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Design and Efficient Synthesis of 2α-(ω-Hydroxyalkoxy)-1α,25-dihydroxyvitamin D_3 Analogues, Including 2-*epi*-ED-71 and Their 20-Epimers with HL-60 Cell Differentiation Activity

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A concise and efficient synthetic approach to 2α-(ω-hydroxyalkoxy)-1α,25-dihydroxyvitamin D_3 (**4a**−**c**), including 2-*epi*-ED-71, was developed starting from D-glucose as a chiral template for the construction of the 2α-modified A-ring precursors (**11a**−**c**). It was found that the best ligand for the bovine thymus vitamin D receptor (VDR) in this series is **4b**, which has 1.8 times greater binding affinity for the bovine thymus VDR than that of the natural hormone **1**. Interestingly, potency in the induction of HL-60 cell differentiation for **4a**−**c** was almost the same or weaker than that of **1** despite the strong binding affinity for the VDR. Next, we were interested in the "double modification" of **1** based on **4a**−**c** with C20-epimerization, affording 2α-(ω-hydroxyalkoxy)-20-*epi*-1α,25-dihydroxyvitamin D_3 (20-*epi*-**4a**−**c**). All three 2α-substituted 20-*epi* analogues of **1** (20-*epi*-**4a**−**c**) exhibited stronger binding affinities for the VDR, and their conformations in the ligand binding domain of VDR were analyzed by molecular modeling. Double-modified analogues of 20-*epi*-**4a**−**c** showed marked HL-60 cell differentiation activity, and 20-*epi*-**4a** possesses an activity 58-fold higher than that of the natural hormone **1**.

Introduction

The physiologically active metabolite of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$, **1**], is the nuclear hormone that regulates cellular growth, differentiation, and apoptosis in addition to its classical role in calcium homeostasis and bone mineralization.[1−4] Most of the biological effects of 1α,25$(OH)_2D_3$ are considered to be mediated via binding to the specific intracellular receptor, vitamin D receptor (VDR), which belongs to the nuclear receptor superfamily acting as a ligand-dependent transcription factor with coactivators.[5] Ubiquitous distribution of VDR makes this hormone a potentially useful therapeutic agent for certain cancers, skin diseases, and immune disorders, and in fact, **1** and some synthetic analogues of **1** are clinically used in the treatment of bone diseases, secondary hyperparathyroidism, and psoriasis.[3] Therefore, it is interesting to design and synthesize analogues of **1** with high VDR affinity in terms of new drug development. To investigate the structure−activity relationships of the natural hormone, we systematically developed the A-ring-modified analogues, such as 2-methyl-,[6] 2α-alkyl-, and 2α-(ω-hydroxyalkyl)-1α,25$(OH)_2D_3$ (Figure 1).[7−10]

One of the striking results was that 2α-methyl-1α,25-$(OH)_2D_3$ (**2a**) showed a VDR binding potency that was 4-fold higher than that of **1**.[6] This simple A-ring modification afforded for the first time an analogue, having the natural side chain, with a VDR binding activity significantly higher than that of the parent hormone **1**; as a

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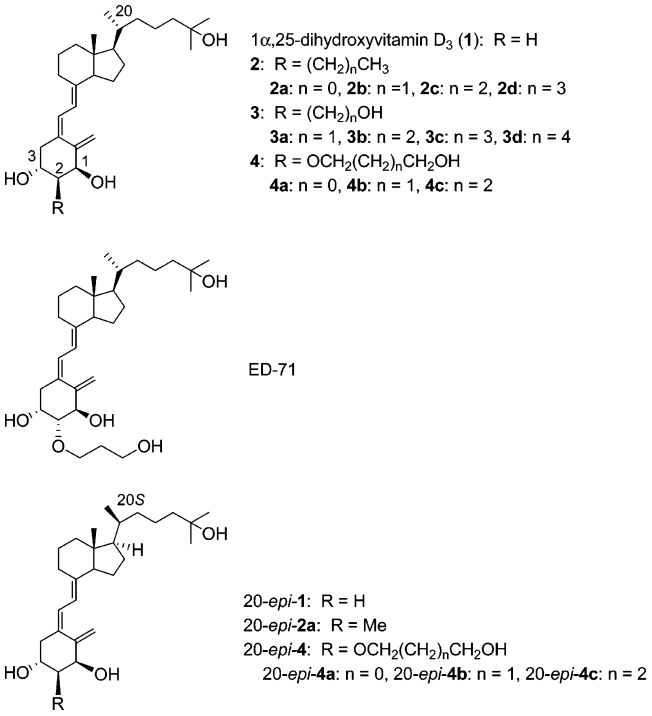

FIGURE 1. Structures of 1α,25-dihydroxyvitamin D_3 (**1**) (and its 2α-substituted analogues **2**−**4**), ED-71, and 20-*epi*-**1** (and its 2α-substituted analogues 20-*epi*-**2a** and 20-*epi*-**4a**−**c**).

result, **2a** shows a marked potency of transactivation of target genes, induction of HL-60 cell differentiation, and elevation of rat serum calcium concentration.[11] Elongation of the 2α-alkyl chain, as in **2b**−**d**, however, caused a decrease in the agonistic activity for VDR.[7a] In regard to the modification with the 2α-(ω-hydroxyalkyl) group, it was found that **3c** with the 2α-(3-hydroxypropyl) group on **1** best fits the cavity of the ligand binding domain (LBD) of VDR among the 2α-hydroxyalkyl series of **3** and the binding activity of **3c** is 3-fold higher than that of **1**.[7] On the other hand, Chugai Pharmaceutical Co. Ltd. developed 2β-(3-hydroxypropoxy)-1α,25$(OH)_2D_3$ (ED-71) as a promising candidate for the treatment of osteoporosis.[3,12] Although ED-71 shows high calcemic activity and a long half-life in plasma due to its strong affinity for vitamin D binding protein (DBP, twice the affinity of 1α,25$(OH)_2D_3$),[12,13] its binding affinity for bovine thymus VDR is weaker than that of the natural hormone (13−93%).[12] We anticipated that 2α-(ω-hydroxyalkoxy)-1α,25$(OH)_2D_3$ compounds (**4a**−**c**), including 2-*epi*-ED-71, could be better ligands for VDR and have potent vitamin D_3 activities.[14] Furthermore, we were interested in a structural cross talk in the vitamin D skeleton toward biological activity, between the A-ring and the CD-ring side chains through VDR binding, which would affect the biological activity profile of 1α,25$(OH)_2D_3$.[7d,15] Among the various synthetic 1α,25$(OH)_2D_3$ analogues, the side-chain structure of 20-*epi*-**1** is especially noteworthy because 20-*epi*-**1** possesses a more potent activity in cell differentiation and an immunosuppressive effect than the natural hormone, despite a practically unchanged calcemic activity.[16] The VDR binding potency of 20-*epi*-**1** relative to that of 1α,25$(OH)_2D_3$ is 4−5 times higher.[16b,17] Thus, 20-*epi* analogues of **4a**−**c** were also synthesized based on Trost's convergent method,[18] and VDR binding affinities and the inducing effects of HL-60 cell differentiation of these compounds were evaluated to understand the details of the structure−activity relationships of 1α,25$(OH)_2D_3$ analogues.

Results and Discussion

Synthesis. Convergent synthesis, in particular, Trost's A-ring/CD-ring connective strategy,[18] seemed to be most useful for synthesizing our target molecules. For the synthesis of A-ring precursor enynes **11a**−**c**, we chose D-glucose as a chiral template for the desired stereochemistry (1α,2α,3β; steroidal numbering) of the A-ring. Methyl α-D-glucoside was converted to the known epoxide **5**,[19] and the regiospecific ring opening[20] by an appropriate alkanediol[12a] at C3 under basic conditions gave the altrose configuration, in which the chiralities of C2, C3,

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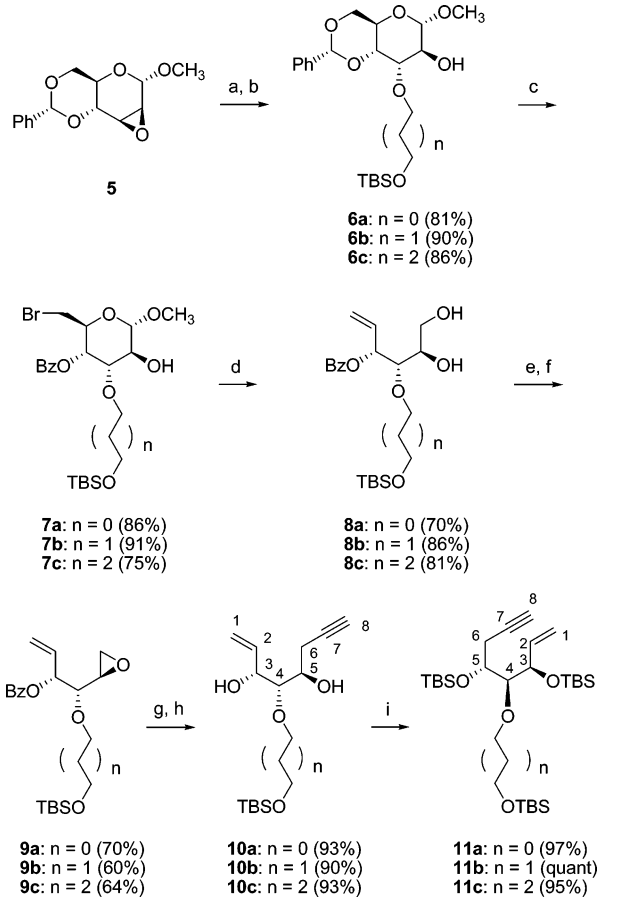
and C4 satisfy the 3β, 2α, and 1α stereochemistries of the target molecules **4**, respectively. Treatment of epoxide **5** with 1,2-ethanediol, 1,3-propanediol, or 1,4-butanediol in the presence of KO^{t}Bu with heat followed by O-silylation afforded protected methyl 3-*O*-(ω-hydroxyalkoxy)altropyranosides **6a**−**c** in 81−90% yield. NBS treatment[21] of benzylidene acetals **6a**−**c** gave bromides **7a**−**c** in 75−91% yield. Previously, we exchanged the resulting benzoyl group of **7** with the TBS group;[14] however, the ester group is resistant to the later steps being exposed under basic conditions, and it has made the process three steps shorter. Reaction of bromides **7a**−**c** with activated zinc powder and $NaBH_3CN$ provided alcohols **8a**−**c** in 70−86% yield.[22] The diols were converted to epoxides **9a**−**c** through sulfonylation of the primary alcohol followed by LiHMDS treatment in 60−70% yield. Ethynylation of **9a**−**c** using lithium TMS acetylide in the presence of $BF_3{\cdot}OEt_2$ in THF and subsequent solvolysis in K_2CO_3/MeOH supplied enynes **10a**−**c** in 90−93% yield. Persilylation with TBSOTf/2,6-lutidine afforded the desired protected enynes **11a**−**c** for the palladium coupling in excellent yield (Scheme 1).

The B-*seco* steroidal structure was constructed by Trost's palladium-catalyzed alkylative cyclization with bromoolefin of the CD-ring counterpart (**12**),[18] and subsequent deprotection furnished the target 2α-(ω-hydroxyalkoxy)-1α,25$(OH)_2D_3$ in 32−66% yield in two steps (Scheme 2). Next, each enyne was connected to the 20-*epi*-CD-ring counterpart (**14**), which was synthesized from vitamin D_2 by our reported method,[17] in the same manner to yield 20-*epi* analogues (20-*epi*-**4a**−**c**) in 45−57% yield (Scheme 3). All analogues were purified with reversed-phase HPLC (recycled) for biological evaluations.

Biological Evaluations. The VDR binding affinities and potencies of induction of HL-60 cell differentiation of the newly synthesized analogues (**4a**−**c** and 20-*epi*-**4a**−**c**) are summarized in Table 1 in comparison with those of the natural hormone **1** and 20-*epi*-**1**.[16,17] In the VDR binding assays[23] using the bovine thymus VDR, **4a** and **4b** showed a greater binding affinity for the VDR (entries 2 and 3) and **4b** reaches a peak in these three analogues with the natural side chain (20*R*).

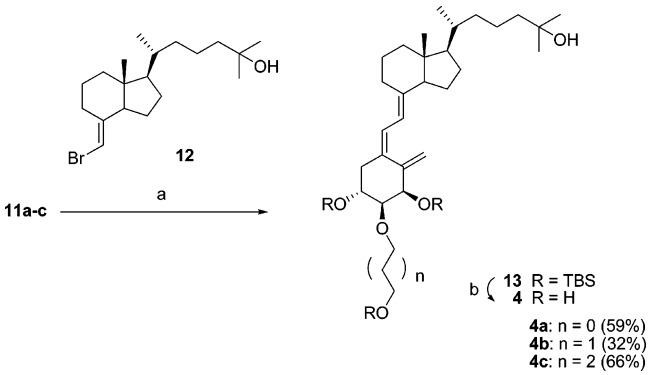
Docking Studies. We investigated a three-dimensional structure of 2α-(3-hydroxypropoxy) analogue **4b** docking in the VDR ligand binding domain (LBD) based on the crystal structure established by Moras et al.[24] All of the important hydrogen bonds, which make the ligand anchor in the LBD, between 1α-OH and both Ser-237 and Arg-274, 3β-OH and both Tyr-143 and Ser-278, and 25-OH and both His-305 and His-397 can remain as in the original X-ray structure, and an additional hydrogen

SCHEME 1. Synthesis of the A-Ring Precursors[a]



[a] Reagents: (a) $HOCH_2(CH_2)_nCH_2OH$, KO^{t}Bu, 110 °C; (b) TBS-Cl, Et_3N, DMAP, CH_2Cl_2; (c) NBS, $BaCO_3$, CCl_4, reflux; (d) Zn powder, $NaBH_3CN$, 1-propanol/H_2O (9/1), 95 °C; (e) 2,4,6-trimethylbenzenesulfonyl chloride, pyridine; (f) LiHMDS, THF, −78 to 0 °C; (g) TMSCCH, BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C to room temperature; (h) K_2CO_3, MeOH; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

SCHEME 2. Synthesis of 2α-(ω-Hydroxyalkoxy)-1α,25$(OH)_2D_3$[a]



[a] Reagents: (a) catalyst $(Ph_3P)_4Pd$, Et_3N/toluene (1/1), reflux, n = 0 (75%), 1 (52%), and 2 (69%); (b) Bu_4NF, THF, n = 0 (78%), 1 (61%), and 2 (96%).

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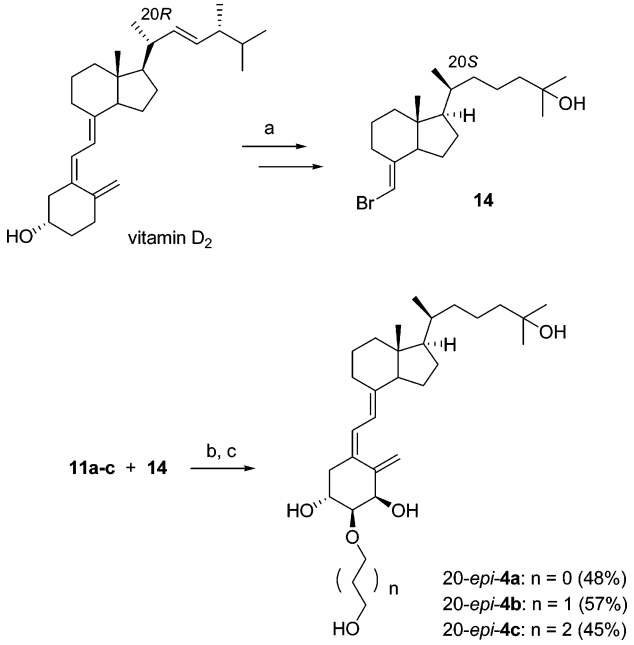
SCHEME 3. Synthesis of 2α-(ω-Hydroxyalkoxy)-20-*epi*-1α,25(OH)$_2$D$_3$[a]



[a] Reagents: (a) see ref 17; (b) catalyst $(Ph_3P)_4Pd$, Et_3N/toluene (1/1), reflux; (c) HF/MeCN, n = 0 (48%), 1 (57%), and 2 (45%) in two steps.

TABLE 1. Relative Binding Affinity for Bovine Thymus VDR and HL-60 Cell Differentiation Activity[a]

compound	VDR	HL-60
1	100	100
4a	120	100
4b	180	70
4c	40	40
20-*epi*-**1**	400	1810
20-*epi*-**4a**	260	5820
20-*epi*-**4b**	165	2120
20-*epi*-**4c**	100	2770

[a] The potency of **1** is normalized to 100. The data are the mean of three separate experiments[26] (see the Supporting Information).

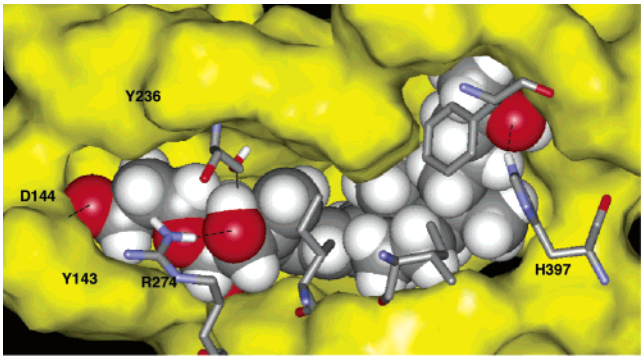


FIGURE 2. Molecular modeling of **4b** in the LBD of VDR.[24,25]

bonding network from the C2α terminal hydroxyl group to Asp-144 and Tyr-236 would be properly formed (Figure 2).

However, the inducing effect of HL-60 cell differentiation[26] was not correlated to the binding affinity, and it was between 70 and 100% of that of **1** despite the stronger affinity for the VDR (Table 1). It could be explained by a possibly weaker stability of the ligand (**4a**−**c**)−VDR with coactivator(s) complex, which switches on the process in transactivation of the target genes.[27]

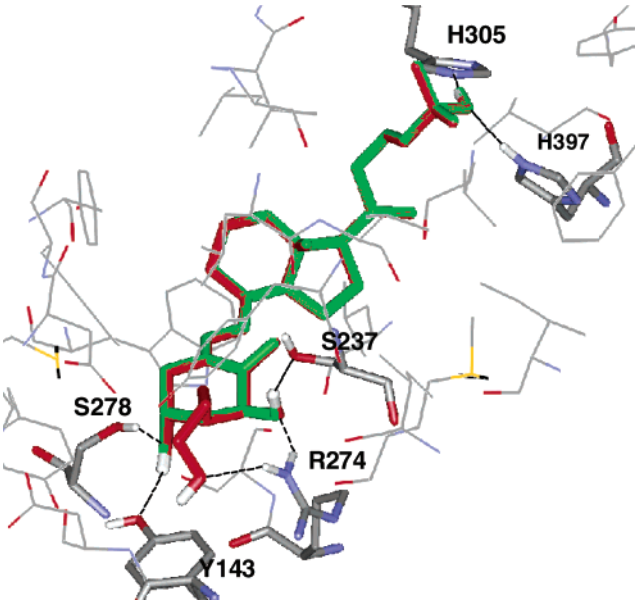


FIGURE 3. Modeled structure of 20-*epi*-**4a** (red) with Moras' X-ray structure of the VDR−20-*epi*-**1** (green) complex.[28]

As noted in the Introduction, 20-*epi*-**1**, itself, exhibits a VDR affinity 4−5 times stronger than that of **1**; however, introduction of the 2α-(3-hydroxypropoxy) group, which strengthens the affinity for VDR in the case of having the 20*R* natural side chain, causes an affinity weaker than that of 20-*epi*-**1**, while these are still better ligands if compared to **1**. The docking study utilizing Moras' crystal structure of the 20-*epi*-**1**−VDR complex[28] explains the different positions of the two hydroxyls (1α,3*β*) on the A-ring of 20-*epi*-**4a** in the LBD of the VDR from the originals that would be located at the ideal positions for the binding of 20-*epi*-**1** (Figure 3).[25] Similar results were obtained when we synthesized 2α-(ω-hydroxyalkyl)-20-*epi*-1α,25-dihydroxyvitamin D_3 derivatives and tested the VDR binding affinity.[7d] When the 2α substituent was introduced, which also strengthens VDR binding affinity in the case of having the natural side chain (20*R*), into the 20-*epi* analogues of **1**, the binding affinity to VDR decreased, compared with that of 20-*epi*-**1**.[7d]

HL-60 cell differentiation activity[26] was markedly high with the 20-*epi* series compared to that of the natural side-chain analogues **4a**−**c** (Table 1).

Conclusions

We have developed an efficient synthetic route to the novel biologically active 2α-(ω-hydroxyalkoxy)-1α,25-(OH)$_2$D$_3$ complexes (**4a**−**c**) and their 20-*epi* counterparts through the new A-ring precursors derived from D-glucose. It was found that the VDR binding affinities of **4a**, **4b**, 20-*epi*-**4a**, and 20-*epi*-**4b** are stronger than that

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of the natural hormone. We investigated the potency of inducing HL-60 cell differentiation and found the two 2α-(ω-hydroxyalkoxy)-1α,25(OH)$_2$D$_3$ compounds (**4b**,**c**) exhibit a rather lower effect, and all their 20-*epi* counterparts (20-*epi*-**4a**−**c**) showed higher potency. So far, in many cases, 20-*epi* analogues of **1** are more potent in cell growth and differentiation than the corresponding compounds with the natural C20 stereochemistry, and 2α-substituted 20-*epi*-**4a**−**c** analogues are no exception. We propose that double modification on the 2α position and the side chain would provide for the design and development of new B-*seco* steroidal drugs for the treatment of rickets, osteoporosis, psoriasis, certain cancers, and so forth.[2−4] These results would contribute to the understanding of the detail of structure−activity relationships on the A-ring with variations of the CD-ring side chain. Further biological testing is underway in our laboratories.

Experimental Section

Methyl 4,6-*O*-Benzylidene-3-*O*-[2-{(*tert*-butyldimethylsilyl)oxy}ethyl]-α-D-altropyranoside (6a). To a suspension of **5** (1.5 g, 5.7 mmol) in ethylene glycol (25 mL) was added KO^{t}Bu (2.1 g, 19 mmol), and the mixture was stirred at 110 °C for 24 h. The mixture was diluted with CH_2Cl_2, and the organic layer was washed with saturated NH_4Cl aqueous solution, saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. To a solution of the crude product (1.9 g) in CH_2Cl_2 (14 mL) were added TBSCl (1.1 g, 7.5 mmol), Et_3N (2.4 mL, 17 mmol), and DMAP (210 mg, 1.7 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. To the mixture was added water, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1−3/1) to give **6a** (2.0 g, 81% in two steps) as a colorless oil: $[\alpha]^{25}_D$ +58.4° (*c* 0.92, $CHCl_3$); IR (neat) 3480, 1649, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.90 (d, *J* = 6.1 Hz, 1H), 3.39 (s, 3H), 3.65−3.90 (m, 5H), 3.92 (dd, *J* = 2.9, 2.9 Hz, 1H), 3.96 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.05 (ddd, *J* = 5.9, 2.9, 0.7 Hz, 1H), 4.25−4.35 (m, 2H), 4.59 (s, 1H), 5.55 (s, 1H), 7.32−7.40 (m, 3H), 7.45−7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.1, 18.5, 26.0, 55.6, 58.5, 63.1, 69.4, 70.3, 73.2, 77.0, 77.1, 101.9, 102.2, 126.1, 128.1, 128.8, 137.5; EI−LRMS *m*/*z* 440 (M$^+$), 351, 305, 259, 121. EI−HRMS calcd for $C_{22}H_{36}O_7Si$ 440.2231. Found 440.2227.

Methyl 4,6-*O*-Benzylidene-3-*O*-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]-α-D-altropyranoside (6b). In a manner similar to that for the synthesis of **6a** from **5**, a crude product, which was obtained from **5** (1.4 g, 5.1 mmol), KO^{t}Bu (1.9 g, 17 mmol), and 1,3-propanediol (25 mL), was dissolved in CH_2Cl_2 (20 mL). To the solution were added Et_3N (2.1 mL, 15 mmol), TBSCl (1.2 g, 7.6 mmol), and DMAP (63 mg, 0.51 mmol), and the mixture was stirred at room temperature for 3 h. After the usual workup, the crude product was purified by column chromatography on silica gel (hexane/AcOEt = 5/1−2/1) to give **6b** (2.1 g, 90% in two steps) as a colorless oil: $[\alpha]^{20}_D$ +68.8° (*c* 3.9, $CHCl_3$); IR (neat) 3463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.78−1.82 (m, 2H), 1.93 (br s, 1H), 3.39 (s, 3H), 3.65−3.80 (m, 6H), 3.95 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.99−4.00 (m, 1H), 4.26−4.33 (m, 2H), 4.89 (s, 1H), 5.55 (s, 1H), 7.34−7.37 (m, 3H), 7.47−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.3, 25.9, 33.3, 55.5, 58.6, 60.2, 68.5, 69.4, 70.0, 76.4, 76.9, 102.0, 102.3, 126.0, 126.2, 128.2, 129.0, 137.7; EI−LRMS *m*/*z* 454 (M$^+$). EI−HRMS calcd for $C_{23}H_{38}O_7Si$ 454.2387. Found 454.2387.

Methyl 4,6-*O*-Benzylidene-3-*O*-[4-{(*tert*-butyldimethylsilyl)oxy}butyl]-α-D-altropyranoside (6c). In a manner similar to that for the synthesis of **6a** from **5**, a crude product, which was obtained from **5** (2.5 g, 9.5 mmol), KO^{t}Bu (3.5 g, 31 mmol), and 1,4-butanediol (45 mL), was dissolved in CH_2Cl_2 (19 mL). To the solution were added Et_3N (6.6 mL, 47 mmol), TBSCl (2.9 g, 19 mmol), and DMAP (116 mg, 0.95 mmol), and the mixture was stirred at room temperature for 19 h. After the usual workup, the crude product was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give **6c** (3.9 g, 86% in two steps) as a colorless oil: $[\alpha]^{20}_D$ +60.7° (*c* 7.7, $CHCl_3$); IR (neat) 3472 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.57−1.65 (m, 4H), 1.82 (d, *J* = 5.8 Hz, 1H), 3.40 (s, 3H), 3.58−3.64 (m, 3H), 3.70−3.78 (m, 2H), 3.80 (t, *J* = 3.1 Hz, 1H), 3.96 (dd, *J* = 9.5, 3.1 Hz, 1H), 4.01 (dd, *J* = 6.1, 3.1 Hz, 1H), 4.28−4.33 (m, 2H), 4.59 (s, 1H), 5.55 (s, 1H), 7.34−7.37 (m, 3H), 7.46−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, 18.5, 26.1, 26.6, 29.6, 55.7, 58.7, 63.1, 69.4, 70.2, 71.7, 76.2, 77.2, 102.0, 102.3, 126.1, 128.1, 128.9, 137.6; EI−LRMS *m*/*z* 468 (M$^+$). EI−HRMS calcd for $C_{24}H_{40}O_7Si$ 468.2543. Found 468.2540.

Methyl 4-*O*-Benzoyl-6-bromo-3-*O*-[2-{(*tert*-butyldimethylsilyl)oxy}ethyl]-6-deoxy-α-D-altropyranoside (7a). To a solution of **6a** (1.9 g, 4.3 mmol) in CCl_4 (44 mL) were added $BaCO_3$ (518 mg, 2.6 mmol) and NBS (817 g, 4.6 mmol) at room temperature, and the mixture was refluxed for 1 h. After the mixture was filtered, to the filtrate were added 10% $Na_2S_2O_3$ aqueous solution and saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 5/1) to give **7a** (2.0 g, 86%) as a colorless oil: $[\alpha]^{25}_D$ +25.4° (*c* 1.0, $CHCl_3$); IR (neat) 3459, 1724, 1361, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 3.03 (br s, 1H), 3.50 (s, 3H), 3.55−3.65 (m, 3H), 3.68−3.83 (m, 4H), 3.99 (dd, *J* = 8.2, 3.7 Hz, 1H), 4.32 (m, 1H), 4.71 (d, *J* = 8.0 Hz, 1H), 5.47 (dd, *J* = 6.4, 4.3 Hz, 1H), 7.45 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.58 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, 18.5, 26.0, 32.9, 56.0, 62.9, 69.6, 70.5, 70.6, 72.6, 77.9, 103.0, 128.3, 129.4, 129.7, 133.2, 165.6; EI−LRMS *m*/*z* 461 (M − ^{t}Bu)$^+$, 429, 308, 179, 105. EI−HRMS calcd for $C_{18}H_{26}O_7{}^{79}BrSi$ (M − ^{t}Bu) 461.0631. Found 461.0627.

Methyl 4-*O*-Benzoyl-6-bromo-3-*O*-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]-6-deoxy-α-D-altropyranoside (7b). In a manner similar to that for the synthesis of **7a** from **6a**, a crude product, which was obtained from **6b** (3.6 g, 7.9 mmol), NBS (1.5 g, 8.3 mmol), and $BaCO_3$ (940 mg, 4.8 mmol) in CCl_4 (79 mL), was purified by column chromatography on silica gel (hexane/AcOEt = 5/1) to give **7b** (3.8 g, 91%) as a colorless oil: $[\alpha]^{20}_D$ +46.0° (*c* 4.2, $CHCl_3$); IR (neat) 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.04 (s, 3H), −0.03 (s, 3H), 0.83 (s, 9H), 1.67−1.73 (m, 2H), 2.52 (br s, 1H), 3.50 (s, 3H), 3.55−3.70 (m, 6H), 3.73 (dd, *J* = 7.3, 4.0 Hz, 1H), 3.97 (dd, *J* = 7.3, 3.3 Hz, 1H), 4.35 (dt, *J* = 3.7, 7.0 Hz, 1H), 4.70 (d, *J* = 3.3 Hz, 1H), 5.45 (dd, *J* = 7.0, 4.0 Hz, 1H), 7.43−7.47 (m, 2H), 7.58 (m, 1H), 8.03−8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.2, 25.9, 32.7, 32.9, 55.9, 60.0, 67.9, 69.3, 69.8, 69.9, 76.9, 102.7, 128.5, 129.5, 129.8, 133.3, 165.7; EI−LRMS *m*/*z* 475 (M − ^{t}Bu)$^+$. EI−HRMS calcd for $C_{19}H_{28}{}^{79}BrO_7Si$ (M − ^{t}Bu)$^+$ 475.0787. Found 475.0786.

Methyl 4-*O*-Benzoyl-6-bromo-3-*O*-[4-{(*tert*-butyldimethylsilyl)oxy}butyl]-6-deoxy-α-D-altropyranoside (7c). In a manner similar to that for the synthesis of **7a** from **6a**, a crude product, which was obtained from **6c** (1.0 g, 2.1 mmol), NBS (460 mg, 2.6 mmol), and $BaCO_3$ (240 mg, 1.2 mmol) in CCl_4 (25 mL), was purified by silica gel column chromatography on silica gel (hexane/AcOEt = 5/1) and gave **7c** (874 mg, 75%) as a colorless oil: $[\alpha]^{20}_D$ +36.0° (*c* 7.7, $CHCl_3$); IR (neat) 3465, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.46−1.62 (m, 4H), 2.37 (d, *J* = 3.7 Hz, 1H), 3.51 (s, 3H), 3.53−3.65 (m, 6H), 3.75 (dd, *J* = 4.0, 7.3 Hz, 1H), 3.99 (dt, *J* = 3.7, 7.3 Hz, 1H), 4.38 (dt, *J* = 3.7, 6.7 Hz, 1H), 4.71 (d, *J* = 3.7 Hz, 1H), 5.47 (dd, *J* = 6.7, 4.0 Hz, 1H), 7.45−7.48 (m, 2H),

7.60 (m, 1H), 8.04−8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 18.3, 26.1, 26.4, 29.4, 32.9, 56.1, 62.8, 69.0, 69.9, 70.7, 76.9, 102.6, 128.4, 129.3, 129.7, 133.3, 165.5; EI−LRMS *m*/*z* 546 (M^+). EI−HRMS calcd for $C_{24}H_{39}{}^{79}BrO_7Si$ 546.1648. Found 546.1640.

(2*R*,3*S*,4*R*)-4-Benzoyloxy-3-[2-(*tert*-butyldimethylsilyloxy)ethoxy]hex-5-ene-1,2-diol (8a). To a solution of **7a** (2.8 g, 5.3 mmol) in 1-propanol/H_2O (9/1, 53 mL) were added activated Zn dust (24 g, 373 mmol) and $NaBH_3CN$ (3.7 g, 59 mmol) at 95 °C, and the mixture was stirred at the same temperature for 1 h. After the mixture was filtered, to the filtrate was added saturated NH_4Cl aqueous solution, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 4/1−2/1) to give **8a** (1.5 g, 70%) as a colorless oil: $[\alpha]^{25}_D$ +1.47° (*c* 2.3, $CHCl_3$); IR (neat) 3438, 1719, 1649, 1271, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 2.51 (m, 1H), 2.61 (br s, 1H), 3.62 (ddd, *J* = 10.6, 8.4, 3.0 Hz, 1H), 3.68−3.88 (m, 6H), 4.03 (ddd, *J* = 10.6, 3.7, 3.2 Hz, 1H), 5.35 (d, *J* = 10.6 Hz, 1H), 5.44 (d, *J* = 17.2 Hz, 1H), 5.68 (dd, *J* = 6.7, 3.9 Hz, 1H), 6.07 (ddd, *J* = 17.2, 10.6, 6.7 Hz, 1H), 7.45 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.58 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, 18.5, 26.0, 62.9, 63.4, 71.2, 74.4, 75.2, 82.5, 119.2, 128.3, 129.5, 132.4, 133.0, 165.2; EI−LRMS *m*/*z* 353 (M − ^{t}Bu)$^+$, 278, 219, 105. EI−HRMS calcd for $C_{17}H_{25}O_6Si$ (M − ^{t}Bu)$^+$ 353.1420. Found 353.1430.

(2*R*,3*S*,4*R*)-4-Benzoyloxy-3-[3-(*tert*-butyldimethylsilyloxy)propoxy]hex-5-ene-1,2-diol (8b). In a manner similar to that for the synthesis of **8a** from **7a**, a crude product, which was obtained from **7b** (3.6 g, 6.8 mmol), activated zinc dust (13 g, 203 mmol), and $NaBH_3CN$ (2.1 g, 34 mmol) in 1-propanol/H_2O (9/1, 68 mL), was purified by flash column chromatography on silica gel (hexane/AcOEt = 3/1) to give **8b** (2.5 g, 86%) as a colorless oil: $[\alpha]^{23}_D$ +26.1° (*c* 3.4, $CHCl_3$); IR (neat) 3406, 1722, 1643, 1271, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.70−1.88 (m, 2H), 2.26 (br s, 1H), 3.05 (br s, 1H), 3.59−3.81 (m, 7H), 3.96 (dt, *J* = 9.1, 5.7 Hz, 1H), 5.34 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H), 5.43 (ddd, *J* = 17.3, 1.2, 1.2 Hz, 1H), 5.68 (dddd, *J* = 6.3, 3.9, 1.2, 1.2 Hz, 1H), 6.05 (ddd, *J* = 17.3, 10.6, 6.3 Hz, 1H), 7.45 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.58 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.1, 18.4, 26.0, 33.0, 60.0, 63.7, 69.5, 71.1, 74.9, 81.0, 118.8, 128.3, 129.5, 129.8, 132.4, 133.1, 165.3; EI−LRMS *m*/*z* 367 (M − ^{t}Bu)$^+$, 293, 263, 233, 185, 105. EI−HRMS calcd for $C_{18}H_{27}O_6Si$ (M − ^{t}Bu)$^+$ 367.1577. Found 367.1583.

(2*R*,3*S*,4*R*)-4-Benzoyloxy-3-[4-(*tert*-butyldimethylsilyloxy)butoxy]hex-5-ene-1,2-diol (8c). In a manner similar to that for the synthesis of **8a** from **7a**, a crude product, which was obtained from **7c** (2.7 g, 4.8 mmol), activated zinc dust (9.5 g, 145 mmol), and $NaBH_3CN$ (1.5 g, 24 mmol) in 1-propanol/H_2O (9/1, 48 mL), was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give **8c** (1.7 g, 81%) as a colorless oil: $[\alpha]^{18}_D$ +21.4° (*c* 1.4, $CHCl_3$); IR (neat) 3424, 1722, 1645, 1603, 1271, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.50−1.73 (m, 4H), 2.17 (m, 1H), 2.78 (d, *J* = 4.9 Hz, 1H), 3.50−3.65 (m, 4H), 3.68−3.82 (m, 3H), 3.86 (ddd, *J* = 9.0, 6.5, 6.5 Hz, 1H), 5.34 (d, *J* = 10.6 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.71 (dd, *J* = 6.2, 4.4 Hz, 1H), 6.03 (ddd, *J* = 17.2, 10.6, 6.4 Hz, 1H), 7.45 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.58 (dd, *J* = 7.5, 7.5 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 18.5, 26.1, 26.7, 29.5, 62.8, 63.9, 70.9, 72.5, 74.8, 80.5, 118.8, 128.3, 129.6, 129.7, 132.4, 133.1, 165.3; EI−LRMS *m*/*z* 381 (M − ^{t}Bu)$^+$, 259, 187, 179, 105. EI−HRMS calcd for $C_{19}H_{29}O_6Si$ (M − ^{t}Bu)$^+$ 381.1733. Found 379.1726.

(3*R*,4*R*,5*R*)-3-Benzoyloxy-4-[2-(*tert*-butyldimethylsilyloxy)ethoxy]-5,6-epoxyhex-1-ene (9a). To a solution of **8a** (380 mg, 0.93 mmol) in pyridine (0.93 mL) was added mesitylenesulfonyl chloride (TmCl) (224 mg, 1.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. To the mixture was added water, and the aqueous layer was extracted with Et_2O, washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The crude product was dissolved in THF (9.3 mL). To the solution was added LiHMDS (1.0 M solution in THF, 1.1 mL, 1.1 mmol) at −78 °C, and the mixture was allowed to warm to 0 °C over 1 h. After the mixture was stirred at 0 °C for 30 min, to the mixture was added saturated NH_4Cl aqueous solution. The aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 20/1) to give **9a** (255 mg, 70% in two steps) as a colorless oil: $[\alpha]^{18}_D$ +33.0° (*c* 1.1, $CHCl_3$); IR (neat) 1725, 1647, 1603, 1269, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 2.65 (dd, *J* = 4.9, 2.8 Hz, 1H), 2.77 (dd, *J* = 4.6, 4.6 Hz, 1H), 3.12 (ddd, *J* = 6.6, 3.8, 2.8 Hz, 1H), 3.29 (dd, *J* = 6.6, 5.3 Hz, 1H), 3.65−3.85 (m, 4H), 5.31 (d, *J* = 10.5 Hz, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.68 (dd, *J* = 6.1, 5.6 Hz, 1H), 6.05 (ddd, *J* = 17.3, 10.5, 6.1 Hz, 1H), 7.45 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.58 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, 18.4, 26.0, 43.6, 52.1, 62.7, 72.3, 74.8, 82.6, 118.1, 128.3, 129.5, 129.7, 132.8, 133.0, 165.0; EI−LRMS *m*/*z* 392 (M^+), 376, 335, 305, 179, 105. EI−HRMS calcd for $C_{21}H_{32}O_5Si$ 392.2019. Found 392.2016.

(3*R*,4*R*,5*R*)-3-Benzoyloxy-4-[3-(*tert*-butyldimethylsilyloxy)propoxy]-5,6-epoxyhex-1-ene (9b). In a manner similar to that for the synthesis of **9a** from **8a**, a crude product, which was obtained from **8b** (2.5 g, 5.8 mmol) and TmCl (1.5 g, 6.7 mmol) in pyridine (5.8 mL), was dissolved in THF (48 mL). To the solution was added LiHMDS (1.0 M solution in THF, 7.2 mL, 7.2 mmol) at −78 °C, and the mixture was allowed to warm to 0 °C over 1 h. After the usual workup, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 30/1) to give **9b** (1.4 g, 60% in two steps) as a colorless oil: $[\alpha]^{19}_D$ +29.4° (*c* 4.8, $CHCl_3$); IR (neat) 1724, 1651, 1601, 1269, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.80 (tt, *J* = 6.4, 6.4 Hz, 2H), 2.62 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.76 (dd, *J* = 4.6, 4.3 Hz, 1H), 3.10 (ddd, *J* = 6.8, 3.9, 2.7 Hz, 1H), 3.18 (dd, *J* = 6.8, 5.1 Hz, 1H), 3.60−3.75 (m, 3H), 3.83 (dt, *J* = 9.5, 6.1 Hz, 1H), 5.31 (d, *J* = 10.7 Hz, 1H), 5.41 (d, *J* = 17.3 Hz, 1H), 5.66 (dd, *J* = 6.1, 5.1 Hz, 1H), 6.04 (ddd, *J* = 17.3, 10.7, 5.1 Hz, 1H), 7.45 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.58 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, 18.3, 26.0, 33.2, 43.6, 52.2, 59.8, 67.5, 74.7, 82.4, 118.2, 128.2, 129.4, 129.8, 132.8, 132.9, 165.0; EI−LRMS *m*/*z* 406 (M^+), 390, 349, 316, 179, 105. EI−HRMS calcd for $C_{22}H_{34}O_5Si$ 406.2175. Found 406.2177.

(3*R*,4*R*,5*R*)-3-Benzoyloxy-4-[4-(*tert*-butyldimethylsilyloxy)butoxy]-5,6-epoxyhex-1-ene (9c). In a manner similar to that for the synthesis of **9a** from **8a**, a crude product, which was obtained from **8c** (536 mg, 1.2 mmol) and TmCl (320 mg, 1.5 mmol) in pyridine (1.2 mL), was dissolved in THF (11 mL). To the solution was added LiHMDS (1.0 M solution in THF, 1.2 mL, 1.2 mmol) at −78 °C, and the mixture was warmed to 0 °C over 1.5 h. After the usual workup, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 25/1) to give **9c** (328 mg, 64% in two steps) as a colorless oil: $[\alpha]^{18}_D$ +31.4° (*c* 2.1, $CHCl_3$); IR (neat) 1725, 1647, 1603, 1269, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.55−1.70 (m, 4H), 2.68 (dd, *J* = 4.8, 2.7 Hz, 1H), 2.77 (dd, *J* = 4.8, 3.9 Hz, 1H), 3.10 (ddd, *J* = 6.9, 3.9, 2.7 Hz, 1H), 3.17 (dd, *J* = 6.9, 5.1 Hz, 1H), 3.55−3.65 (m, 3H), 3.76 (dt, *J* = 9.3, 5.9 Hz, 1H), 5.31 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H), 5.41 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1H), 5.66 (dddd, *J* = 6.3, 5.1, 1.2, 1.2 Hz, 1H), 6.04 (ddd, *J* = 17.2, 10.6, 6.3 Hz, 1H), 7.45 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.58 (dd, *J* = 7.7, 7.7 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 18.5, 26.1, 26.5, 29.5, 43.7, 52.4, 62.9, 71.0, 74.8, 82.4,

118.3, 128.3, 129.5, 129.8, 132.8, 133.0, 165.1; EI−LRMS *m/z* 420 (M^+), 405, 363, 241, 217, 179, 105. EI−HRMS calcd for $C_{23}H_{36}O_5Si$ 420.2232. Found 420.2235.

(3*R*,4*S*,5*R*)-4-[2-(*tert*-Butyldimethylsilyloxy)ethoxy]oct-1-en-7-yne-3,5-diol (10a). To a solution of trimethylsilylacetylene (0.35 mL, 2.5 mmol) in THF (2 mL) was added ^{n}BuLi (1.5 M solution in hexane, 1.5 mL, 2.3 mmol) at −78 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture were added a solution of **9a** (384 mg, 0.98 mmol) in THF (6 mL) and BF_3·OEt_2 (0.14 mL, 1.1 mmol) at −78 °C, and the resulting mixture was warmed to 0 °C over 2 h. To the mixture was added saturated NH_4Cl aqueous solution, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was dissolved in MeOH (3 mL). To the solution was added K_2CO_3 (406 mg, 2.9 mmol), and the mixture was stirred at room temperature for 2 h. To the mixture was added H_2O, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 4/1) to give **10a** (285 mg, 93% in two steps) as a colorless oil: $[\alpha]^{18}_D$ −7.91° (*c* 1.1, $CHCl_3$); IR (neat) 3438, 3314, 2122, 1645, 1255, 1103 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 2.02 (t, *J* = 2.7 Hz, 1H), 2.46 (ddd, *J* = 16.6, 5.9, 2.7 Hz, 1H), 2.55 (ddd, *J* = 16.6, 7.1, 2.7 Hz, 1H), 3.18 (br d, *J* = 3.9 Hz, 1H), 3.24 (d, *J* = 5.4 Hz, 1H), 3.53 (dd, *J* = 3.7, 3.7 Hz, 1H), 3.70−3.85 (m, 4H), 3.93 (m, 1H), 4.43 (m, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.40 (d, *J* = 17.0 Hz, 1H), 5.96 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.1, 18.5, 23.5, 26.0, 63.0, 69.9, 70.4, 72.7, 73.2, 80.6, 82.2, 116.6, 136.1; EI−LRMS *m/z* 257 (M − ^{t}Bu)$^+$, 239, 183, 171, 119. EI−HRMS calcd for $C_{12}H_{21}O_4Si$ (M − ^{t}Bu)$^+$ 257.1210. Found 257.1197.

(3*R*,4*S*,5*R*)-4-[3-(*tert*-Butyldimethylsilyloxy)propoxy]-oct-1-en-7-yne-3,5-diol (10b). In a manner similar to that for the synthesis of **10a** from **9a**, a crude product, which was obtained from **9b** (1.2 g, 2.9 mmol), lithium trimethylsilylacetylide [prepared from trimethylacetylene (1.1 mL, 7.4 mmol) and ^{n}BuLi (1.52 M solution in hexane, 4.4 mL, 6.7 mmol)], and BF_3·OEt_2 (0.41 mL, 3.24 mmol) in THF (24 mL), was treated with K_2CO_3 (1.2 g, 8.8 mmol) in MeOH (2.9 mL). After the usual workup, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 3/1) to give **10b** (861 mg, 90% in two steps) as a colorless oil: $[\alpha]^{21}_D$ −10.5° (*c* 1.1, $CHCl_3$); IR (neat) 3393, 2121, 1647, 1255, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 9H), 1.81 (tt, *J* = 5.7, 5.7 Hz, 2H), 2.01 (t, *J* = 2.6 Hz, 1H), 2.40−2.60 (m, 2H), 2.86 (d, *J* = 5.5 Hz, 1H), 2.96 (d, *J* = 5.5 Hz, 1H), 3.41 (dd, *J* = 4.4, 2.4 Hz, 1H), 3.60−3.90 (m, 4H), 4.00 (m, 1H), 4.48 (m, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.42 (d, *J* = 17.1 Hz, 1H), 5.95 (ddd, *J* = 17.1, 10.5, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, 18.3, 23.6, 26.0, 33.0, 59.7, 68.0, 69.8, 70.3, 72.2, 80.6, 80.7, 116.1, 136.8; EI−LRMS *m/z* 271 (M − ^{t}Bu)$^+$, 241, 185, 171, 133, 75. EI−HRMS calcd for $C_{13}H_{23}O_4Si$ (M − ^{t}Bu)$^+$ 271.1365. Found 271.1356.

(3*R*,4*S*,5*R*)-4-[4-(*tert*-Butyldimethylsilyloxy)butoxy]oct-1-en-7-yne-3,5-diol (10c). In a manner similar to that for the synthesis of **10a** from **9a**, a crude product, which was obtained from **9c** (855 mg, 2.0 mmol), lithium trimethylsilylacetylide [prepared from trimethylacetylene (0.72 mL, 5.1 mmol) and ^{n}BuLi (1.52 M solution in hexane, 3.1 mL, 4.7 mmol)], and BF_3·OEt_2 (0.28 mL, 32 mmol) in THF (24 mL), was treated with K_2CO_3 (842 mg, 6.1 mmol) in MeOH (4 mL). After the usual workup, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 4/1) to give **10c** (647 mg, 93% in two steps) as a colorless oil: $[\alpha]^{18}_D$ −6.30° (*c* 0.98, $CHCl_3$); IR (neat) 3314, 2122, 1645, 1255, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.55−1.73 (m, 4H), 2.01 (t, *J* = 2.6 Hz, 1H), 2.50 (dd, *J* = 7.1, 2.6 Hz, 2H), 2.76 (br d, *J* = 4.2 Hz, 1H), 2.93 (br d, *J* = 5.8 Hz, 1H), 3.38 (dd, *J* = 4.8, 2.1 Hz, 1H), 3.55 (dt, *J* = 9.1, 6.4 Hz, 1H), 3.63 (t, *J* = 6.1 Hz, 2H), 3.75 (dt, *J* = 9.1, 6.3 Hz, 1H), 5.62 (m, 1H), 4.48 (m, 1H), 5.27 (ddd, *J* = 10.6, 1.6, 1.6 Hz, 1H), 5.43 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.93 (ddd, *J* = 17.2, 10.6, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.12, 18.4, 23.8, 26.0, 26.6, 29.4, 62.8, 69.8, 70.3, 71.4, 72.4, 80.5, 80.7, 116.2, 136.9; EI−LRMS *m/z* 285 (M − ^{t}Bu)$^+$, 211, 187, 147, 89. EI−HRMS calcd for $C_{14}H_{25}O_4Si$ (M − ^{t}Bu)$^+$ 285.1522. Found 285.1525.

(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[2-(*tert*-butyldimethylsilyloxy)ethoxy]oct-1-en-7-yne (11a). To a solution of **10a** (273 mg, 0.87 mmol) in CH_2Cl_2 (2.9 mL) were added 2,6-lutidine (0.31 mL, 2.7 mmol) and TBSOTf (0.5 mL, 2.2 mmol) at 0 °C, and the mixture was stirred at the same temperature for 3 h. To the mixture was added H_2O, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 30/1) to give **11a** (456 mg, 97%) as a colorless oil: $[\alpha]^{14}_D$ +0.24° (*c* 1.2, $CHCl_3$); IR (neat) 2124, 1647, 1255, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.054 (s, 6H), 0.068 (s, 3H), 0.087 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 0.90 (s, 9H), 1.95 (t, *J* = 2.7 Hz, 1H), 2.34 (ddd, *J* = 16.8, 6.0, 2.7 Hz, 1H), 2.52 (ddd, *J* = 16.8, 5.4, 2.7 Hz, 1H), 3.40 (dd, *J* = 5.3, 3.5 Hz, 1H), 3.61 (m, 1H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.78 (m, 1H), 3.90 (dd, *J* = 5.6, 5.6 Hz, 1H), 4.32 (dddd, *J* = 6.8, 3.7, 1.5, 1.2 Hz, 1H), 5.12 (ddd, *J* = 10.3, 1.7, 1.2 Hz, 1H), 5.21 (ddd, *J* = 17.3, 1.7, 1.5 Hz, 1H), 5.97 (ddd, *J* = 17.3, 10.3, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.06, −5.00, −4.47, −4.06, −3.90, −3.87, 18.2, 18.3, 18.5, 24.1, 26.0, 26.1, 62.7, 69.9, 71.7, 73.8, 74.5, 82.1, 85.3, 115.9, 138.7; EI−LRMS *m/z* 542 (M^+), 485, 371, 327, 233, 183, 171, 159. EI−HRMS calcd for $C_{28}H_{58}O_4Si_3$ 542.3643. Found 542.3654.

(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[3-(*tert*-butyldimethylsilyloxy)propoxy]oct-1-en-7-yne (11b). In a manner similar to that for the synthesis of **11a** from **10a**, a crude product, which was prepared from **10b** (104 mg, 0.32 mmol), TBSOTf (0.18 mL, 0.78 mmol), and 2,6-lutidine (0.11 mL, 0.94 mmol) in CH_2Cl_2 (3 mL), was purified by flash column chromatography on silica gel (hexane/AcOEt = 50/1) to give **11b** (177 mg, quantitative) as a colorless oil: $[\alpha]^{21}_D$ +0.3° (*c* 0.9, $CHCl_3$); IR (neat) 2122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 6H), 0.07 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 0.90 (s, 9H), 1.74−1.80 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 2.35 (ddd, *J* = 16.9, 5.5, 2.6 Hz, 1H), 2.49 (ddd, *J* = 16.9, 5.5, 2.6 Hz, 1H), 3.35 (dd, *J* = 5.5, 3.5 Hz, 1H), 3.60−3.76 (m, 4H), 3.88 (dt, *J* = 9.1, 5.5 Hz, 1H), 4.30 (dd, *J* = 7.0, 3.5 Hz, 1H), 5.12 (br d, *J* = 10.3 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.95 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.5, −4.1, −3.9, 18.2, 18.3, 18.5, 24.2, 26.0, 26.1, 33.7, 60.6, 69.5, 69.8, 71.6, 74.5, 82.1, 85.1, 115.8, 138.7; EI−LRMS *m/z* 499 (M − ^{t}Bu)$^+$. EI−HRMS calcd for $C_{25}H_{51}O_4Si_3$ (M − ^{t}Bu)$^+$ 499.3096. Found 499.3074.

(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[3-(*tert*-butyldimethylsilyloxy)butoxy]oct-1-en-7-yne (11c). In a manner similar to that for the synthesis of **11a** from **10a**, a crude product, which was obtained from **10c** (615 mg, 1.8 mmol), TBSOTf (1.0 mL, 4.5 mmol), and 2,6-lutidine (0.65 mL, 5.6 mmol) in CH_2Cl_2 (3.6 mL), was purified by column chromatography on silica gel (hexane/AcOEt = 30/1) to give **11c** (971 mg, 95%) as a colorless oil: $[\alpha]^{20}_D$ −2.1° (*c* 6.3, $CHCl_3$); IR (neat) 2122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 0.90 (s, 9H), 1.24−1.28 (m, 2H), 1.57−1.60 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 2.35 (ddd, *J* = 16.8, 5.5, 2.6 Hz, 1H), 2.49 (ddd, *J* = 16.8, 5.5, 2.6 Hz, 1H), 3.36 (dd, *J* = 5.5, 3.7 Hz, 1H), 3.55−3.69 (m, 4H), 3.86 (dt, *J* = 9.1, 5.5 Hz, 1H), 4.30 (dd, *J* = 3.7, 6.9 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 5.20 (d, *J* = 17.4 Hz, 1H), 5.96 (ddd, *J* = 17.4, 10.4, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.5, −4.1, −3.9, −3.8, 18.3, 18.4, 18.5, 24.2, 26.0, 26.1, 26.2, 26.8, 29.7, 63.2, 69.8, 71.7, 72.5, 74.6,

82.1, 85.0, 115.8, 138.7; EI−LRMS *m/z* 513 (M − ^{t}Bu)$^+$. EI−HRMS calcd for $C_{26}H_{53}O_4Si_3$ (M − ^{t}Bu)$^+$ 513.3252. Found 513.3251.

2α-(3-Hydroxyethoxy)-1α,25-dihydroxyvitamin D$_3$ (4a). To a solution of **12** (50 mg, 140 μmol) and **11a** (50 mg, 92 μmol) in toluene (1 mL) were added Et_3N (1 mL) and $Pd(PPh_3)_4$ (32 mg, 28 μmol), and the mixture was stirred at 120 °C for 2 h. The mixture was filtered through a silica gel pad. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane−hexane/AcOEt = 95/5) to give the coupling product **13a** (57 mg, 75%) as a colorless oil, which was used without any further purification. To the THF (3 mL) solution of **13a** (30 mg, 37 μmol) was added TBAF (1 M solution in THF, 0.18 mL, 0.18 mmol), and the mixture was stirred at room temperature for 4 days. After the solution was concentrated, the residue was purified by a preparative TLC (10% MeOH in CH_2Cl_2) to give **4a** (14 mg, 78%) as a white powder. Further purification of **4a** for biological assays was conducted by reversed-phase recycle HPLC (YMC−Pack ODS column, 20 × 150 mm, 9.9 mL/min, CH_3CN/H_2O = 6/4): $[\alpha]^{20}_D$ +59.1° (*c* 0.12, $CHCl_3$); UV (MeOH) λ_{max} 269 nm; ^{1}H NMR (400 MHz, $CDCl_3/D_2O$) δ 0.54 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.21 (s, 6H), 1.25−1.80 (m, 14H), 1.83−1.89 (m, 1H), 1.96−2.01 (m, 2H), 2.23 (dd, *J* = 13.0, 9.5 Hz, 1H), 2.67 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.83 (m, 1H), 3.38 (dd, *J* = 8.1, 3.3 Hz, 1H), 3.72 (ddd, *J* = 9.5, 4.8, 2.7 Hz, 1H), 3.77−3.84 (m, 4H), 4.07 (ddd, *J* = 9.5, 7.9, 4.8 Hz, 1H), 4.43 (d, *J* = 3.4 Hz, 1H), 5.10 (d, *J* = 1.7 Hz, 1H), 5.38 (d, *J* = 1.7 Hz, 1H), 6.01 (d, *J* = 11.1 Hz, 1H), 6.43 (d, *J* = 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.8, 22.2, 23.5, 27.7, 29.1, 29.2, 29.4, 36.1, 36.4, 40.5, 41.2, 44.4, 45.9, 56.4, 56.6, 62.0, 68.6, 71.1, 71.4, 72.5, 85.0, 116.6, 117.1, 125.6, 131.4, 143.7, 144.1; EI−LRMS *m/z* 476 (M$^+$), 458, 440. EI−HRMS calcd for $C_{29}H_{48}O_5$ (M$^+$) 476.3503. Found 476.3527.

2α-(2-Hydroxypropoxy)-1α,25-dihydroxyvitamin D$_3$ (4b). In a manner similar to that for the synthesis of **4a** from **11a** and **12**, a crude product, which was obtained from **12** (219 mg, 0.39 mmol), **11b** (130 mg, 0.36 mmol), and $Pd(PPh_3)_4$ (125.8 mg, 0.109 mmol) in toluene/Et_3N (1/1, 10 mL), was purified by silica gel column chromatography (hexane−hexane/AcOEt = 95/5) to give the coupling product **13b** (157 mg, 52%) as a colorless oil, which was used without any further purification. The coupling product **13b** (157 mg, 0.19 mmol) was subjected to desilylation by TBAF (1 M solution in THF, 0.94 mL, 0.94 mmol) in THF (3 mL) at room temperature for 4 days. After the usual workup, the crude product was purified by preparative TLC (10% MeOH in CH_2Cl_2) to give **4b** (56 mg, 61%) as a white powder. Further purification of **4b** for biological assays was conducted by reversed-phase recycle HPLC (YMC−Pack ODS column, 20 × 150 mm, 9.9 mL/min, CH_3CN/H_2O = 6/4): $[\alpha]^{25}_D$ +46.4° (*c* 0.55, $CHCl_3$); UV (MeOH) λ_{max} 267 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.21 (s, 6H), 1.25−2.10 (m, 23H), 2.24 (dd, *J* = 13.4, 9.2 Hz, 1H), 2.69 (dd, *J* = 13.4, 4.4 Hz, 1H), 2.82 (m, 1H), 3.38 (dd, *J* = 7.5, 3.2 Hz, 1H), 3.75−3.91 (m, 5H), 4.05 (m, 1H), 4.44 (br d, *J* = 2.8 Hz, 1H), 5.10 (d, *J* = 1.8 Hz, 1H), 5.39 (br s, 1H), 6.01 (d, *J* = 11.3 Hz, 1H), 6.42 (d, *J* = 11.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.8, 22.2, 23.5, 27.7, 29.1, 29.2, 29.4, 31.9, 36.1, 36.4, 40.5, 41.0, 44.4, 45.9, 56.4, 56.6, 61.2, 68.4, 68.5, 71.1, 71.9, 84.5, 116.1, 117.1, 125.5, 131.5, 143.6, 144.3; EI−LRMS *m/z* 490 (M$^+$), 472, 454. EI−HRMS calcd for $C_{30}H_{50}O_5$ 490.3660. Found 490.3638.

2α-(3-Hydroxybutoxy)-1α,25-dihydroxyvitamin D$_3$ (4c). In a manner similar to that for the synthesis of **4a** from **11a** and **12**, a crude product, which was obtained from **11c** (26 mg, 0.05 mmol), **12** (52 mg, 0.15 mmol), and $Pd(PPh_3)_4$ (16 mg, 14 μmol) in toluene/Et_3N (1/3, 2.5 mL), was purified by preparative TLC (hexane/AcOEt = 4/1) to give the coupling product **13c** (26.5 mg, 69%) as a colorless oil, which was used without any further purification. The coupling product **13c** was subjected to desilylation by TBAF (1 M solution in THF, 0.2 mL, 0.2 mmol) in THF (3 mL) at room temperature for 36 h. After the usual workup, the crude product was purified by preparative TLC (10% MeOH in CH_2Cl_2) to yield **4c** (15.1 mg, 66%, two steps from **11c**). Further purification of **4c** for biological assays was conducted by reversed-phase recycle HPLC (YMC−Pack ODS column, 20 × 150 mm, 9.9 mL/min, CH_3CN/H_2O = 6/4): $[\alpha]^{20}_D$ −22.1° (*c* 0.054, $CHCl_3$); UV (MeOH) λ_{max} 267 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.21 (s, 6H), 1.25−2.00 (m, 25H), 2.23 (dd, *J* = 13.3, 9.3 Hz, 1H), 2.68 (dd, *J* = 13.3, 4.6 Hz, 1H), 2.83 (m, 1H), 3.35 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.61 (dt, *J* = 9.5, 6.0 Hz, 1H), 3.68−3.77 (m, 4H), 4.05 (ddd, *J* = 8.6, 7.6, 4.6 Hz, 1H), 4.42 (d, *J* = 3.0 Hz, 1H), 5.10 (d, *J* = 2.1 Hz, 1H), 5.39 (br s, 1H), 6.02 (d, *J* = 11.3 Hz, 1H), 6.42 (d, *J* = 11.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.8, 22.2, 23.5, 26.9, 27.6, 29.1, 29.2, 29.4, 29.7, 36.1, 36.4, 40.5, 40.8, 44.4, 45.9, 56.4, 56.5, 62.6, 68.2, 70.0, 71.1, 71.8, 84.6, 116.2, 117.1, 125.5, 131.5, 143.6, 144.2; EI−LRMS *m/z* 504 (M$^+$), 486, 468. EI−HRMS calcd for $C_{31}H_{52}O_5$ 504.3817. Found 504.3823.

20-*epi*-2α-(2-Hydroxyethoxy)-1α,25-dihydroxyvitamin D$_3$ (20-*epi*-4a). To a solution of **14** (31 mg, 87 μmol) and **11a** (71 mg, 0.13 mmol) in toluene (2 mL) were added Et_3N (2 mL) and $Pd(PPh_3)_4$ (30 mg, 26 μmol), and the mixture was stirred at 110 °C for 1.5 h. After the mixture was filtered through a silica gel short column (hexane/AcOEt = 10/1), the filtrate was concentrated to give the crude product 20-*epi*-vitamin D_3 (45 mg). To a solution of the crude vitamin D_3 in MeCN (1 mL) was added HF/MeCN (1/9, 1 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. To the mixture was added saturated $NaHCO_3$ aqueous solution at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC (AcOEt) to give 20-*epi*-**4a** (20 mg, 48% in two steps) as a colorless oil. Further purification of 20-*epi*-**4a** for biological assays was conducted by reversed-phase recycle HPLC (YMC−Pack ODS column, 20 × 150 mm, 9.9 mL/min, CH_3CN/H_2O = 6/4): $[\alpha]^{19}_D$ +12.4° (*c* 0.82, $CHCl_3$); UV (MeOH) λ_{max} 266 nm; IR (neat) 3374, 1647, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 1.21 (s, 6H), 1.10−2.05 (m, 21H), 2.24 (dd, *J* = 12.5, 11.5 Hz, 1H), 2.67 (dd, *J* = 12.5, 4.6 Hz, 1H), 2.83 (m, 1H), 3.37 (dd, *J* = 7.9, 3.0 Hz, 1H), 3.70 (m, 1H), 3.73−3.85 (m, 4H), 4.07 (m, 1H), 4.43 (d, *J* = 2.9 Hz, 1H), 5.09 (d, *J* = 1.5 Hz, 1H), 5.37 (d, *J* = 1.5 Hz, 1H), 6.01 (d, *J* = 11.1 Hz, 1H), 6.42 (d, *J* = 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 18.7, 21.0, 22.2, 23.6, 27.4, 29.2, 29.3, 29.4, 35.5, 36.1, 40.5, 41.4, 44.4, 46.0, 56.2, 56.4, 61.9, 68.5, 71.1, 71.3, 72.5, 85.1, 116.6, 117.1, 125.3, 131.3, 143,3, 143.8; EI−LRMS *m/z* 476 (M$^+$), 458, 440, 396, 378. EI−HRMS calcd for $C_{29}H_{48}O_5$ 476.3502. Found 476.3503.

20-*epi*-2α-(3-Hydroxypropoxy)-1α,25-dihydroxyvitamin D$_3$ (20-*epi*-4b). In a manner similar to that for the synthesis of 20-*epi*-**4a** from **14** and **11a**, a crude product, which was obtained from **14** (22 mg, 60 μmol), **11b** (51 mg, 91 μmol), and $Pd(PPh_3)_4$ (21 mg, 18 μmol) in toluene/Et_3N (1/1, 4 mL), was dissolved in MeCN. To the solution was added HF/MeCN (1/9, 1 mL) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. After the usual workup, the crude product was purified by preparative TLC (AcOEt) to give 20-*epi*-**4b** (17 mg, 57% in two steps) as a colorless oil. Further purification of 20-*epi*-**4b** for biological assays was conducted by reversed-phase recycle HPLC (YMC−Pack ODS column, 20 × 150 mm, 9.9 mL/min, CH_3CN/H_2O = 6/4): $[\alpha]^{21}_D$ +11.0° (*c* 1.31, $CHCl_3$); UV (MeOH) λ_{max} 267 nm; IR (neat) 3389, 1647, 1265, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 1.20 (s, 6H), 1.10−1.73 (m, 15H), 1.75−1.90 (m, 4H), 1.90−2.00 (m, 2H), 2.22 (dd, *J* = 13.4, 9.2 Hz, 1H), 2.64 (br s, 3H), 2.66 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.81 (m, 1H), 3.36 (dd, *J* = 7.4, 3.3 Hz, 1H), 3.70−3.90 (m, 4H), 4.04 (m, 1H), 4.43 (br d, *J* = 3.2 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 5.37 (s, 1H), 6.01 (d, *J* = 11.2 Hz, 1H), 6.40 (d, *J* = 11.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 18.5, 20.6, 22.1,

23.5, 27.3, 29.0, 29.2, 31.8, 35.4, 36.0, 40.4, 41.0, 44.3, 45.9, 56.1, 56.4, 61.1, 68.3, 68.4, 71.1, 71.9, 84.5, 116.1, 117.1, 125.4, 131.6, 143.4, 144.3; EI−LRMS *m*/*z* 490 (M^+), 473, 472, 396, 267. EI−HRMS calcd for $C_{30}H_{50}O_5$ 490.3660. Found 490.3676.

20-*epi*-2α-(2-Hydroxybutoxy)-1α,25-dihydroxyvitamin D_3 (20-*epi*-4c). In a manner similar to that for the synthesis of 20-*epi*-**4a**, a crude product, which was obtained from **14** (40 mg, 0.11 mmol), **11c** (96 mg, 0.17 mmol), and $Pd(PPh_3)_4$ (39 mg, 34 μmol) in toluene/Et_3N (1/1, 4 mL), was dissolved in MeCN (1 mL). To the solution was added HF/MeCN (1/9, 1 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. After the usual workup, the crude product was purified by preparative TLC (AcOEt) to give 20-*epi*-**4c** (25 mg, 45% in two steps) as a colorless oil. Further purification of 20-*epi*-**4c** for biological assays was conducted by reversed-phase recycle HPLC (YMC−Pack ODS column, 20 × 150 mm, 9.9 mL/min, CH_3CN/H_2O = 6/4): $[\alpha]^{18}_D$ +8.1° (*c* 1.82, $CHCl_3$); UV (MeOH) λ_{max} 269 nm; IR (neat) 3376, 1645, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 1.10 (s, 6H), 1.08−2.05 (m, 25H), 2.23 (dd, *J* = 13.4, 9.3 Hz, 1H), 2.50 (br s, 1H), 2.67 (dd, *J* = 13.4, 4.5 Hz, 1H), 2.83 (m, 1H), 3.34 (dd, *J* = 7.6, 3.1 Hz, 1H), 3.60 (dt, *J* = 9.5, 5.8 Hz, 1H), 3.68 (t, *J* = 5.7 Hz, 2H), 3.74 (dt, *J* = 9.5, 5.9 Hz, 1H), 4.05 (ddd, *J* = 8.8, 7.6, 4.6 Hz, 1H), 4.41 (br d, *J* = 3.1 Hz, 1H), 5.09 (d, *J* = 1.6 Hz, 1H), 5.38 (d, *J* = 1.6 Hz, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.41 (d, *J* = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 18.7, 21.0, 22.2, 23.6, 27.0, 27.4, 29.2, 29.3, 29.4, 29.7, 35.5, 36.1, 40.5, 41.0, 44.4, 46.0, 56.2, 56.4, 62.3, 68.2, 69.9, 71.1, 71.8, 84.5, 116.1, 117.1, 125.3, 131.4, 143.2, 144.0; EI−LRMS *m*/*z* 504 (M^+), 486, 396, 378. EI−HRMS calcd for $C_{31}H_{52}O_5$ 504.3815. Found 504.3814.

Binding Assays to the Bovine Thymus VDR. Bovine thymus VDR was obtained from a commercial supplier, and the affinity was evaluated according to the literature.[23]

Assays for Induction of HL-60 Cell Differentiation. The activity was estimated by superoxide anion production as previously described.[26] The superoxide radicals reduce the cytochrome *c*, and the reduced cytochrome *c* is measured by spectrophotometry at 550 nm.

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Supporting Information Available: General experimental details, ^1H NMR and ^{13}C NMR spectra for all new compounds (**6a**−**11a**, **6b**−**11b**, **6c**−**11c**, **4a**−**c**, 20-*epi*-**4a**−**c**), charts of VDR binding assays of compounds **4a**−**c** and 20-*epi*-**4a**−**c**, and a chart for assays of induction of HL-60 cell differentiation activity of compounds **4a**−**c** and 20-*epi*-**4a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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