORVITAMIN $D_3$ WITH AN AMIDE CONJUGATE

**Yoshitomo Suhara,[1,†] Keiichiro Ono,[1] Akihiro Yoshida,[1,‡] Toshie Fujishima,[1] Nozomi Saito,[1] Shinobu Honzawa,[1] Seishi Kishimoto,[2] Takayuki Sugiura,[2] Keizo Waku,[2] Hiroaki Takayama,[1] and Atsushi Kittaka*,[1]**

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-0195, Japan, [2]Department of Hygienic Chemistry and Nutrition, Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-0195, Japan

akittaka@pharm.teikyo-u.ac.jp

**Abstract** – The diene system of 1α,25-dihydroxy-19-norvitamin $D_3$ was replaced by a stable amide bond. A 3-hydroxypropoxy group, which was effective on enhancing binding affinity of 1α,25-dihydroxyvitamin $D_3$ for vitamin D receptor (VDR), was introduced to the C2-position of the amide type analogue of 1α,25-dihydroxy-19-norvitamin $D_3$. The amide analogue was found to be not suitable for binding to the ligand binding domain of the bovine thymus VDR, and additional modification at the C2-position did not improve the affinity. Potency in induction of HL-60 cell differentiation was evaluated for the novel amide analogues (**3a-c**).

## INTRODUCTION

1α,25-Dihydroxyvitamin $D_3$ (**1**) has been recognized as a hormone and the most active metabolite of vitamin $D_3$ involved in a variety of biological processes, including calcium and phosphorus metabolism, cellular differentiation and proliferation, and immune reactions.[1,2] The large majority of analogues of **1** were modified at the side chain.[2] The importance of 1α,25-dihydroxy-19-norvitamin $D_3$ (**2**) with deletion of the A-ring 10(19)-exomethylene group on **1** and its analogues in dissociating calcemic activity from cellular differentiation activities has been well established.[3,4] We were interested in

modifying the diene part, connecting between the A-ring and the CD-ring moieties, in the 19-nor skeleton, since only few experiments on structure-activity relationship of the diene in **2** or the trine in **1** have been studied.[5] Previously, we found that introduction of some functional groups into the C2-position increased biological activity of **1** markedly.[6-11] Introducing the 2-(3-hydroxypropoxy) group to the A-ring with the 2β-orientation was effective on enhancing vitamin D receptor (VDR) binding affinity of the natural hormone (**1**), that is, **1a** showed 1.8-fold higher affinity for the VDR than that of **1**.[8,9] The terminal hydroxyl group of the 2β-substituent of **1a** would form hydrogen bonding to Asp-144 in the ligand binding domain (LBD) of the VDR, and it seems to stabilize the ligand (**1a**)-VDR complex.[8] Moreover, 2β-(3-hydroxypropoxy)-1α,25-Dihydroxyvitamin $D_3$ (ED-71) has received considerable attention as a promising candidate for the treatment of osteoporosis.[12] We describe here synthesis and biological evaluation of 1α,25-dihydroxy-19-norvitamin $D_3$ analogues with an amide bond (**3a-c**), in which the A-ring moiety consists of (3*S*,5*S*)-3,5-dihydroxypiperidine (Figure 1).[13]

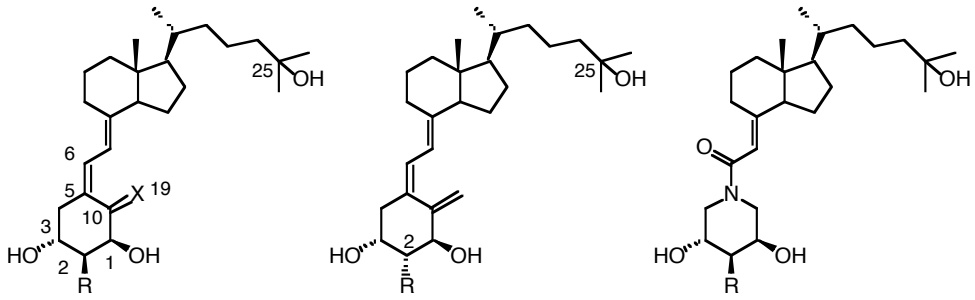


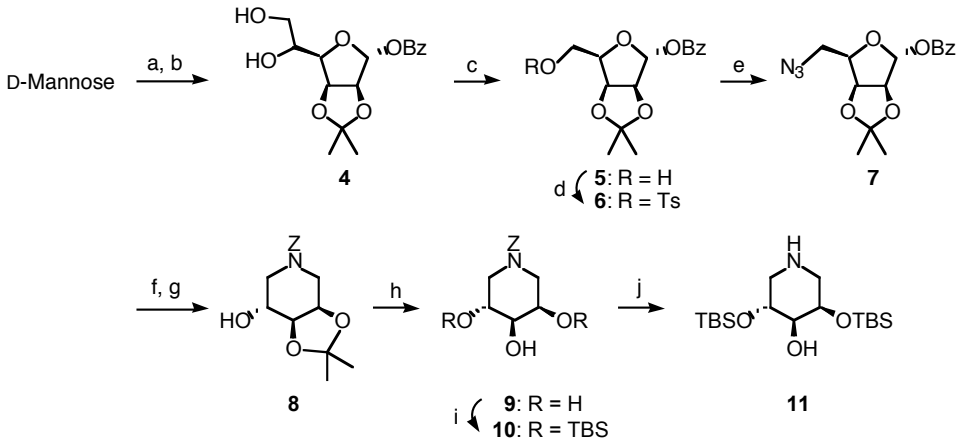

**Figure 1.** Structures of the natural hormone (**1**), it's 2β-(3-hydroxypropoxy) analogue (**1a**), ED-71, 1α,25-dihydroxy-19-norvitamin $D_3$ (**2**), and 19-nor amide derivatives (**3a**-**c**).

## RESULTS AND DISCUSSION

Our designed amide-19-norvitamin $D_3$ analogues (**3a-c**) are shown in Figure 1.[14] The A-ring moiety was substituted with a piperidine ring having two hydroxyls at C1β and C3β (*seco*-steroidal numbering) with the appropriate stereochemistry, which play a crucial role in VDR binding and biological actions. It is well known that epimerization of 1α- or 3β-hydroxyl group dramatically decreases the vitamin D activity by *ca.* 100 times for 1α and 10 times for 3β.[15] The diene part was converted to the stable amide bond to connect with the normal CD-ring moiety. We also planned modification at the C2 position with the substituent of the 3-hydroxypropoxyl group, because we have found this motif can strengthen binding affinity for VDR.[8,9] The amide structures (**3a**-**c**) would allow the N-C6 bond to rotate, whose original structure of the C5-C6 bond is fixed in the natural hormone (**1**). The relative positions of the two hydroxyls at C1β and C3β toward the LBD of the VDR are retained with the rotation, and the artificial

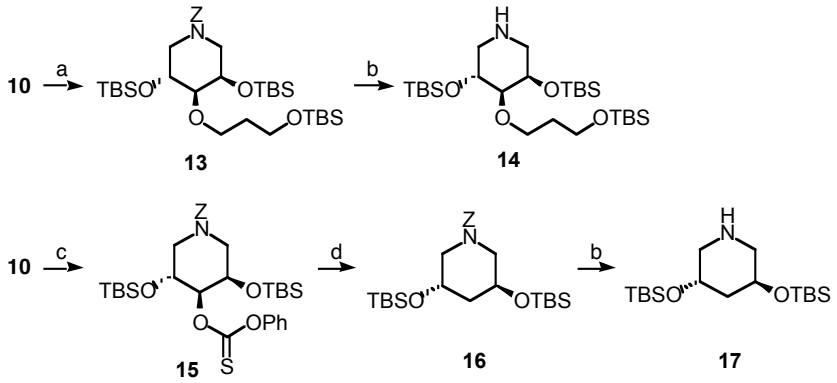
C2 substituent may settle down in an  or a -orientation in preference when **3b** or **3c** complexes with the LBD.

Synthesis of the A-ring piperidine portions (**10**), a synthetic intermediate for **3a** and **3c**, and (**11**) for **3b** are shown in Scheme 1. Although the 5-azido sugar (**7**) is a known compound, it has been prepared from expensive D-lyxose.[16] We tried to synthesize **7** from D-mannose instead of D-lyxose. Treatment of D-mannose with anhydrous $CuSO_4$ and a catalytic amount of conc. $H_2SO_4$ in acetone followed by benzoylation of the anomeric hydroxyl group gave a D-mannofuranose derivative in 86% yield. Selective deprotection of the O4-O6 acetonide using 70% aqueous acetic acid produced 1-*O*-benzoyl-D-mannofuranose (**4**). Oxidative diol cleavage of **4** with sodium periodate, and reduction of the resultant aldehyde afforded the primary alcohol (**5**). Azide (**7**) was prepared from the alcohol through tosylate (**6**) in good yield. After removal of the benzoyl group of **7**, reductive amination with $H_2$/cat. $Pd(OH)_2$ in methanol followed by protection of the amino group with Cbz gave the piperidine derivative (**8**) in 87% yield. Deprotection of the acetonide of **8**, and then introduction of the TBS group to the C1 and C3 hydroxyl groups afforded **10** in a high yield. Finally, the Cbz group was removed by hydrogenation with cat. 10% Pd/C to give the desired A-ring part **11** for **3b** in 71% yield.



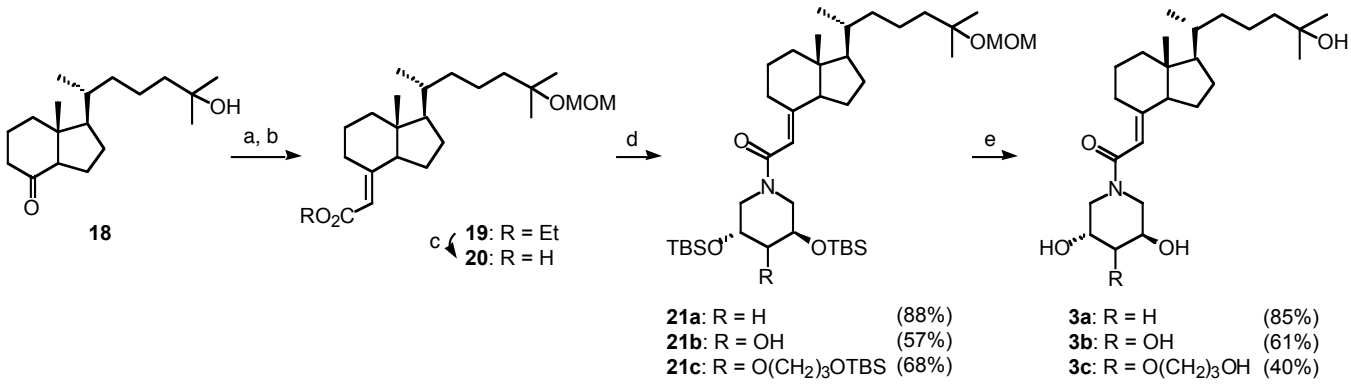

**Scheme 1**. Reagents and conditions: (a) (i) anhydrous $CuSO_4$, acetone, conc. $H_2SO_4$, (ii) BzCl, pyridine (86% in 2 steps); (b) 70% aq. AcOH (quant); (c) (i) $NaIO_4$, $Et_2O$, $H_2O$, (ii) $NaBH_4$, MeOH (64% in 3 steps); (d) TsCl, pyridine (75%); (e) $NaN_3$, DMF (72%); (f) 1 *N* aq. NaOH, MeOH (97%); (g) (i) $H_2$, cat. $Pd(OH)_2$, MeOH, (ii) CbzCl, $Et_2O$, sat. aq. $NaHCO_3$ (87% in 2 steps); (h) 80% aq. AcOH, 90°C (92%); (i) TBSCl, $Et_3N$, DMF (87%); (j) $H_2$, cat. 10% Pd/C, MeOH (71%).

We synthesized two additional piperidine derivatives (**14**) and (**17**) from **10** as shown in Scheme 2. The A-ring portion (**14**) was synthesized by Williamson ether synthesis using 3-bromopropoxy-*tert*-butyldimethylsilane (**12**) and sodium hydride, followed by hydrogenolysis of the Cbz group. On the other hand, the natural type of the A-ring portion (**17**) was obtained by tributyltin radical mediated reduction of thiocarbonate (**15**) in good yield.




**Scheme 2**. Reagents and conditions: (a) $TBSO(CH_2)_3Br$ (**12**), NaH, DMF (20%); (b) $H_2$, 10% Pd/C, MeOH (quant.); (c) PhOC(S)Cl, DMAP, $CH_3CN$ (36%); (d) $Bu_3SnH$, AIBN, benzene (95%).

The CD-ring portion was prepared from 25-hydroxy Grundmann's ketone (**18**)[17] as shown in Scheme 3. After protecting the C25 hydroxyl group with MOM, Horner-Wadsworth-Emmons reaction using triethyl phosphonoacetate and sodium hydride in THF gave the ester (**19**).[4] This reaction proceeded with 92:8 of *E*/*Z*-ratio in 98% yield. Chemical shifts of the vinilic proton of the *E*- and *Z*- isomers were 5.45 and 5.65 ppm, respectively. Trost *et al*. reported that stereochemistry of the corresponding CD-ring bromoolefins, in which the vinilic proton of the *E*-isomer (5.63 ppm) appeared in a higher field than that of the *Z*-isomer (5.93 ppm) due to the anisotropy of the C–C single bond of the five-memberd D-ring.[18] Ethyl ester of **19** was subjected to hydrolysis by 1 *N* aqueous NaOH in a MeOH solution to afford the desired carboxylic acid (**20**) in 86% yield. Subsequent condensation of **20** with the piperidine derivatives (**11**, **14**, and **17**) obtained above using a BOP reagent[19] and DIEA provided the amides (**21a**-**c**) in good yields, respectively. Finally, deprotection under acidic conditions furnished the target amide analogues (**3a**-**c**) in considerable yield.




**Scheme 3.** Reagents and conditions: (a) MOMCl, DIEA, $CH_2Cl_2$ (quant.); (b) triethyl phosphonoacetate, NaH, THF (98%); (c) 1 *N* aq. NaOH, MeOH (86%); (d) **11**, **14**, or **17**, BOP, DIEA, DMF (68-88%); (e) *p*-TsOH, MeOH (40-85%).

Next, we tested biological activity of the new amide analogues (**3a-c**); that is, VDR binding affinity using bovine thymus VDR[13,20,21] and potency in inducing differentiation of HL-60 cells, which are human

promyelocytic leukemia cells, by NBT reduction method.[22] There was no activity we tested in the range of $10^{-10}$ – $10^{-6}$ M. Introducing the 2-(3-hydroxypropoxy) group to the A-ring of the amide analogue (**3a**) did not contribute to stabilize the ligand–VDR complex. Most of the biological actions of **1** are mediated by VDR,[23] therefore no HL-60 cell differentiation activity would be shown by these amide type of analogues having almost no affinity for the VDR.

In summary, we have developed an efficient systematic route for synthesizing new stable amide analogues of 1α,25-dihydroxy-19-norvitamin $D_3$ (**3a**-**c**) with a unique A-ring modification starting from inexpensive D-mannose. Our amide analogues can be applied to a combinatorial synthetic procedure and would easily provide many kinds of this class of $D_3$ analogues.[24] We consider that these synthetic analogues would contribute to the elucidation of the active vitamin $D_3$ action mechanisms.

## EXPERIMENTAL

**General:** NMR spectra were recorded on a JEOL GSX-400 or a JEOL EPC-600 spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. MS spectra (EIMS) and high-resolution MS spectra (HREIMS) were recorded on a JEOL JMX-SX 102A mass spectrometer. IR spectra were recorded on a JASCO FT/IR-8000 spectrophotometer. Optical rotations were determined by using a JASCO DIP-370 digital polarimeter. Recycling HPLC was performed on a Waters LC (YMC-Pack ODS column, 20 X 150 mm). Column chromatography was carried out on silica gel (Silica Gel 60, Cica-reagent). Thin-layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F254, Merck).

**1-*O*-Benzoyl-2,3-*O*-isopropylidene-α-D-lyxofuranose (5).** To a solution of D-mannose (25.0 g, 134 mmol) in acetone (500 mL) were added anhydrous $CuSO_4$ (20.0 g, 12.5 mmol) and conc. $H_2SO_4$ (2 mL) at rt. After stirring for 16 h, the reaction mixture was filtered. The filtrate was diluted with $CH_2Cl_2$, and the solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in pyridine (100 mL), and benzoyl chloride (16 mL, 140 mmol) was added at 0 °C. After stirring at rt for 16 h, the reaction mixture was diluted with $CH_2Cl_2$, and the mixture was washed with aqueous 10% $CuSO_4$, $H_2O$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 5 : 1) afforded 43.7 g of 1-*O*-benzoyl-2,3:5,6-diacetone D-mannose derivative as an amorphous solid (86% in two steps). This compound was used without further purification for the next step. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.39 (s, 3H), 1.46 (s, 3H), 1.53 (s, 3H), 4.06 (dd, *J* = 4.3, 8.9 Hz, 1H), 4.12 (dd, *J* = 6.2, 8.9 Hz, 1H), 4.14 (dd, *J* = 3.7, 7.9 Hz, 1H), 4.49 (ddd, *J* = 4.3, 6.2, 7.9 Hz, 1H), 4.88 (d, *J* = 5.9 Hz,1H), 4.95 (dd, *J* = 3.7, 5.9 Hz, 1H), 6.38 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 7.5

Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) 24.8, 25.3, 26.1, 27.1, 66.9, 72.9, 79.4, 82.6, 85.2, 101.5, 109.3, 113.3, 128.3, 129.4, 129.7, 133.3, 164.7.

A solution of the compound thus obtained above (43.7 g, 124 mmol) in 70% AcOH (450 mL) was stirred at rt for 2 days. After the reaction mixture was concentrated, the residue was dissolved in $CH_2Cl_2$. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude diol was dissolved in $Et_2O$ (600 mL), and the solution of $NaIO_4$ (31.8 g, 149 mmol) in $H_2O$ (300 mL) was added at 0 °C. The mixture was stirred at rt for 1 h, vigorously. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$. The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was dissolved in MeOH (250 mL), and the MeOH solution of $NaBH_4$ (4.69 g, 124 mmol) was added at 0 °C. After stirring at the same temperature for 30 min, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 3 : 1) afforded 23.3 g of **5** as a colorless oil (64% in three steps). $[\alpha]_D^{22}$ +43.6° (*c* 0.5, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) 1.36 (s, 3H), 1.53 (s, 3H), 2.10 (br s, 1H), 3.92-4.03 (m, 2H), 4.33 (dd, *J* = 4.1, 5.4 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.92 (dd, *J* = 4.1, 6.0 Hz, 1H), 6.43 (s, 1H), 7.44 (t, *J* = 7.7Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) 24.9, 26.1, 61.0, 79.8, 82.0, 85.3, 101.2, 113.4, 128.3, 129.4, 129.6, 133.3. IR (neat) 3509, 2990, 2944, 1727, 1603, 1586, 1455, 1375, 1264, 1094, 949, 872, 714 cm$^{-1}$. EIMS *m*/*z* 294 ($M^+$). HREIMS calcd for $C_{15}H_{18}O_6$ ($M^+$) 294.1104, found 294.1100.

**1-*O*-Benzoyl-2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-D-lyxofuranose (6).** To a solution of **5** (234 mg, 0.78 mmol) in pyridine (8 mL) was added TsCl (225 mg, 1.18 mmol) at 0 °C. After stirring at rt for 13 h, the reaction mixture was concentrated. The residue was partitioned between AcOEt and aqueous 10% $CuSO_4$, the organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 3 : 1) afforded 252 mg of **6** as a colorless oil (quant). $[\alpha]_D^{20}$ +3.8° (*c* 1.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) 1.30 (s, 3H), 1.39 (s, 3H), 2.42 (s, 3H), 4.19-4.24 (m, 1H), 4.36-4.43 (m, 2H), 4.83 (d, *J* = 5.7 Hz, 1H), 4.87 (dd, *J* = 3.4, 5.7 Hz, 1H), 6.34 (s, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 7.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) 21.8, 24.9, 26.0, 67.2, 79.1, 79.6, 85.0, 101.1, 113.5, 128.0, 128.3, 129.2, 129.6, 129.7, 132.5, 133.4, 144.8, 164.6. IR (neat) 2988, 2940, 1730, 1599, 1364, 1291, 1262, 1179, 1092, 980, 959, 714, 664 cm$^{-1}$. EIMS *m*/*z* 448 ($M^+$). HREIMS calcd for $C_{22}H_{24}O_8S$ ($M^+$) 448.1191, found 448.1198.

**5-Azido-1-*O*-benzoyl-5-deoxy-2,3-*O*-isopropylidene-D-lyxofuranose (7).** To a solution of **6** (796 mg, 1.72 mmol) in dry DMF (17 mL) was added $NaN_3$ (350 mg, 5.38 mmol) at rt. After stirring at

80 °C for 16 h, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 4 : 1) afforded 469 mg of **7** as an amorphous solid (85%). $[\alpha]_D^{20}$ +15.3° (*c* 0.84, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.37 (s, 3H), 1.53 (s, 3H), 3.63 (d, *J* = 6.6 Hz, 2H), 4.31 (br t, *J* = 6.6 Hz, 1H), 4.89 (br s, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.0, 26.1, 49.5, 79.2, 80.7, 85.1, 101.2, 113.5, 128.3, 129.6, 133.4, 164.6. IR (neat) 2996, 2950, 2091, 1723, 1258, 1206, 1162, 1117, 1090, 1026, 968, 895, 862, 712 $cm^{-1}$. EIMS *m*/*z* 304 ($M^+$). HREIMS calcd for $C_{14}H_{14}N_3O_5$ ($M^+$) 304.0934, found 304.0941.

**5-Azido-5-deoxy-2,3-*O*-isopropylidene-α/β-D-lyxofuranose.** To a solution of **7** (6.25 g, 19.6 mmol) in MeOH (100 mL) was added aqueous 1 M NaOH (10 mL) at rt. After stirring at the same temperature for 30 min, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 4 : 1) afforded 4.10 g of the title compound as a colorless oil (97%). $[\alpha]_D^{20}$ +13.5° (*c* 0.56, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.32 (s, 3H), 1.46 (s, 3H), 2.69 (br s, 1H), 3.50-3.56 (m, 2H), 4.30 (ddd, *J* = 3.7, 5.6, 7.1 Hz, 1H), 4.64 (d, *J* = 5.9 Hz, 1H), 4.76 (dd, *J* = 3.7, 5.9 Hz, 1H), 5.42 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.8, 26.1, 50.0, 78.8, 79.7, 85.5, 101.1, 112.8. IR (neat) 3443, 2988, 2946, 2105, 1377, 1271, 1211, 1163, 1071, 862 $cm^{-1}$. EIMS *m*/*z* 200 $(M - Me)^+$. HREIMS calcd for $C_7H_{10}N_3O_4$ $(M - Me)^+$ 200.0671, found 200.0667.

**(3*R*,4*S*,5*R*)-1-Benzyloxycarbonyl-4,5-isopropylidenedioxypiperidin-3-ol (8).** To a solution of the azide obtained above (4.10 g, 19.1 mmol) in dry MeOH (200 mL) was added $Pd(OH)_2$ (0.8 g), and the mixture was stirred at rt under a hydrogen atmosphere (1 atm) for 14 h. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated. The crude product was dissolved in $Et_2O$ (20 mL), and aqueous $NaHCO_3$ (80 mL) was added. CbzCl (16.2 mL, 28.6 mmol) was added dropwise at 0 °C, and the mixture was stirred at rt for 21 h. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 10 : 1 → 2 : 1) afforded 5.08 g of **8** as a colorless oil (87%). $[\alpha]_D^{24}$ –4.7° (*c* 0.92, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.34 (s, 3H), 1.44 (s, 3H), 3.06 (br s, 1H), 3.39 (br s, 1H), 3.52 (br d, *J* = 13.6 Hz, 1H), 3.65 (br d, *J* = 13.6 Hz, 1H), 3.96 (m, 2H), 4.10 (m, 1H), 4.33 (br s, 1H), 5.14 (s, 2H), 7.34 (br s, 5H). EIMS *m*/*z* 307 ($M^+$). HREIMS calcd for $C_{16}H_{21}NO_5$ ($M^+$) 307.1419, found 307.1409.

**(3*R*,5*R*)-1-Benzyloxycarbonyl-3,5-bis(*tert*-butyldimethylsilyloxy)piperidin-4-ol (10).** A solution of **8** (2.39 g, 7.78 mmol) in 80% AcOH (100 mL) was stirred at 90 °C for 18 h, and the mixture was concentrated. The crude product was dissolved in dry DMF (25 mL), and $Et_3N$ (4.2 mL, 30.1 mmol) and TBSCl (2.84 g, 18.8 mmol) were added at 0 °C. After stirring at rt for 2 h, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The combined extracts were washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 8 : 1) afforded 3.23 g of **10** as a colorless oil (80% in two steps). $[\alpha]_D^{24}$ –0.74° (*c* 0.95, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.03, 0.04, 0.05, 0.08, 0.10, 0.11, and 0.13 (each as s, 12H), 0.84, 0.87, 0.90, and 0.92 (each as s, 18H), 2.30 (br s, 0.4H), 2.40 (br s, 0.6H), 3.07 (dd, *J* = 9.6, 12.8 Hz, 0.6H), 3.25 (dd, *J* = 8.8, 12.8 Hz, 0.4H), 3.41 (br d, *J* = 13.2 Hz, 0.6H), 3.43 (br d, *J* = 13.2 Hz, 0.4H), 3.55-3.65 (m, 2.4H), 3.82-3.86 (m, 1.6H), 3.99 (m, 1H), 4.96 (d, *J* = 12.4 Hz, 0.6H), 5.02 (d, *J* = 12.6 Hz, 0.4H), 5.21 (d, *J* = 12.6 Hz, 0.4H), 5.23 (d, *J* = 12.4 Hz, 0.6H), 7.30-7.35 (m, 5H). IR (neat) 3468, 2953, 2892, 2859, 1709, 1464, 1431, 1362, 1254, 1223, 1103, 1005, 974, 911, 889, 839, 777, 698 $cm^{-1}$. EIMS *m*/*z* 438 (M – $^t$Bu)$^+$. HREIMS calcd for $C_{21}H_{36}NO_5Si_2$ (M – $^t$Bu)$^+$ 438.2132, found 438.2134.

**(3*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)piperidin-4-ol (11).** To a solution of **10** (74 mg, 0.15 mmol) in dry MeOH (4 mL) was added 10%Pd/C (30 mg), and the mixture was stirred at rt under a hydrogen atmosphere (1 atm) for 15 h. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 1 : 1) afforded 38 mg of **11** as a colorless oil (71%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.08 (br s, 12H), 0.91 (br s, 18H), 2.17 (m, 1H), 2.36 (m, 0.5H), 2.47-2.52 (m, 0.5H), 2.17-2.97 (m, 2H), 3.48 (m, 1H), 3.84 (m, 1H), 4.01-4.03 (m, 1H). EIMS *m*/*z* 361 ($M^+$). HREIMS calcd for $C_{17}H_{39}NO_3Si_2$ ($M^+$) 361.2468, found 361.2466.

**3-Bromo-1-(*tert*-butyldimethylsilyloxy)propane (12).** To a solution of 3-bromo-1-propanol (1.40 g, 10.1 mmol) in dry DMF (5 mL) were added imidazole (3.0 g, 44.1 mmol) and TBSCl (3.30 g, 21.9 mmol) at 0 °C under an argon atmosphere. After stirring at rt for 90 min, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The combined extracts were washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 10 : 1) afforded 2.54 g of **12** as a colorless oil (quant.). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.67 (s, 6H), 0.90 (s, 9H), 2.03 (tt, *J* = 5.6, 6.4 Hz, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.73 (t, *J* = 5.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ –5.2, 18.4, 25.8, 26.0, 30.7, 35.7, 60.5.

**(3*R*,5*R*)-1-Benzyloxycarbonyl-3,5-bis(*tert*-butyldimethylsilyloxy)-4-[3'-(*tert*-butyldimethylsilyloxy)propoxy]piperidine (13).** To a solution of **10** (394.6 mg, 0.796 mmol) in dry DMF (6 mL) was

added NaH (48 mg, 2 mmol) at 0 °C. After stirring at rt for 1 h, the DMF (2 mL) solution of **12** (409 mg, 1.6 mmol) was added. After stirring at rt for 3 h, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The combined extracts were washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 20 : 1) afforded 110.7 mg of **13** as a colorless oil (20%). $[\alpha]_D^{18}$ –0.90° (*c* 0.22, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.04, 0.07, 0.08, 0.09, and 0.10 (each as s, 18H), 0.84, 0.85, 0.87, and 0.89 (each as s, 27H), 1.74-1.80 (m, 2H), 3.24 (m, 1H), 3.40-3.46 (m, 3H), 3.58-3.85 (m, 6H), 4.02 (m, 1H), 4.97 and 4.99 (each as d, *J* = 12.4 Hz, 2H), 5.22 (d, *J* = 12.4 Hz, 1H), 7.29-7.34 (m, 5H). IR (neat) 2953, 2930, 2857, 1713, 1462, 1431, 1254, 1223, 1107, 837, 777 $cm^{-1}$. EIMS *m*/*z* 667 ($M^+$). HREIMS calcd for $C_{34}H_{65}NO_6Si_3$ ($M^+$) 667.4117, found 667.4125.

**(3*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[3-(*tert*-butyldimethylsilyloxy)propoxy]piperidine (14).** To a solution of **13** (17 mg, 0.26 mmol) in dry MeOH (2.5 mL) was added 10%Pd/C (7 mg), and the mixture was stirred at rt under a hydrogen atmosphere (1 atm) for 13 h. The mixture was filtered, and the filtrate was concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 2 : 1) afforded 7 mg of **14** as a colorless oil (52%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.06 (br s, 18H), 0.89 (br s, 27H), 1.79 (m, 2H), 2.42 (m, 1.5H), 2.60 (br d, *J* = 14.4 Hz, 0.5H), 2.81 (dd, *J* = 6.8, 13.4 Hz, 0.5H), 2.92-2.99 (m, 2H), 3.13 (br s, 1H), 3.55-3.62 (m, 1H), 3.68-3.75 (m, 4.5H), 3.88 (m, 0.5H), 3.96 (m, 0.5H), 4.09 (m, 0.5H). EIMS *m*/*z* 533 ($M^+$). HREIMS calcd for $C_{26}H_{59}NO_4Si_3$ ($M^+$) 533.3752, found 533.3754.

**(3*R*,5*R*)-1-Benzyloxycarbonyl-3,5-bis(*tert*-butyldimethylsilyloxy)-4-(1-imidazolylcarbothioyloxy)-piperidine (15).** To a solution of **10** (143 mg, 0.29 mmol) in dry THF (2.5 mL) were added DMAP (7 mg, 0.29 mmol) and thiocarbonyl-1,1'-diimidazole (102 mg, 0.57 mmol) at rt. After stirring at 80 °C for 21 h, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The combined extracts were washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane : AcOEt = 3 : 1) afforded 152 mg of **15** as a colorless oil (87%). $[\alpha]_D^{18}$ –43.4° (*c* 0.36, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.10 (br s, 12H), 0.85 (br s, 18H), 2.19 (dd, *J* = 7.7, 13.1 Hz, 0.5H), 3.34 (dd, *J* = 6.5, 13.6 Hz, 0.5H), 3.41 (br d, *J* = 13.9 Hz, 0.5H), 3.56 (br d, *J* = 12.9 Hz, 0.5H), 3.63-3.75 (m, 1.5H), 3.94 (br. d, *J* = 12.2 Hz, 0.5H), 4.20-4.30 (m, 2H), 4.98 (d, *J* = 12.2 Hz, 0.5H), 5.04 (d, *J* = 12.5 Hz, 0.5H), 5.22 (d, *J* = 12.2 Hz, 0.5H), 5.27 (d, *J* = 12.5 Hz, 0.5H), 5.45-5.50 (m, 1H), 7.05 (s, 1H), 7.31-7.35 (m, 5H), 7.61 (s, 1H), 8.35 (s, 1H). IR (neat) 2953, 2932, 2894, 2859, 1711, 1462, 1431, 1389, 1325, 1287, 1217, 1113, 1005, 972, 839, 779 $cm^{-1}$. EIMS *m*/*z* 605 ($M^+$). HREIMS calcd for $C_{29}H_{47}N_3O_5SSi_2$ ($M^+$) 605.2775, found 605.2776.

**(3*S*,5*S*)-1-Benzyloxycarbonyl-3,5-bis(*tert*-butyldimethylsilyloxy)piperidine (16).** To a solution of **15** (123 mg, 0.195 mmol) in dry toluene (2 mL) were added allyltributyltin (150 μL, 0.585 mmol) and AIBN (10 mg, 60 μmol) at rt. After stirring at 80 °C for 90 min, the mixture was concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 8 : 1) afforded 89 mg of **16** as a colorless oil (95%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.73-1.78 (m, 1H), 1.64-1.70 (m, 1H), 3.15 (dd, *J* = 7.1, 12.9 Hz, 1H), 3.38-3.48 (m, 2H), 3.65 (dd, *J* = 2.0, 12.9 Hz, 1H), 4.01-4.04 (m, 2H), 5.01 (d, *J* = 12.5 Hz, 1H), 5.22 (d, *J* = 12.5 Hz, 1H), 7.29-7.35 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ –4.83, –4.78, –4.74, –4.69, 18.2, 25.83, 25.86, 42.1, 50.5, 64.7, 65.3, 67.0, 127.7, 128.2, 136.7, 155.6. IR (neat) 2953, 2930, 2892, 2859, 1709, 1464, 1431, 1254, 1227, 1156, 1096, 1030, 968, 837, 777, 696 cm$^{-1}$. EIMS *m*/*z* 422 (M – $^t$Bu)$^+$. HREIMS calcd for $C_{21}H_{36}NO_4Si_2$ (M – $^t$Bu)$^+$ 422.2183, found 422.2184.

**(3*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)piperidine (17).** To a solution of **16** (60 mg, 0.13 mmol) in dry MeOH (2.5 mL) was added $Pd(OH)_2$ (30 mg), and the mixture was stirred at rt under hydrogen atmosphere (1 atm) for 1 day. The mixture was filtered, and the filtrated was concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 5 : 1 → 0 : 1) afforded 42 mg of **17** as a colorless oil (97%). $[\alpha]_D^{22}$ –4.88° (0.31, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.63 (t, *J* = 5.4 Hz, 1H), 1.72 (t, *J* = 5.2 Hz, 1H), 2.00 (br s, 1H), 2.22 (dd, *J* = 6.2, 11.4 Hz, 1H), 2.53 (dd, *J* = 13.2 Hz, 1H), 2.73-2.81 (m, 2H), 3.93 (m, 1H), 4.03 (m, 1H). EIMS *m*/*z* 345 (M$^+$). HREIMS calcd for $C_{17}H_{39}NO_2Si_2$ (M$^+$) 345.2519, found 345.2519.

**[(1*R*,2*E*,6*R*,7*R*)-7-[(*R*)-6-Methoxymethoxy-6-methylheptan-2-yl]-6-methylbicyclo[4.3.0]nonan-2-ylidene]acetic acid (20).** To a solution of **19**[4] (462 mg, 1.17 mmol) in MeOH (12 mL) was added aqueous 1 M NaOH (5 mL) at rt. After stirring at 50 °C for 38 h, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The combined extracts were washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 4 : 1) afforded 402 mg of **20** as a colorless oil (94%). $[\alpha]_D^{22}$ +86.3° (*c* 1.00, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 1.72-1.75 (m, 2H), 1.86-1.92 (m, 1H), 2.00-2.04 (m, 1H), 2.10 (t, *J* = 9.2 Hz, 1H), 3.36 (s, 3H), 3.83-3.86 (m, 1H), 4.14-4.17 (m, 2H), 4.70 (s, 2H), 5.45 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.5, 18.9, 20.7, 22.3, 24.0, 26.4, 26.5, 27.6, 29.7, 29.8, 36.1, 36.4, 40.2, 42.4, 47.2, 55.1, 56.8, 56.9, 59.5, 76.3, 91.0, 111.9, 163.1, 166.7. IR (neat) 2944, 2870, 2774, 2124, 2060, 1958, 1717, 1647, 1466, 1381, 1368, 1308, 1271, 1254, 1146, 1096, 1042, 918, 866, 754 cm$^{-1}$. EIMS *m*/*z* 394 (M$^+$). HREIMS calcd for $C_{24}H_{42}O_4$ (M$^+$) 394.3083, found 394.3091.

**(1*R*,3*R*,7*E*)-6-Oxo-5-aza-9,10-seco-19-norcholest-7-ene-1,2,3,25-tetraol (3b).** To a solution of **20** (49 mg, 133 μmol) and **11** (48 mg, 133 μmol) in DMF (1.3 mL) were added BOP reagent (88 mg, 0.20 mmol) and DIEA (46 μL, 0.27 mmol) at 0 °C. After stirring at rt for 18 h, the reaction mixture was poured into saturated aqueous $NH_4Cl$, and the mixture was extracted with AcOEt. The combined extracts were washed with saturated aqueous $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated. Purification on silica gel column chromatography (hexane / AcOEt = 3 : 1) afforded a crude amide (78 mg, 83%). To a solution of the crude amide (8 mg, 11 μmol) in MeOH (0.5 mL) was added $TsOH \cdot H_2O$ (11 mg, 58 μmol). After stirring at rt for 3 days, the reaction mixture was neutralized with aqueous 0.1 M NaOH. After the solution was concentrated, purification on preparative thin-layer chromatography ($CHCl_3$ / MeOH = 10 : 1) afforded 3 mg of **3a** as a white solid (61%). $^1$H NMR (600 MHz, $CD_2Cl_2$) δ 0.61 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 1H), 1.07 (t, *J* = 8.1 Hz, 1H), 1.92 (m, 1H), 2.03-2.06 (m, 2H), 2.74-2.83 (m, 2H), 2.95-3.02 (m, 1H), 3.23 (br d, *J* = 13.2 Hz, 1H), 3.50 (br d, *J* = 6.0 Hz, 1H), 3.57 (br d, *J* = 6.0 Hz, 1H), 3.78 (br s, 1H), 3.85 (br d, *J* = 13.2 Hz, 0.6H), 3.94-3.97 (m, 1H), 4.04 (br s, 0.4H), 4.34 (br d, *J* = 10.8 Hz, 1H), 5.58 (s, 1H). EIMS *m*/*z* 437 ($M^+$). HREIMS calcd for $C_{25}H_{43}NO_5$ ($M^+$) 437.31442, found 437.3148.

**(1*R*,3*R*,7*E*)-2-(3-Hydroxypropoxy)-6-oxo-5-aza-9,10-seco-19-norcholest-7-ene-1,3,25-triol (3c).** A crude product, which was obtained from the condensation reaction of **20** (6 mg, 15 μmol) and **14** (8 mg, 15 μmol) using BOP reagent (10 mg, 23 μmol) and DIEA (5 μL, 30 mmol) followed by the deprotection step in the same manner as that for the synthesis of **3b**, was purified on preparative thin-layer chromatography ($CHCl_3$ / MeOH = 5 : 1) afforded 2 mg of **3c** as a white solid (27% in two steps). $^1$H NMR (600 MHz, $CD_2Cl_2$, selected) δ 0.61 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 1H), 3.63-3.67 (m, 4H, $OC\underline{H_2}CH_2C\underline{H_2}OH$), 5.56 (s, 1H). EIMS *m*/*z* 495 ($M^+$). HREIMS calcd for $C_{28}H_{49}NO_6$ ($M^+$) 495.3560, found 495.3558.

**(1*R*,3*R*,7*E*)-6-Oxo-5-aza-9,10-seco-19-norcholest-7-ene-1,3,25-triol (3a).** A crude product, which was obtained from the condensation reaction of **20** (21 mg, 61 μmol) and **17** (24 mg, 66 μmol) using BOP reagent (40 mg, 91 μmol) and DIEA (20 μL, 120 mmol) followed by the deprotection step in the same manner as that for the synthesis of **3b**, was purified on preparative thin-layer chromatography ($CHCl_3$ / MeOH = 10 : 1) afforded 17 mg of **3a** as a white solid (75% in two steps). $^1$H NMR (600 MHz, $CD_3OD$) δ 0.66 (s, 3H), 0.97 (d, *J* = 6.6 Hz, 1H), 1.05-1.10 (m, 1H), 1.16-1.18 (m, 7H), 1.23-1.29 (m, 2H), 1.31-1.48 (m, 9H), 1.54-1.59 (m, 2H), 1.62-1.67 (m, 2H), 1.73-1.80 (m, 2H), 1.85-1.89 (m, 1H), 1.92-1.98 (m, 1H), 2.04 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.04-2.10 (m, 1H), 2.72 (dt, *J* = 13.6, 2.9 Hz, 1H), 3.27 (dd, *J* = 6.9, 12.9 Hz, 1H), 3.38 (dd, *J* = 6.0, 13.2 Hz, 1H), 3.53 (dd, *J* = 3.0, 13.2 Hz, 1H), 3.84 (dd, *J* = 3.3, 12.9 Hz, 1H), 3.95-4.00 (m, 2H), 5.61 (s, 1H). EIMS *m*/*z* 421 ($M^+$). HREIMS calcd for $C_{25}H_{43}NO_4$ ($M^+$) 421.3192, found 421.3181.

**ACKNOWLEDGEMENTS**

We thank Dr. Masaaki Kurihara (National Institute of Health Sciences) for his valuable discussions. We also thank Ms. Junko Shimode and Ms. Maroka Kitsukawa (Teikyo University) for spectroscopic measurements. This study was supported by Kanagawa Academy of Science and Technology Research Grants and partially by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

**REFERENCES AND NOTES**

† Present address: Department of Hygienic Sciences, Kobe Pharmaceutical University, Higashinada-ku, Kobe, Hyogo 658-8558, Japan.

‡ Present address: The Noguchi Institute and Japan Chemical Innovation Institute (JCII), Kaga, Itabashi-ku, Tokyo 173-0003, Japan.

1. 'Vitamin D', ed. by D. Feldman, F. H. Glorieux, and J. W. Pike, Academic Press, New York, 1997.
2. R. Bouillon, W. H. Okamura, and A. W. Norman, *Endocr. Rev.*, 1995, **16**, 200.
3. (a) K. L. Perlman, R. R. Sicinski, H. K. Schnoes, and H. F. DeLuca, *Tetrahedron Lett.*, 1990, **31**, 1823; (b) K. L. Perlman, R. E. Swenson, H. E. Paaren, H. K. Schnoes, and H. F. DeLuca, *Tetrahedron Lett.*, 1991, **32**, 7663; (c) R. R. Sicinski, K. L. Perlman, and H. F. DeLuca, *J. Med. Chem.*, 1994, **37**, 3730; (d) R. R. Sicinski, J. M. Prahl, C. M. Smith, and H. F. DeLuca, *J. Med. Chem.*, 1998, **41**, 4662; (e) R. R. Sicinski, P. Rotkiewicz, A. Kolinski, W. Sicinska, J. M. Prahl, C. M. Smith, and H. F. DeLuca, *J. Med. Chem.*, 2002, **45**, 3366; (f) P.-Q. Huang, K. Sabbe, M. Pottie, and M. Vandewalle, *Tetrahedron Lett.*, 1995, **36**, 8299; (g) H. Hilpert and B. Wirz, *Tetrahedron*, 2001, **57**, 681; (h) T. Hanazawa, H. Inamori, T. Masuda, S. Okamoto, and F. Sato, *Org. Lett.*, 2001, **3**, 2205; (i) Y. Wu, Y. Zhao, H. Tian, P. De Clercq, M. Vandewalle, M. Berthier, G. Pellegrino, P. Maillos, and J.-C. Pascal, *Eur. J. Org. Chem.*, 2001, 3779; (j) T. Okano, K. Nakagawa, N. Kubodera, K. Ozono, A. Isaka, A. Osawa, M. Terada, and K. Mikami, *Chem. Biol.*, 2000, **7**, 173; (k) K. Mikami, A. Osawa, A. Isaka, M. Terada, and T. Okano, *Tetrahedron Lett.*, 1998, **39**, 3359; (l) K. Mikami, Y. Koizumi, A. Osawa, M. Terada, H. Takayama, K. Nakagawa, and T. Okano, *Synlett*, 1999, 1899; (m) M. Shimizu, Y. Iwasaki, Y. Shibamoto, M. Sato, H. F. DeLuca, and S. Yamada, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 809.
4. (a) A. Yoshida, K. Ono, Y. Suhara, N. Saito, H. Takayama, and A. Kittaka, *Synlett*, 2003, 1175. (b) K. Ono, A. Yoshida, N. Saito, T. Fujishima, S. Honzawa, Y. Suhara, S. Kishimoto, T. Sugiura, K. Waku, H. Takayama, and A. Kittaka, *J. Org. Chem.*, 2003, **68**, in press.
5. Singlet oxygen adducts to the trine system in **1**: (a) S. Yamada, K. Yamamoto, H. Naito, T. Suzuki, M. Ohmori, H. Takayama, Y. Shiina, C. Miyaura, H. Tanaka, E. Abe, T. Suda, I. Matsunaga, and Y.

Nishii, *J. Med. Chem.*, 1985, **28**, 1148; (b) Y. Shiina, C. Miyaura, H. Tanaka, E. Abe, S. Yamada, K. Yamamoto, E. Ino, H. Takayama, I. Matsunaga, Y. Nishii, and T. Suda, *J. Med. Chem.*, 1985, **28**, 1153.

6. (a) For 2-methyl series: K. Konno, S. Maki, T. Fujishima, Z. Liu, D. Miura, M. Chokki, and H. Takayama, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 151; (b) K. Konno, T. Fujishima, S. Maki, Z. Liu, D. Miura, M. Chokki, S. Ishizuka, K. Yamaguchi, Y. Kan, M. Kurihara, N. Miyata, C. Smith, H. F. DeLuca, and H. Takayama, *J. Med. Chem.*, 2000, **43**, 4247.
7. For 2□-alkyl and 2□-(□-hydroxyalkyl) series: (a) Y. Suhara, K. Nihei, H. Tanigawa, T. Fujishima, K. Konno, K. Nakagawa, T. Okano, and H. Takayama, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1129; (b) Y. Suhara, K. Nihei, M. Kurihara, A. Kittaka, K. Yamaguchi, T. Fujishima, K. Konno, N. Miyata, and H. Takayama, *J. Org. Chem.*, 2001, **66**, 8760; (c) S. Honzawa, Y. Suhara, K. Nihei, N. Saito, S. Kishimoto, T. Fujishima, M. Kurihara, T. Sugiura, K. Waku, H. Takayama, and A. Kittaka, *Bioorg. Med. Chem. Lett.*, 2003, **13**, in press.
8. A. Kittaka, Y. Suhara, H. Takayanagi, T. Fujishima, M. Kurihara, and H. Takayama, *Org. Lett.*, 2000, **2**, 2619.
9. H. Takayama, A. Kittaka, T. Fujishima, and Y. Suhara, 'Vitamin D Analogs in Cancer Prevention and Therapy, Recent Results in Cancer Research 164,' ed. by J. Reichrath, M. Friedrich, and W. Tilgen, Springer-Verlag, Berlin Heidelberg, 2003, pp. 289-317.
10. Y. Suhara, A. Kittaka, S. Kishimoto, M. J. Calverley, T. Fujishima, N. Saito, T. Sugiura, K. Waku, and H. Takayama, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3255.
11. A. Kittaka, M. Kurihara, S. Peleg, Y. Suhara, and H. Takayama, *Chem. Pharm. Bull.*, 2003, **51**, 357.
12. (a) K. Miyamoto, E. Murayama, K. Ochi, H. Watanabe, and N. Kubodera, *Chem. Pharm. Bull.*, 1993, **41**, 1111; (b) N. Tsugawa, K. Nakagawa, M. Kurobe, Y. Ono, N. Kubodera, K. Ozono, and T. Okano, *Biol. Pharm. Bull.*, 2000, **23**, 66.
13. A part of this study has been published as a communication: Y. Suhara, A. Kittaka, K. Ono, M. Kurihara, T. Fujishima, A. Yoshida, and H. Takayama, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3533.
14. Molecular modeling study on compound (**3a**) docking in the ligand binding domain of the VDR was reported in ref. 13.
15. (a) K. R. Muralidharan, A. R. de Lera, S. D. Isaeff, A. W. Norman, and W. H. Okamura, *J. Org. Chem.*, 1993, **58**, 1895. (b) A. W. Norman, R. Bouillon, M. C. Farach-Carson, J. E. Bishop, L.-X. Zhou, L. Nemere, J. Zhao, K. R. Muralidharan, and W. H. Okamura, *J. Biol. Chem.*, 1993, **268**, 20022. (c) T. Fujishima, K. Konno, K. Nakagawa, M. Kurobe, T. Okano, and H. Takayama, *Bioorg. Med. Chem.*, 2000, **8**, 123.
16. Y. Ichikawa, Y. Igarashi, M. Ichikawa, and Y. Suhara, *J. Am. Chem. Soc.*, 1998, **120**, 3007.

17. J. Kiegiel, P. M. Wovkulich, and M. R. Uskokovic, *Tetrahedron Lett*., 1991, **32**, 6057.
18. B. M. Trost, J. Dumas, and M. Villa, *J. Am. Chem. Soc*., 1992, **114**, 9836.
19. S. T. Anisfeld and P. Lansbury, Jr., *J. Org. Chem*., 1990, **55**, 5560.
20. Y. Imae, A. Manaka, N. Yoshida, Y. Ishimi, T. Shinki, E. Abe, T. Suda, K. Konno, H. Takayama, and S. Yamada, *Biochim. Biophys. Acta*, 1994, **1213**, 302.
21. The binding affinity of active 19-norvitamin $D_3$ (**2**) for the porcine VDR was reported as 30% of the natural hormone **1**, see: X. Zhou, G.-D. Zhu, D. Van Haver, M. Vandewalle, P. J. De Clercq, A. Verstuyf, and R. Bouillon, *J. Med. Chem*., 1999, **42**, 3539. For the bovine thymus VDR, it was 17%, see: ref. 4b.
22. S. J. Collins, F. W. Ruscetti, R. E. Gallagher, and R. C. Gallo, *J. Exp. Med*., 1979, **149**, 969.
23. (a) K. Umesono, K. K. Murakami, C. C. Thompson, and R. M. Evans, *Cell*, 1991, **65**, 1255; (b) R. M. Evans, *Science*, 1988, **240**, 889.
24. T. Doi, I. Hijikuro, and T. Takahashi, *J. Am. Chem. Soc*., 2001, **123**, 3716.