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Synthesis of 2α- and 2β-substituted-14-*epi*-previtamin D_3 and their genomic activity

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ABSTRACT

2α- and 2β-Substituted analogs of 14-*epi*-previtamin D_3 were synthesized and isolated after thermal isomerization of 14-*epi*-vitamin D_3 triene at 80 °C. The VDR binding affinity and transactivation activity of osteocalcin promoter in HOS cells were tested, and the 2α-methyl-substituted analog was found to have greater genomic activity than 14-*epi*-previtamin D_3. We found that modification at the C2 position of the *seco*-steroidal skeleton afforded interesting effects for biological genomic activity for the previtamin D form as well as the natural vitamin D form.

1. Introduction

In our group, the systematic synthesis of vitamin D_3 analogs with C2-modifications has been initiated and a number of C2-modified analogs with greater vitamin D receptor (VDR)-agonistic activity than the active vitamin D_3, 1α,25-dihyrdoxyvitamin D_3 (**1**, 1α,25$(OH)_2D_3$), have been successfully synthesized.[1-5] We have also synthesized highly potent VDR-antagonists, which belong to a series of TEI-9647 analogs with C2α-functionalization as well as 24-alkyl modification on the lactone ring.[6] In particular, (23*S*,24*S*)-2α-(3-hydroxypropoxy)-24-propylvitamin D_3-26,23-lactone was found to exhibit approximately 850-fold greater antagonistic activity (IC_{50}=7.4 pM) than the parent antagonist, TEI-9647 (IC_{50}=6.3 nM).[7,8] The mechanism of the C2α-effects on enhanced VDR binding was explained by X-ray crystallographic analyses of the VDR-ligand complexes.[9] One of the important characteristics of the vitamin D_3 molecule is that vitamin D_3 is present in thermal equilibrium with previtamin D_3 via [1,7]-sigmatropic hydrogen shift. In this equilibrium, the 6-*s*-trans isomer, that is, the vitamin D form (**A**), is more stable and major than the 6-*cis* isomer of the previtamin D form (**B**) (Scheme 1). The biologically most active metabolite of vitamin D_3, 1α,25$(OH)_2D_3$ (**1**), also contains 5–10% of its previtamin D form, 1α,25$(OH)_2$preD_3 (**pre-1**) at 37 °C in similar equilibrium.[10] Most scientists have focused on the analogs of the major vitamin D form for therapeutic evaluation rather than the previtamin D form, because previtamin D_3 is easily transformed to vitamin D_3 through thermal equilibrium and is almost impossible to isolate in the pure form.[10] While **1** is a ligand of the nucleic receptor (vitamin D receptor, VDR), regulates gene transcription, and exhibits various biological responses as a hormone,[11] **pre-1** is thought to be a weak ligand of VDR and a poor activator of the above genomic actions,[12] however, **pre-1** has been studied as a precursor of rapid responses,[13] such as stimulation of intestinal Ca^{2+} transport (transcaltachia),[14] activation of PKC[15] and MAP[16] kinases, and so on, which are called non-genomic actions.

Okamura et al. reported that the thermal equilibrium ratio between the vitamin D form (**A**) and previtamin D form (**B**) at 80 °C was reversed by epimerizing the CD-ring bridgehead hydrogen of C14,[17] that is to say, 14-*epi*-1α,25$(OH)_2$preD_3 (**14-*epi*-pre-1**) was major and dominant over 14-*epi*-1α,25$(OH)_2D_3$ (**14-*epi*-1**), and **14-*epi*-pre-1** is expected to be isolated stable as a single isomer at room temperature. Therefore, we focused on the synthesis of **14-*epi*-pre-1** analogs with A-ring modification, and aimed to identify their more detailed biological properties and potential as therapeutic agents of the previtamin D_3 skeleton. In this paper, we present the details of the synthesis and biological evaluation of C2-modified previtamin D_3 analogs.

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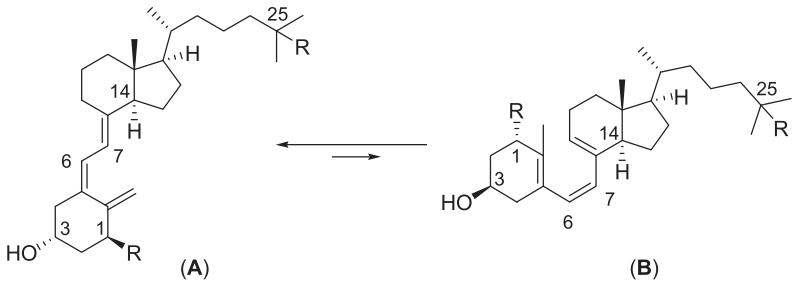
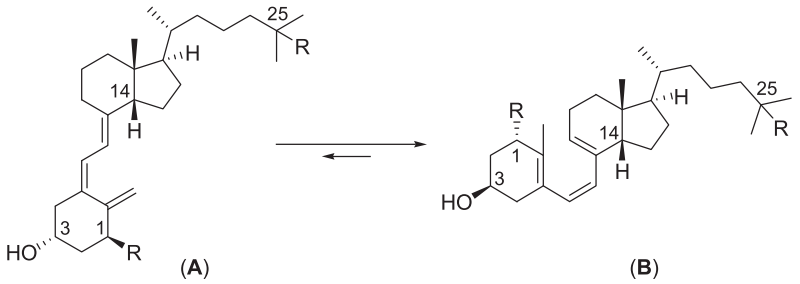


vitamin D_3: R = H
1: R = OH (1α,25-dihydroxyvitamin D_3, 1α,25(OH)$_2$$D_3$)

previtamin D_3: R = H
pre-1: R = OH (1α,25(OH)$_2$preD_3)



14-epi-1: R = OH (14-epi-1α,25(OH)$_2$$D_3$)

14-epi-pre-1: R = OH (14-epi-1α,25(OH)$_2$preD_3)

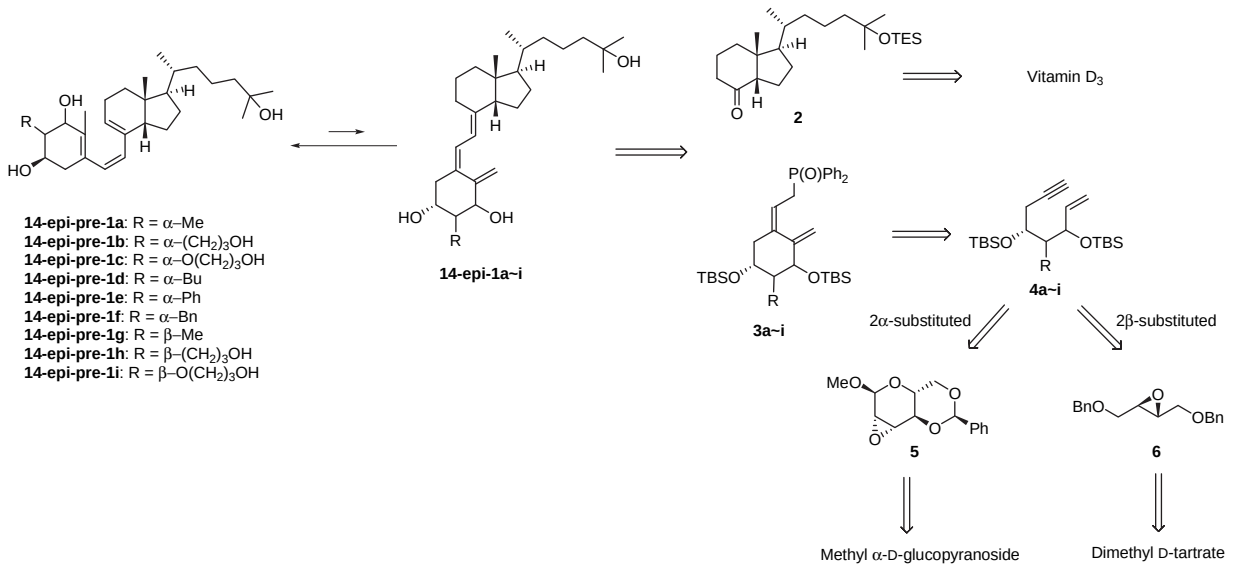
Scheme 1. Equilibrium between vitamin D_3 and previtamin D_3.

2. Results and discussion

2.1. Retrosynthetic analysis

Previously, we found that 2α-alkyl and 2α-(ω-hydroxyalkyl) substitution afforded great improvements of VDR binding affinity and the subsequent genomic actions.[1-4] Also, it is well-known that 2β-hydroxypropoxy substitution afforded great improvement of genomic activity.[18] For the comprehensive study of the previtamin D skeleton, we were interested in various 2β-substitutions and stereochemistry of the 1-hydroxy group at the A-ring moiety. We therefore decided to synthesize analogs with 2α- and 2β-substitutions (**14-*epi*-pre-1a**–**1i**) in this study (Scheme 2).[19,20]

14-*epi*-pre-1 should be prepared from **14-*epi*-1** by thermal isomerization, so we planned to synthesize **14-*epi*-1** analogs as the temporary first targets, and using their thermal isomerization, we could obtain **14-*epi*-pre-1** analogs. This strategy would help to understand the equilibrium between vitamin D_3 and previtamin D_3. The **14-*epi*-1** analogs were divided into two fragments, CD-ring and A-ring fragments, which should be coupled by the Roche coupling method.[21] The CD-ring fragment **2** should be obtained by epimerization at H14 in Grundmann's ketone derivative, which was derived from vitamin D_3.[22] In the A-ring fragment, the phosphine oxide **3a**–**i** could be synthesized from enyne **4a**–**i**, and they were derived from methyl α-D-glucoside through epoxide **5** for 2α-substitutions (**4a**–**f**), and from dimethyl D-tartrate through epoxide **6**



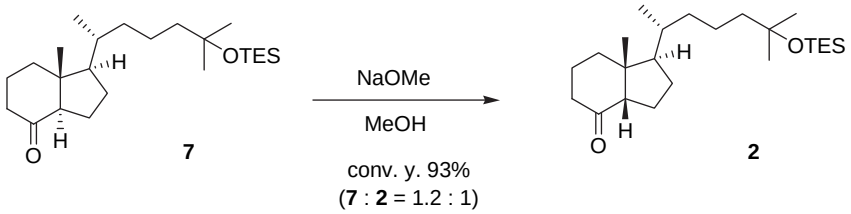
14-epi-pre-1a: R = α–Me
14-epi-pre-1b: R = α–$(CH_2)_3$OH
14-epi-pre-1c: R = α–O$(CH_2)_3$OH
14-epi-pre-1d: R = α–Bu
14-epi-pre-1e: R = α–Ph
14-epi-pre-1f: R = α–Bn
14-epi-pre-1g: R = β–Me
14-epi-pre-1h: R = β–$(CH_2)_3$OH
14-epi-pre-1i: R = β–O$(CH_2)_3$OH

Scheme 2. Retrosynthetic analysis of 2-substituted 14-*epi*-1α,25(OH)$_2$preD_3.

for 2β-substitutions (**4g**–**i**). Thus, we could introduce various alkyl groups at 2α- and 2β-positions by nucleophilic epoxide opening reactions.[2,23,24]

2.2. Synthesis of CD-ring fragment

The CD-ring fragment (**2**) was synthesized from the known ketone, TES-protected 25-hydroxy Grundmann's ketone (**7**) (Scheme 3).[22,25] According to the literature, epimerization of H14 was successfully conducted by NaOMe with recovery of the starting material, which was easily separated by column chromatography.[17] Thus, we were able to obtain the CD-ring fragment in short steps.



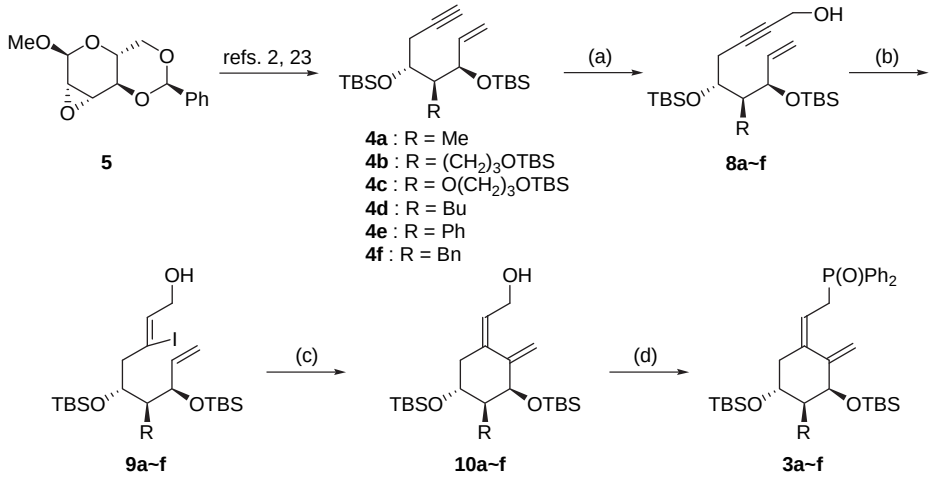
Scheme 3. Synthesis of the CD-ring fragment.

2.3. Synthesis of 2α-substituted A-ring fragments

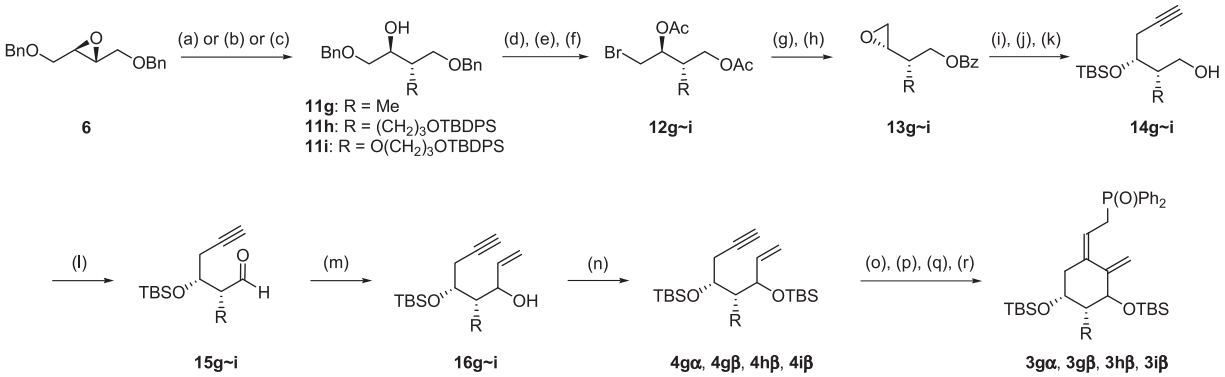
2α-Substituted A-ring fragments (**3a**–**f**) were prepared from the known epoxide **5** derived from methyl α-D-glucoside (Scheme 4).[2,19,23] According to the literature, **5** was transformed to enyne **4a**–**f**, which had various alkyl groups at 2α-position by nucleophilic epoxide opening reaction.[2,23] Then, enyne **4a**–**f** reacted with ^{n}BuLi and then $(CH_2O)_n$ to give alcohol **8a**–**f** in good to excellent yield. Then, hydroalumination and subsequent iodination of the alkyne gave the vinyl iodide **9a**–**f**. Next, cyclization by Heck reaction proceeded smoothly to afford a six-membered A-ring,[24] whose hydroxy group was converted into chloride with *N*-chlorosuccinimide (NCS). This allyl chloride was easily substituted by Ph_2PH and ^{n}BuLi, and the generated phosphine was oxidized to phosphine oxide **3a**–**f**. As above, we were able to prepare 2α-substituted A-ring fragments in good overall yield.

2.4. Synthesis of 2β-substituted A-ring fragments

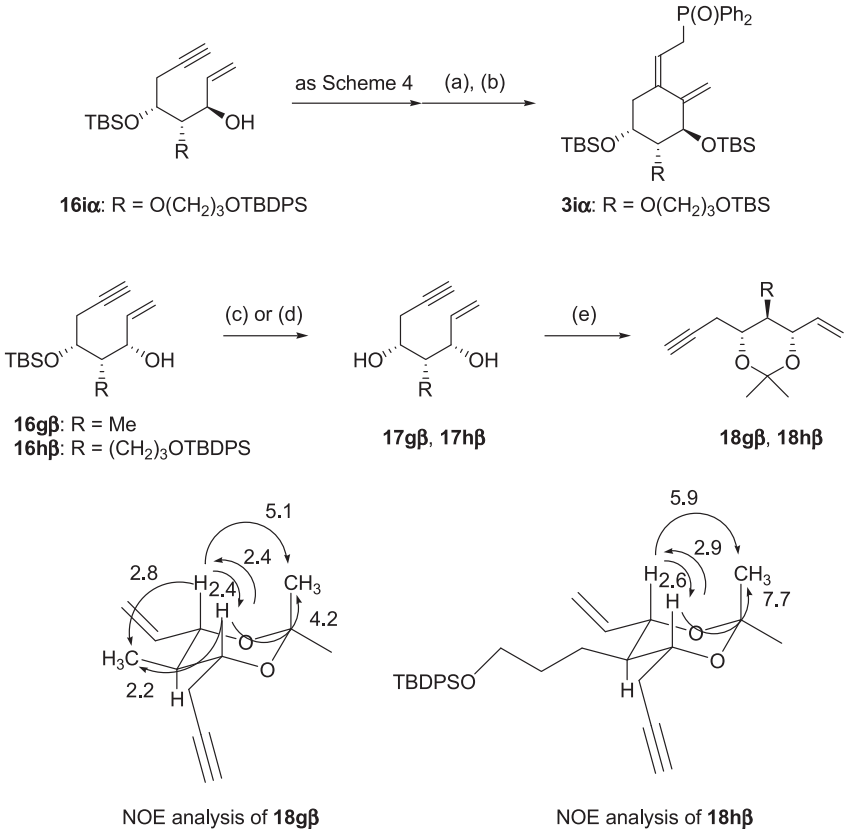
2β-Substituted A-ring fragments (**3g**–**i**) were prepared from the known epoxide **6** derived from dimethyl D-tartrate (Scheme 5).[24,26] Using the nucleophilic epoxide opening reaction with compound **6**, three substitutions were introduced as follows: methyl cuprate gave the methyl substitution; allylation by Grignard reaction followed by hydroboration with 9-borabicyclo[3,3,1]nonane (9-BBN) and subsequent H_2O_2 oxidation afforded the hydroxypropyl substitution; and propylene glycol and KO^{t}Bu gave hydroxypropoxy substitution.[24a,d] After their primary alcohol was protected as *tert*-butyldiphenylsilyl (TBDPS) ether (**11g**–**i**), they were converted to bromide **12g**–**i** by the known procedure.[27] Methanolysis of both acetyl groups under basic conditions caused epoxide formation, and the resultant hydroxy group was transformed into benzyl ester **13g**–**i**. The addition of (trimethylsilyl)acetylene to the epoxide using ^{n}BuLi was straightforward, and the generated secondary alcohol was protected as *tert*-butyldimethylsilyl (TBS) ether, and removal of the terminal trimethylsilyl (TMS) group and benzoyl group gave alkyne **14g**–**i**. The primary alcohol was oxidized to aldehyde by DMSO and SO_3·pyridine complex (**15g**–**i**), to which a vinyl group was introduced to give a diastereomixture of alcohol **16g**–**i**. The stereochemistry of the new hydroxy group is discussed below (Scheme 6), and both isomers of **16g** and the major isomer of **16h** and **16i** were used for further transformation after separation by column chromatography. The hydroxy group of **16g**–**i** was protected by the TBS group, and we were able to synthesize 2β-substituted enyne **4g**–**i**. Similar transformation as Scheme 4 from



Scheme 4. Synthesis of the A-ring fragments. Conditions: (a) ^{n}BuLi, $(CH_2O)_n$, THF, 91% for **8a**, 92% for **8b**, 89% for **8c**, 91% for **8d**, 81% for **8e**, 94% for **8f**; (b) Red-Al, Et_2O, then I_2, THF, 73% for **9a**, 70% for **9b**, 75% for **9c**, 75% for **9d**, 67% for **9e**, 76% for **9f**; (c) $Pd(PPh_3)_4$, Et_3N, MeCN, 93% for **10a**, 89% for **10b**, 82% for **10c**, 93% for **10d**, 99% for **10e**, 92% for **10f**; (d) (i) NCS, Me_2S, CH_2Cl_2, (ii) $PHPh_2$, ^{n}BuLi, THF, (iii) H_2O_2 aq, 77% for **3a**, 74% for **3b**, 76% for **3c**, 76% for **3d**, 39% for **3e**, 83% for **3f**.



Scheme 5. Sythesis of the 2β-substituted A-ring fragments. Conditions. (a) for **11g** MeLi, CuI, Et_2O, 98%; (b) for **11h** (i) allylmagnesium chloride, toluene, (ii) 9-BBN, THF, H_2O_2, NaOH, (iii) TBDPSCl, imidazole, DMF, 90% (three steps); (c) for **11i** (i) propylene glycol, KO^{t}Bu, (ii) TBDPSCl, imidazole, DMF, 92% (two steps); (d) Pd/C, H_2, MeOH; (e) $MeC(OMe)_3$, PPTS, CH_2Cl_2; (f) AcBr, CH_2Cl_2, 60% for **12g**, 52% for **12h**, 55% for **12i** (three steps); (g) K_2CO_3, MeOH; (h) BzCl, Et_3N, CH_2Cl_2, 80% for **13g**, 95% for **13h**, 83% for **13i** (two steps); (i) (trimethylsilyl)acetylene, ^{n}BuLi, $BF_3\cdot OEt_2$, THF; (j) TBSOTf, iPr_2EtN, CH_2Cl_2; (k) K_2CO_3, MeOH, 68% for **14g**, 83% for **14h**, 95% for **14i** (three steps); (l) $SO_3\cdot Py$, Et_3N, DMSO, 77% for **15g**, 99% for **15h**, 95% for **15i**; (m) vinylmagnesium chloride, THF, 93% (α/β 46/47) for **16g**, 95% (α/β 37/58) or **16h**, 73% (α/β 15/58) for **16i** (two steps); (n) TBSOTf, iPr_2EtN, CH_2Cl_2, 100% for **4gα**, 97% for **4gβ**, 99% for **4hβ**, 99% for **4iβ**; (o) ^{n}BuLi, $(CH_2O)_n$, THF; (p) Red-Al, Et_2O, then I_2, THF; (q) $Pd(PPh)_4$, Et_3N, MeCN; (r) (i) NCS, Me_2S, CH_2Cl_2, (ii) ^{n}BuLi, $PHPh_2$, THF, then H_2O_2 aq, 49% for **3gα**, 57% for **3gβ**, 27% for **3hβ**, 28% for **3iβ** (four steps).



Scheme 6. Determination of the stereochemistry of the 1-hydroxy group of **16g**–**i**. Conditions. (a) TBAF, THF; (b) TBSOTf, iPr_2EtN, CH_2Cl_2, 70% (two steps); (c) for **16gβ**, TBAF, THF, 100%; (d) for **16hβ**, PPTS, EtOH, 60%; (e) dimethoxypropane, PPTS, DMF, 70% for **18gβ**, 90% for **18hβ**.

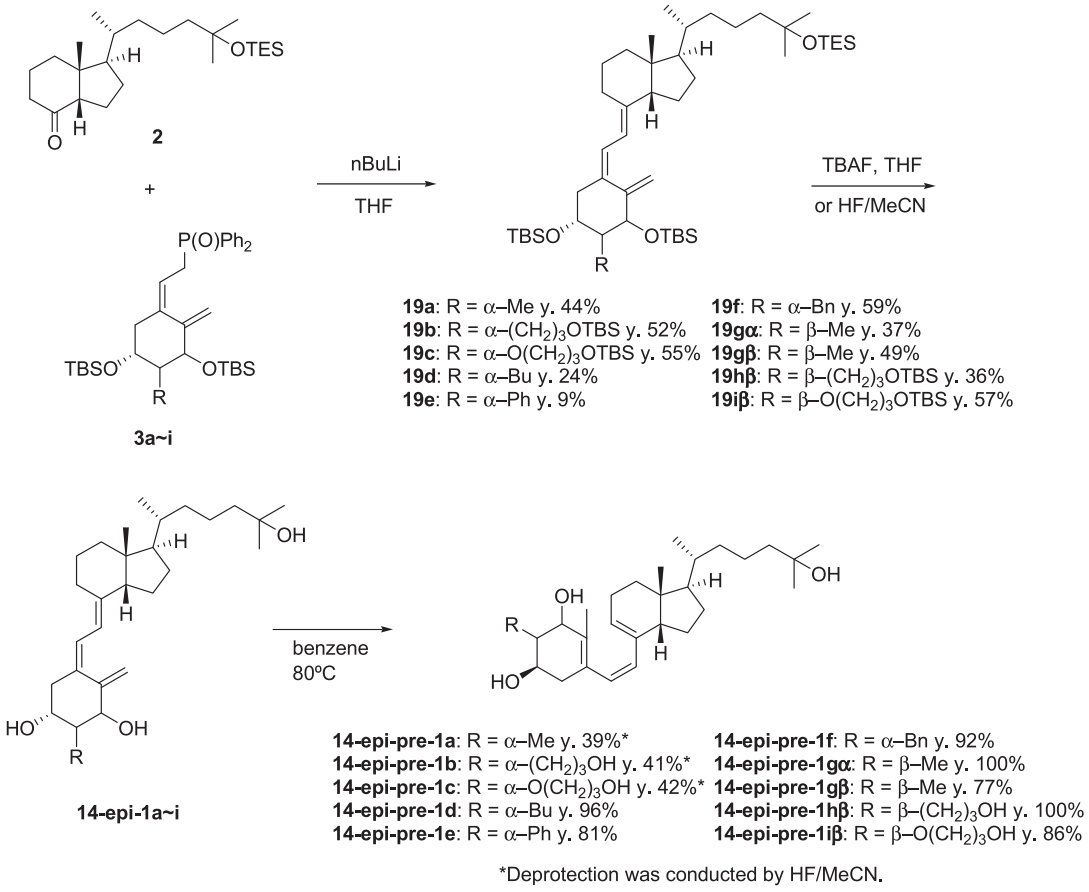
enyne into phosphine oxide afforded the 2β-substituted A-ring fragment **3g**–**i**.

2.5. Determination of the stereochemistry of 1-hydroxy group of 16g–i

The minor diastereomer of **16i** (**16iα**) was converted to the phosphine oxide **3iα** by the same strategy as shown in Scheme 4 followed by exchange of the protecting group from TBDPS to TBS, and **3iα** was identical to the known compound reported by Hatakeyama et al. (Scheme 6).[24a] Therefore, the stereochemistry of its 1-hydroxy group was found to be α-configuration, and the major diastereomer of **16i** was determined to have the 1β-hydroxy group (**16iβ**). For **16g** and **16h**, the TBS group of each major diastereomer (**16gβ** and **16hβ**) was removed, and the resultant 1,3-dihydroxy groups was converted to acetonide **18gβ**[28], which is known, and **18hβ**, respectively. Their NOE analyses are described in Scheme 6, and the stereochemistry of the 1,3-dihydroxy groups is *syn*, that is, **18hβ** also has the 1β,3β-dihydroxy groups. As above, we found that all of the major diastereomers of **16g**–**i** had the 1β-hydroxy group, and we continued further synthesis with **3gα**, **3gβ**, **3hβ**, and **3iβ**.

2.6. Coupling reaction and isomerization

Using the CD- and A-ring fragments prepared above, we attempted the coupling reaction under basic conditions using ^{n}BuLi (Scheme 7).[17,21] Small excess amounts of the A-ring fragment worked well and we obtained the coupled product **19a**–**i**, although some reactions resulted in low yield. At this point, isomerization to the previtamin D form was seldom observed and small amounts of the pre-form were present, probably because TBS groups at the A-ring should have steric hindrance to reach the transition state for the [1,7]-sigmatropic hydrogen shift between the vitamin D form and the previtamin D form. Then, all silyl groups in **19a**–**i** were removed in one step with excess TBAF or HF/MeCN, and considerable amounts of deprotected compounds remained in the vitamin D form (**14-*epi*-1a**–**i**) under these reaction conditions. However, once they were heated at 80 °C in benzene, isomerization was found to proceed smoothly by NMR observation. After 2 h, most of the vitamin D form had been converted to the previtamin D form, and isomerization seemed to reach thermal equilibrium, in which the ratio of the compounds was about 5/95 (vitamin D/previtamin D) based on ^{1}H NMR studies.[29] Using HPLC, the mixture of both forms was separated, and we were able to obtain **14-*epi*-pre-1a**–**i** as each pure form, which were used for further biological studies.



Scheme 7. Coupling reaction and synthesis of 2-substituted 14-*epi*-1α,25(OH)$_2$preD$_3$.

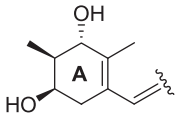
2.7. Biological evaluation

The VDR binding affinity and osteocalcin promoter transactivation activity of the new compounds were evaluated using chick intestinal VDR[30] and HOS cells[31], respectively. The results are summarized in Table 1 in comparison with the natural hormone **1** and 14-*epi*-1α,25(OH)$_2$preD$_3$ (**14-*epi*-pre-1**), which was synthesized in a similar manner in our laboratory. The new compounds showed lower activity than the natural hormone **1**. Remarkably, much lower activity was observed with the 2β-substituted analogs regardless of the stereochemistry at 1-hydroxy group; however, some 2α-substituted analogs showed higher activity than **14-*epi*-pre-1**. In particular, **14-*epi*-pre-1a**, the 2α-methyl-substituted analog, showed a considerable increase in VDR binding affinity and transactivation activity. It is worth noting that **14-*epi*-pre-1** analogs gain genomic activity, and 2-substitution on the A-ring seems to have great effects on the biological actions of the previtamin D form.

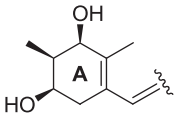
3. Conclusion

We synthesized the 2α- and 2β-substituted analogs of **14-*epi*-1** for the first time and were able to isolate these new analogs (**14-*epi*-pre-1a**–**i**) after thermal isomerization at 80 °C. Using them, we evaluated the VDR binding affinity and transactivation activity of osteocalcin promoter in HOS cells, among which 2α-methyl-substituted analog (**14-*epi*-pre-1a**) was found to have 17-fold greater binding affinity for VDR and fourfold stronger transactivation activity than those of **14-*epi*-pre-1**, respectively. It is known that 6-s-*cis*-conformer analog of 1α,25-dihydroxylumisterol$_3$ shows non-genomic actions acting on genomic responses that are linked to cell differentiation, and the non-genomic

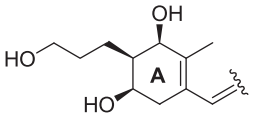
Table 1
Relative binding affinity for chick intestinal VDR and osteocalcin promoter transactivation activity in HOS cells of 2-substituted 14-*epi*-1α,25(OH)$_2$preD$_3$



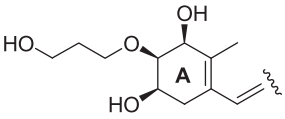
14-epi-pre-1gα



14-epi-pre-1gβ



14-epi-pre-1hβ



14-epi-pre-1iβ

Compound	VDR[a]	Osteocalcin transactivation activity (EC_{50} (nM))
1	100	0.03
14-*epi*-pre-1	0.5	0.46
14-*epi*-pre-1a	8.4	0.12
14-*epi*-pre-1b	1.4	0.69
14-*epi*-pre-1c	0.17	0.95
14-*epi*-pre-1d	0.27	5.77
14-*epi*-pre-1e	< 0.03	0.88
14-*epi*-pre-1f	0.03	30.2
14-*epi*-pre-1gα	0.08	1.34
14-*epi*-pre-1gβ	0.08	9.12
14-*epi*-pre-1hβ	0.18	1.01
14-*epi*-pre-1iβ	0.01	1.24

[a] The potency of **1** is normalized to 100.

pathway-mediated responses induced by **1** and 1α,25-dihydroxylumisterol$_3$ are able to be evaluated by using the NB4 cell (human acute promyelocytic leukemia cell) differentiation system.[32] Although the non-genomic action of **14-*epi*-pre-1a** was tested using NB4 cells, the activity could not be observed so far (data not shown). It was found that 2-modification afforded important effects on biological genomic activity for the previtamin D form as well as the natural vitamin D form reported previously.[1–4,23]

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-400 NMR (400 MHz) and ECP-600 NMR (600 MHz) spectrometers. ^{1}H NMR spectra were referenced with $(CH_3)_4Si$ (δ 0.00 ppm) as an internal standard. ^{13}C NMR spectra were referenced with deuterated solvent (δ 77.0 ppm for $CDCl_3$, and 128.0 ppm for C_6D_6). IR spectra were recorded on JASCO FT-IR-800 Fourier Transform Infrared Spectrophotometer. Low- and high resolution mass spectra were recorded on a JEOL JMS-SX 102A mass spectrometer. FAB mass spectra were measured using *m*-nitrobenzyl alcohol matrix. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Column chromatography was performed on silica gel 60 N (Kanto Chemical Co., Inc., 100–210 μm) or silica gel 60 (Merck, 0.040–0.063 mm). Preparative thin layer chromatography was performed on silica gel 60 F_{254} (Merck, 0.5 mm). High performance liquid chromatography (HPLC) was carried out on a SHIMADZU HPLC system consisting of the following equipments: pump, LC-6AD; detector, SPD-10A; column, YMC-Pack ODS-A. All experiments were performed under anhydrous conditions in an atmosphere of argon, unless otherwise mentioned.

4.2. (1*R*,3a*S*,7a*R*)-1-[(*R*)-6-Triethylsilanyloxy-6-methylheptan-2-yl]-7a-methylhexahydro-1*H*-inden-4(2*H*)-one (2)

To a solution of **7**[25] (6.9 g, 17.4 mmol) in MeOH (35 mL) was added NaOMe (2.4 g, 43.6 mmol) at 0 °C and stirred at room temperature for 3 h. After the reaction was quenched by aqueous NH_4Cl at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flush column chromatography on silica gel (hexane/AcOEt=20/1) to give **2** (5.5 g, 80%) as a colorless oil:$[\alpha]_D^{19}$ +35.1 (*c* 0.01, $CHCl_3$); IR (neat) 1711, 1236, 1213 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (dd, *J*=7.6, 15.6 Hz, 6H), 0.9 (d, *J*=7.3 Hz, 3H), 0.93 (t, *J*=8.1 Hz, 9H), 1.03 (s, 3H), 1.17 (s, 7H), 1.27–1.42 (m, 7H), 1.53–1.61 (m, 2H), 1.72–1.92 (m, 5H), 2.10–2.16 (m, 1H), 2.26–2.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2 (3C), 7.5 (3C), 19.5, 21.4, 21.6, 23.4, 28.1, 30.2, 30.3, 34.7, 36.4, 36.8, 40.5, 45.8, 49.0, 50.9, 58.7, 61.8, 73.7, 213.8; FABMS *m*/*z* 417 $(M+Na)^+$, HRFABMS calcd for $C_{24}H_{46}NaO_2Si$, 417.3159, found 417.3136.

*4.2.1. (5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-methylnon-8-en-2-yn-1-ol (**8a**).* To a solution of **4a**[23b] (1.06 g, 2.77 mmol) in dry THF (9.2 mL) was added ^{n}BuLi (1.53 M hexane solution, 2.75 mL, 4.03 mmol) at −78 °C and stirred for 1 h at the same temperature. To the mixture was added paraformaldehyde (250 mg, 9.04 mmol) at −78 °C and stirred at the same temperature for 1 h. The mixture was warmed up to room temperature over 2 h, and stirred at room temperature for 2 h. To the mixture was added saturated NH_4Cl aqueous solution at 0 °C, and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give **8a** (1.00 g, 91%) as a colorless oil: $[\alpha]_D^{25}$ +1.71 (*c* 3.69, $CHCl_3$); IR (neat) 3331, 2340, 1644, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 0.75 (t, *J*=10.0 Hz, 3H), 0.886 (s, 9H), 0.893 (s, 9H), 1.41 (t, *J*=6.0 Hz, 1H), 1.86 (ddq, *J*=10.5, 10.0, 3.5 Hz, 1H), 2.40–2.42 (m, 2H), 3.98–4.03 (m, 2H), 4.23 (dt, *J*=6.0, 2.1 Hz, 2H), 5.08–5.15 (m, 2H), 5.73 (ddd, *J*=18.0, 9.8, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.4, −3.9, −3.3, 9.6, 18.2, 18.3, 25.9 (3C), 26.0 (3C), 26.2, 43.8, 51.4, 70.7, 76.0, 80.1, 83.6, 115.6, 139.9; EI-LRMS *m*/*z* 395 $(M-OH)^+$, 355, 343, 223, 171; EI-HRMS calcd for $C_{22}H_{43}O_2Si_2$ $(M\text{-}OH)^+$ 395.2802, found 395.2803.

*4.2.2. (5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-[3-(tert-butyldimethylsilanyloxy)propyl]non-8-en-2-yn-1-ol (**8b**).* In the same procedure for **8a**, **8b** (330 mg, 92%) was obtained from **4b**[23c] (339 mg, 0.627 mmol), ^{n}BuLi (1.53 M hexane solution, 0.61 mL, 0.93 mmol), paraformaldehyde (60 mg, 1.20 mmol), and THF (2.1 mL). Colorless oil; $[\alpha]_D^{24}$ +1.00 (*c* 3.31, $CHCl_3$); IR (neat) 3441, 2226, 1642, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 27H), 1.24 (m, 1H), 1.42 (m, 1H), 1.57–1.65 (m, 3H), 1.71 (ddt, *J*=5.9, 5.7, 3.4 Hz,

1H), 2.41–2.44 (m, 2H), 3.56 (m, 2H), 4.01 (dt, *J*=6.1, 3.4 Hz, 1H), 4.10 (dd, *J*=6.7, 5.7 Hz, 1H), 4.22 (dt, *J*=6.1, 2.1 Hz, 2H), 5.08 (dd, *J*=10.1, 1.0 Hz, 1H), 5.13 (dd, *J*=17.2, 1.0 Hz, 1H), 5.83 (ddd, *J*=17.2, 10.1, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.2, −4.6, −4.3, −4.1, −3.5, 18.1, 18.2, 18.4, 22.2, 25.9 (3C), 26.0 (3C), 26.5 (3C), 32.5, 49.4, 51.3, 63.6, 71.5, 76.1, 80.0, 84.0, 115.4, 140.3; EI-LRMS *m/z* 553 (M-OH)$^+$, 513, 438, 381, 369, 171; EI-HRMS calcd for $C_{30}H_{61}O_3Si_3$ (M−OH)$^+$ 553.3928, found 553.3928.

*4.2.3. (5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-[3-(tert-butyldimethylsilanyloxy)propoxy]-non-8-en-2-yn-1-ol (**8c**).* In the same procedure for **8a**, **8c** (2.07 g, 89%) was obtained from **4c**[2] (2.31 g, 4.15 mmol), ^{n}BuLi (1.53 M hexane solution, 3.9 mL, 5.97 mmol), paraformaldehyde (424 mg, 14.1 mmol), and THF (13.1 mL). Colorless oil; $[\alpha]_D^{25}$ +0.42 (*c* 2.62, $CHCl_3$); IR (neat) 3443, 2290, 1644, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 0.90 (s, 9H), 1.54 (t, *J*=6.1 Hz, 1H), 1.71–1.82 (m, 2H), 2.38 (ddt, *J*=18.8, 6.4, 5.4 Hz, 1H), 2.53 (ddt, *J*=16.8, 6.8, 5.7 Hz, 1H), 3.33 (dd, *J*=5.5, 3.3 Hz, 1H), 3.59–3.76 (m, 4H), 3.84 (dt, *J*=5.7, 5.5 Hz, 1H), 4.23 (m, 2H), 4.30 (m, 1H), 5.12 (ddd, *J*=10.3, 1.7, 1.0 Hz, 1H), 5.22 (ddd, *J*=17.3, 1.7, 1.2 Hz, 1H), 5.95 (ddd, *J*=17.3, 10.3, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), −4.7, −4.3, −4.1, −4.0, 18.2, 18.3, 18.4, 24.4, 25.9, 27.0, 26.0, 33.5, 51.4, 60.6, 69.3, 71.8, 74.5, 79.8, 84.2, 85.1, 115.9, 138.7; EI-LRMS *m/z* 569 (M-OH)$^+$, 529, 415, 339, 327, 115; EI-HRMS calcd for $C_{30}H_{61}O_4Si_3$ (M−OH)$^+$ 569.3898, found 569.3888.

*4.2.4. (5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-butylnon-8-en-2-yn-1-ol (**8d**).* In the same procedure for **8a**, **8d** (1.03 g, 91%) was obtained from **4d**[23d] (1.135 g, 2.50 mmol), ^{n}BuLi (1.57 M hexane solution, 2.4 mL, 3.77 mmol), paraformaldehyde (226 mg, 7.52 mmol), and THF (8.3 mL). Colorless oil; $[\alpha]_D^{20}$ +1.46 (*c* 2.54, $CHCl_3$); IR (neat) 3347, 2957, 2228, 1253, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.07 (s, 3H), 0.84–0.87 (m, 2H), 0.87 (s, 9H), 0.87 (s, 9H), 1.22–1.32 (m, 6H), 1.37 (dt, *J*=6.0, 0.9 Hz, 1H), 1.68 (dd, *J*=5.2, 3.8 Hz, 1H), 2.40–2.42 (m, 2H), 3.95 (ddd, *J*=6.2, 6.2, 3.7 Hz, 1H), 4.10 (dd, *J*=7.2, 6.5 Hz, 1H), 4.21 (dd, *J*=2.0, 2.0 Hz, 1H), 4.22 (dd, *J*=2.0, 2.0 Hz, 1H), 5.04 (dd, *J*=10.1, 1.1 Hz, 1H), 5.83 (ddd, *J*=17.3, 10.1, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.3, −4.1, −3.6, 14.1, 18.1, 23.2, 25.9 (3C), 25.9 (3C), 26.3, 31.5, 49.6, 51.4, 71.8, 75.8, 79.7, 84.4, 115.1, 140.4; EI-LRMS *m/z* 397 (M−^{t}Bu)$^+$, 265, 131, 115; EI-HRMS calcd for $C_{21}H_{41}O_3Si_2$ (M−^{t}Bu)$^+$ 397.2495, found 397.2582.

*4.2.5. (5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-phenylnon-8-en-2-yn-1-ol (**8e**).* In the same procedure for **8a**, **8e** (360 mg, 81 %) was obtained from **4e**[23e] (470 mg, 1.0 mmol), ^{n}BuLi (1.56 M hexane solution 1.0 mL, 1.56 mmol), paraformaldehyde (95 mg, 3.1 mmol), and THF (3 mL). White amorphous solid; $[\alpha]_D^{21}$ −37.3 (*c* 0.01, $CHCl_3$); IR (neat) 3346, 1253, 1217 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.10 (s, 6H), 0.86 (s, 9H), 0.92 (s, 9H), 1.33 (s, 1H), 2.03 (ddd, *J*=16.4, 9.5, 2.0 Hz, 1H), 2.28 (dt, *J*=16.4, 2.2 Hz, 1H), 2.97 (dd, *J*=2.4, 9.0 Hz, 1H), 4.27 (s, 2H), 4.47–4.53 (m, 2H), 4.86 (dd, *J*=1.2, 10.3 Hz, 1H), 4.92 (dd, *J*=17.1, 1.2 Hz, 1H), 5.53 (ddd, *J*=17.1, 10.3, 8.8 Hz, 1H), 7.14–7.21 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.2, −4.1, −4.0, −2.5, 14.2, 18.2, 18.3, 22.7, 25.9 (3C), 26.1 (2C), 26.3, 31.6, 51.4, 56.7, 69.7, 75.2, 80.6, 83.3, 117.0, 126.2, 127.0, 131.2, 137.4, 140.2; FABMS *m/z* 497 (M+Na)$^+$, HRFABMS calcd for $C_{27}H_{47}NaO_3Si_2$ (M+Na)$^+$ 497.2878, found 497.2855.

*4.2.6. (5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-benzylnon-8-en-2-yn-1-ol (**8f**).* In the same procedure for **8a**, **8f** (1.18 g, 94%) was obtained from **4f**[23e] (1.18 g, 2.58 mmol), ^{n}BuLi (1.56 M hexane solution 2.5 mL, 3.90 mmol), paraformaldehyde (232 mg, 7.83 mmol), and THF (8.6 mL). Colorless oil; $[\alpha]_D^{23}$ +0.78 (*c* 2.15, $CHCl_3$); IR (neat) 3358, 2955, 2363, 1254, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.04 (s, 3H), 0.877 (s, 9H), 0.884 (s, 9H), 1.32 (t, *J*=6.0 Hz, 1H), 2.18–2.25 (m, 2H), 2.33 (dd, *J*=16.8, 6.4 Hz, 1H), 2.60 (dd, *J*=14.3, 5.5 Hz, 1H), 2.66 (dd, *J*=14.3, 7.1 Hz, 1H), 4.02 (ddd, *J*=6.5, 6.4, 2.4 Hz, 1H), 4.14–4.19 (m, 3H), 5.06 (d, *J*=10.0 Hz, 1H), 5.14 (d, *J*=17.2 Hz, 1H), 5.18 (ddd, *J*=17.2, 10.0, 7.5 Hz, 1H), 7.11–7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.4, −4.1, −3.5, 18.2, 18.3, 26.0 (3C), 26.0 (3C), 26.1, 32.1, 51.4, 51.6, 71.0, 75.9, 79.8, 84.3, 115.7, 125.5, 128.0 (2C), 129.2 (2C), 140.4, 142.1; EI-LRMS *m/z* 431 (M−^{t}Bu)$^+$, 339, 287, 207; EI-HRMS calcd for $C_{24}H_{39}O_3Si_2$ (M−^{t}Bu)$^+$ 431.2438, found 431.2455.

*4.2.7. (2Z)-(5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-3-iodo-6-methylnona-2,8-dien-1-ol (**9a**).* To a solution of **8a** (1.00 g, 2.43 mmol) in dry Et_2O (25 mL) was added Red-Al® (65% toluene solution, 1.73 mL, 5.76 mmol) at 0 °C and stirred at room temperature for 4 h. To the mixture was added ethyl acetate (0.41 mL, 4.20 mmol) at 0 °C, and then cooled to −78 °C and added I_2 (1.28 g, 5.03 mmol) in THF (2 mL) and stirred at the same temperature for 30 min. The mixture was warmed up to room temperature over 1.5 h and stirred for 10 min. The mixture was diluted with Et_2O, added 10% $Na_2S_2O_3$ aqueous solution and saturated $NaHCO_3$ aqueous solution at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give **9a** (985 mg, 62%) as a colorless oil: $[\alpha]_D^{24}$ +1.22 (*c* 2.38, $CHCl_3$); IR (neat) 3328, 1644, 1252, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.73 (d, *J*=7.2 Hz, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.51 (br s, 1H), 1.57 (ddq, *J*=7.3, 7.2, 2.0 Hz, 1H), 2.69–2.70 (m, 2H), 3.98 (dd, *J*=7.8, 7.3 Hz, 1H), 4.20 (d, *J*=5.6 Hz, 2H), 4.32 (dt, *J*=6.6, 2.0 Hz, 1H), 5.08–5.13 (m, 2H), 5.71 (ddd, *J*=17.8, 9.6, 7.8 Hz, 1H), 5.88 (t, *J*=5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.3, −4.0, −3.4, −3.0, 9.5 (2C), 18.3, 18.3, 26.0 (3C), 26.2 (3C), 42.9, 50.9, 67.3, 70.1, 76.4, 116.0, 135.7, 140.7; EI-LRMS *m/z* 483 (M−^{t}Bu)$^+$, 415, 355, 241, 115; EI-HRMS calcd for $C_{18}H_{36}IO_3Si_2$ (M−^{t}Bu)$^+$ 483.1248, found 483.1247.

*4.2.8. (2Z)-(5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-[3-(tert-butyldimethylsilanyloxy)propyl]-3-iodonona-2,8-dien-1-ol (**9b**).* In the same procedure for **9a**, **9b** (1.01 g, 70%) was obtained from **8b** (1.19 g, 2.08 mmol), Red-Al® (65% toluene solution, 1.75 mL, 5.83 mmol), ethyl acetate (0.32 mL, 3.28 mmol), Et_2O (25 mL), I_2 (1.27 g, 4.99 mmol), and THF (2 mL). Colorless oil; $[\alpha]_D^{25}$ +1.89 (*c* 2.54, $CHCl_3$); IR (neat) 3320, 1644, 1254, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 12H), 0.07 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 1.29–1.31 (m, 2H), 1.56–1.64 (m, 4H), 2.70 (dd, *J*=7.2, 6.2 Hz, 2H), 3.57 (t, *J*=6.4 Hz, 2H), 4.12–4.23 (m, 4H), 5.06 (dd, *J*=10.3, 1.2 Hz, 1H), 5.13 (dd, *J*=17.2, 1.2 Hz, 1H), 5.86 (t, *J*=6.2 Hz, 1H), 5.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1 (2C), −4.5, −3.9, −3.6, −3.4, 18.2, 18.2, 18.4, 18.4, 22.4, 26.0 (3C), 26.1 (6C), 32.3, 49.5, 50.8, 63.5, 67.4, 71.4, 75.9, 107.6, 115.4, 136.1, 140.7; EI-LRMS *m/z* 641 (M−^{t}Bu)$^+$ 553, 509, 341, 283, 171; EI-HRMS calcd for $C_{26}H_{54}IO_4Si_3$ (M−^{t}Bu)$^+$ 641.2374, found 641.2363.

*4.2.9. (2Z)-(5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-6-[3-(tert-butyldimethylsilanyloxy)propoxy]-3-iodonona-2,8-dien-1-ol (**9c**).* In the same procedure for **9a**, **9c** (1.88 g, 75%) was obtained from **8c** (2.07 g, 3.52 mmol), Red-Al® (65% toluene solution, 2.4 mL, 7.99 mmol), ethyl acetate (0.35 mL, 3.58 mmol), Et_2O (35 mL), I_2 (1.79 g, 7.06 mmol), and THF (10 mL). Colorless oil; $[\alpha]_D^{25}$ +2.08 (*c* 4.46, $CHCl_3$); IR (neat) 3331, 2930, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 9H), 0.06 (s, 3H), 0.08 (s, 3H), 0.885 (s, 9H), 0.893 (s, 9H), 1.53 (t, *J*=6.0 Hz, 1H), 1.78 (tt, *J*=6.3, 6.3 Hz, 2H), 2.63 (dd, *J*=14.2, 8.3 Hz, 1H), 2.78 (dd, *J*=14.2, 4.3 Hz, 1H), 3.28 (dd, *J*=4.3, 3.1 Hz, 1H), 3.59 (dt, *J*=9.3, 6.4 Hz, 1H), 3.66–3.77 (m, 3H), 4.06 (ddd, *J*=8.3, 4.3, 3.8 Hz, 1H), 4.16 (m, 2H), 4.34 (dd, *J*=7.3,

3.1 Hz, 1H), 5.12 (d, *J*=17.4 Hz, 1H), 5.21 (d, *J*=10.2 Hz, 1H), 5.87 (t, *J*=5.9 Hz, 1H), 5.94 (ddd, *J*=17.4, 10.4, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), −4.7, −4.3, −4.1, −4.0, 18.2, 18.3, 24.4, 25.9 (3C), 26.0 (3C), 26.0 (3C), 26.1, 33.5, 51.5, 60.6, 69.3, 71.8, 74.6, 79.8, 84.2, 85.1, 115.9, 138.7; EI-LRMS *m*/*z* 657 (M−^{t}Bu)$^+$, 639, 525, 467, 397; EI-HRMS calcd for $C_{26}H_{54}IO_5Si_3$ (M−^{t}Bu)$^+$ 657.2324, found 657.2323.

*4.2.10. (2Z)-(5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-3-iodo-6-butylnona-2,8-dien-1-ol (**9d**).* In the same procedure for **9a**, **9d** (992 mg, 75%) was obtained from **8d** (1.03 g, 2.27 mmol), Red-Al® (65% toluene solution, 1.71 mL, 5.70 mmol), ethyl acetate (0.40 mL, 4.06 mmol), Et_2O (23 mL), I_2 (1.15 g, 4.56 mmol), and THF (8 mL). Colorless oil; $[\alpha]_D^{22}$ +2.56 (*c* 2.15, $CHCl_3$); IR (neat) 3326, 2950, 1644, 1470, 1254, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.020 (s, 3H), 0.023 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 0.86 (s, 9H), 0.85–0.89 (m, 2H), 1.21–1.29 (m, 6H), 1.43 (t, *J*=5.9 Hz, 1H), 1.61 (m, 1H), 2.64 (dd, *J*=14.1, 4.4 Hz, 1H), 2.71 (dd, *J*=14.1, 7.4 Hz, 1H), 4.07 (ddd, *J*=7.4, 4.4, 3.0 Hz, 1H), 4.14–4.20 (m, 3H), 5.03 (dd, *J*=10.0, 1.3 Hz, 1H), 5.10 (dd, *J*=17.3, 1.4 Hz, 1H), 5.83 (t, *J*=5.8 Hz, 1H), 5.88 (ddd, *J*=17.3, 10.0, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −3.9, −3.6, −3.5, 14.1, 18.1, 18.2, 23.1, 26.0, 26.0 (3C), 26.0 (3C), 31.1, 49.8, 50.8, 67.3, 71.4, 75.7, 107.8, 115.2, 136.1, 140.8; EI-LRMS *m*/*z* 525 (M−^{t}Bu)$^+$, 509, 341, 283, 209; EI-HRMS calcd for $C_{21}H_{42}IO_3Si_2$ (M−^{t}Bu)$^+$ 525.1718, found 525.1724.

*4.2.11. (2Z)-(5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-3-iodo-6-phenylnona-2,8-dien-1-ol (**9e**).* In the same procedure for **9a**, **9e** (89 mg, 67%) was obtained from **8e** (130 mg, 0.27 mmol), Red-Al® (65% toluene solution, 0.2 mL, 0.68 mmol), ethyl acetate (40 μL, 0.44 mmol), Et_2O (3 mL), I_2 (270 mg, 1.1 mmol), and THF (1 mL). Colorless oil; $[\alpha]_D^{21}$ +10.7 (*c* 0.009, $CHCl_3$); IR (neat) 3356, 2928, 1732, 1462, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.09 (s, 6H), 0.19 (s, 3H), 0.90 (s, 9H), 0.93 (s, 9H), 1.23–1.26 (m, 1H), 2.38 (dd, *J*=13.9, 9.3 Hz, 1H), 2.45–2.50 (m, 1H), 2.59 (dd, *J*=9.3, 2.0 Hz, 1H), 4.15–4.24 (m, 2H), 4.46 (t, *J*=9.0 Hz, 1H), 4.74–4.82 (m, 3H), 5.45 (ddd, *J*=19.0, 10.3, 9.0 Hz 1H), 5.74 (t, *J*=5.9 Hz, 1H), 7.15–7.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.2, −3.9, −3.8, −2.5, 18.1, 18.2, 25.9 (3C), 26.2 (3C), 50.4, 55.7, 67.1, 69.6, 75.4, 105.3, 116.6, 126.2, 127.1 (2C), 131.2 (2C), 136.0, 137.5, 140.4; EI-LRMS *m*/*z* 602 (M−^{t}Bu)$^+$; EI-HRMS calcd for $C_{27}H_{47}IO_3Si_2$ (M−^{t}Bu)$^+$ 602.2113, found 602.2102.

*4.2.12. (2Z)-(5R,6S,7R)-5,7-Bis(tert-butyldimethylsilanyloxy)-3-iodo-6-benzylnona-2,8-dien-1-ol (**9f**).* In the same procedure for **9a**, **9f** (1.13 g, 76%) was obtained from **8f** (1.18 g, 2.42 mmol), Red-Al® (65% toluene solution, 1.8 mL, 6.00 mmol), ethyl acetate (0.38 mL, 3.89 mmol), Et_2O (25 mL), I_2 (1.22 g, 4.88 mmol), and THF (4 mL). Colorless oil; $[\alpha]_D^{21}$ +2.46 (*c* 2.15, $CHCl_3$); IR (neat) 3329, 2955, 1645, 1471, 1254, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.08 (s, 3H), −0.06 (s, 3H), 0.02 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 0.90 (s, 9H), 1.31 (t, *J*=6.1 Hz, 1H), 2.02 (m, 1H), 2.49 (dd, *J*=14.1, 5.5 Hz, 1H), 2.56 (dd, *J*=14.2, 9.5 Hz, 1H), 2.60 (dd, *J*=14.1, 7.2 Hz, 1H), 2.75 (dd, *J*=14.2, 3.9 Hz, 1H), 4.00–4.11 (m, 3H), 4.22 (ddd, *J*=7.3, 5.1, 0.5 Hz, 1H), 5.08 (dd, *J*=10.2, 1.6 Hz, 1H), 5.17 (ddd, *J*=17.2, 1.6, 0.5 Hz, 1H), 5.40 (t, *J*=5.7 Hz, 1H), 5.90 (ddd, *J*=17.2, 10.2, 7.3 Hz, 1H), 7.15 (m, 1H), 7.20–7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.2, −3.7, −3.5, 18.2, 18.3, 26.1 (3C), 26.1 (3C), 31.9, 50.4, 51.8, 67.2, 70.6, 75.8, 106.8, 115.8, 125.7, 128.1 (2C), 129.4 (2C), 136.4, 140.4, 142.0; EI-LRMS *m*/*z* 559 (M−^{t}Bu)$^+$, 541, 415, 245; EI-HRMS calcd for $C_{24}H_{40}IO_3Si_2$ (M−^{t}Bu)$^+$ 559.1560, found 559.1153.

*4.2.13. (Z)-2-[(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-methyl-2-methylenecyclohexylidene]ethanol (**10a**).* To a solution of $Pd(PPh_3)_4$ (135 mg, 0.119 mmol) in dry MeCN (19 mL) were added **9a** (632 mg, 1.17 mmol) in dry MeCN (10 mL) and Et_3N (1.63 mL, 1.23 mmol) at 0 °C and stirred at 90 °C for 1 h. The mixture was cooled to room temperature, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=12/1) to give **10a** (633 mg, 82%) as a white powder: $[\alpha]_D^{25}$ +0.53 (*c* 2.85, $CHCl_3$); IR (neat) 3353, 2953, 1458, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 6H), 0.06 (s, 3H), 0.88 (s, 18H), 0.92 (d, *J*=6.9 Hz, 3H), 1.13 (t, *J*=5.7 Hz, 1H), 1.83 (ddq, *J*=6.9, 6.9, 3.7 Hz, 1H), 2.11 (dd, *J*=13.5, 7.0 Hz, 1H), 2.48 (dd, *J*=10.5, 3.6 Hz, 1H), 3.82 (ddd, *J*=7.0, 6.9, 3.6 Hz, 1H), 4.20 (dd, *J*=6.3, 5.7 Hz, 2H), 4.31 (d, *J*=3.7 Hz, 1H), 4.77 (d, *J*=1.5 Hz, 1H), 5.13 (d, *J*=1.5 Hz, 1H), 5.51 (t, *J*=6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.8, −4.5, −4.4, 13.0, 18.1, 18.3, 25.8 (3C), 25.9 (3C), 42.9, 45.5, 59.7, 72.0, 75.1, 111.7, 126.2, 139.5, 146.5; EI-LRMS *m*/*z* 412 (M)$^+$, 394, 381, 355, 337, 223, 183; EI-HRMS calcd for $C_{22}H_{44}O_3Si_2$ (M)$^+$ 412.2829, found 412.2815. Anal. Calcd for $C_{22}H_{44}O_3Si_2$: C, 64.01; H, 10.75. Found: C, 64.01; H, 10.42.

*4.2.14. (Z)-2-[(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-{3-(tert-butyldimethylsilanyloxy)propyl}-2-methylenecyclohexylidene]ethanol (**10b**).* In the same procedure for **10a**, **10b** (404 mg, 89%) was obtained from **9b** (609 mg, 0.87 mmol), $Pd(PPh_3)_4$ (106 mg, 0.092 mmol), Et_3N (1.21 mL, 8.68 mmol), and MeCN (44 mL). Colorless oil; $[\alpha]_D^{24}$ −2.90 (*c* 1.69, $CHCl_3$); IR (neat) 3322, 2955, 1640, 1472, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 6H), 0.05 (s, 6H), 0.06 (s, 3H), 0.88–0.89 (m, 27H), 1.21–1.32 (m, 2H), 1.43–1.66 (m, 4H), 2.11 (dd, *J*=13.7, 6.3 Hz, 1H), 2.46 (dd, *J*=13.7, 3.6 Hz, 1H), 3.58 (t, *J*=6.2 Hz, 2H), 3.92 (d, *J*=6.3 Hz, 1H), 4.20 (d, *J*=6.8 Hz, 2H), 4.43 (d, *J*=2.9 Hz, 1H), 4.76 (s, 1H), 5.14 (s, 1H), 5.50 (t, *J*=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), −5.0, −4.7, −4.5, −4.4, 18.1, 18.3, 18.4, 22.2, 25.9 (3C), 25.9 (3C), 26.1 (3C), 31.2, 42.6, 50.7, 59.7, 63.6, 70.3, 73.0, 111.5, 126.1, 139.3, 146.5; EI-LRMS *m*/*z* 570 (M)$^+$, 552, 513, 423, 381, 289; EI-HRMS calcd for $C_{30}H_{62}O_4Si_3$ (M)$^+$ 570.3956, found 570.3964.

*4.2.15. (Z)-2-[(3R,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-{3-(tert-butyldimethylsilanyloxy)propoxy}-2-methylenecyclohexylidene]ethanol (**10c**).* In the same procedure for **10a**, **10c** (633 mg, 82%) was obtained from **9c** (936 mg, 1.31 mmol), $Pd(PPh_3)_4$ (153 mg, 0.132 mmol), Et_3N (1.82 mL, 13.1 mmol), and MeCN (33 mL). Colorless oil; $[\alpha]_D^{25}$ −3.03 (*c* 2.85, $CHCl_3$); IR (neat) 3346, 2955, 1645, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.05 (s, 3H), 0.07 (s, 6H), 0.08 (s, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 1.12 (m, 1H), 1.76 (m, 2H), 2.07 (dd, *J*=13.4, 5.2 Hz, 1H), 2.56 (d, *J*=13.4 Hz, 1H), 3.28 (m, 1H), 3.58–3.79 (m, 4H), 4.01 (dd, *J*=5.2, 5.0 Hz, 1H), 4.19 (dd, *J*=6.2, 5.9 Hz, 2H), 4.42 (s, 1H), 4.62 (s, 1H), 5.22 (s, 1H), 5.50 (dd, *J*=6.7, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.0, −4.7 (2C), −4.5, −4.4, 18.1, 18.3, 18.4, 22.2, 25.9 (3C), 25.9 (3C), 26.1 (3C), 31.2, 50.7, 59.7, 63.6, 70.3, 72.9, 111.4, 126.1, 139.4, 146.5; EI-LRMS *m*/*z* 586 (M)$^+$, 543, 529, 453, 397, 339; EI-HRMS calcd for $C_{30}H_{62}O_5Si_3$ (M)$^+$ 586.3905, found 586.3890.

*4.2.16. (Z)-2-[(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-butyl-2-methylenecyclohexylidene]ethanol (**10d**).* In the same procedure for **10a**, **10d** (723 mg, 93%) was obtained from **9d** (992 mg, 1.70 mmol), $Pd(PPh_3)_4$ (199 mg, 0.172 mmol), Et_3N (2.4 mL, 17.2 mmol), and MeCN (43 mL). Colorless oil; $[\alpha]_D^{21}$ −0.98 (*c* 1.54, $CHCl_3$); IR (neat) 3329, 2955, 1640, 1472, 1254, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.027 (s, 3H), 0.030 (s, 3H), 0.04 (s, 3H), 0.86 (s, 18H), 0.86–0.89 (m, 2H), 1.13–1.30 (m, 6H), 1.42 (m, 1H), 1.59 (m, 1H), 2.09 (dd, *J*=13.7, 6.6 Hz, 1H), 2.45 (dd, *J*=13.7, 3.6 Hz, 1H), 3.90 (ddd, *J*=6.6, 6.6, 3.6 Hz, 1H), 4.18 (br d, *J*=6.8 Hz, 1H), 4.39 (br d, *J*=3.4 Hz, 1H), 4.74 (d, *J*=1.6 Hz, 1H), 5.12 (d, *J*=1.6 Hz, 1H), 5.48 (t, *J*=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.8, −4.5, −4.4, 14.1 (2C), 18.1, 18.3, 23.0, 25.4, 25.8 (3C), 25.9 (3C), 29.9, 50.7, 59.6, 70.2, 72.9, 111.4, 126.1, 139.3, 146.7; EI-

LRMS *m/z* 454 $(M)^+$, 436, 397, 379, 265, 223; EI-HRMS calcd for $C_{25}H_{50}O_3Si_2$ $(M)^+$ 454.3298, found 454.3291.

*4.2.17. (Z)-2-[(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-phenylcyclohexylidene]ethanol (**10e**).* In the same procedure for **10a**, **10e** (77 mg, 99%) was obtained from **9e** (89 mg, 0.15 mmol), $Pd(PPh_3)_4$ (17 mg, 15 μmol), Et_3N (0.2 mL, 1.5 mmol), and MeCN (4 mL). Colorless oil; $[\alpha]_D^{22}$ +32.6 (*c* 0.007, $CHCl_3$); IR (neat) 3323, 2955, 1638, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), −0.02 (s, 3H), −0.01 (s, 3H), 0.01 (s, 3H), 0.64 (s, 9H), 0.84 (s, 9H), 2.28 (t, *J*=12.6 Hz, 1H), 2.66 (dd, *J*=4.9, 12.6 Hz, 1H), 2.85 (dd, *J*=2.7, 9.5 Hz, 1H), 4.08–4.21 (m, 2H), 4.25–4.31 (m, 2H), 4.41–4.46 (m, 1H), 4.83 (t, *J*=1.6 Hz 1H), 5.13 (s, 1H), 5.65 (t, *J*=6.8 Hz, 1H), 7.14–7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.0, −4.5, −3.9, 17.9, 18.1, 25.6 (3C), 25.9 (3C), 45.6, 58.4, 59.9, 69.5, 77.3, 113.0, 125.2, 126.2, 126.7, 127.5, 128.1, 129.0, 129.8, 138.8, 140.3, 146.9; FABMS *m/z* 492 $(M+Na)^+$, HRFABMS calcd for $C_{27}H_{46}NaO_3Si_2$ $(M+Na)^+$ 497.2878, found 497.2860.

*4.2.18. (Z)-2-[(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-benzyl-2-methylenecyclohexylidene]ethanol (**10f**).* In the same procedure for **10a**, **10f** (824 mg, 92%) was obtained from **9f** (1.13 g, 1.84 mmol), $Pd(PPh_3)_4$ (218 mg, 0.189 mmol), Et_3N (2.6 mL, 18.7 mmol), and MeCN (36 mL). Colorless oil; $[\alpha]_D^{22}$ −3.84 (*c* 1.54, $CHCl_3$); IR (neat) 3333, 2955, 1638, 1254, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.10 (s, 3H), −0.09 (s, 3H), 0.02 (s, 3H), 0.04 (s, 3H), 0.81 (s, 9H), 0.92 (s, 9H), 1.15 (br s, 1H), 2.10 (dd, *J*=13.7, 4.6 Hz, 1H), 2.10 (m, 1H), 2.43 (dd, *J*=14.2, 9.2 Hz, 1H), 2.57 (d, *J*=13.7 Hz, 1H), 2.88 (dd, *J*=14.2, 6.2 Hz, 1H), 3.81 (dd, *J*=4.8, 4.6 Hz, 1H), 4.15–4.26 (m, 2H), 4.46 (d, *J*=2.7 Hz, 1H), 4.79 (s, 1H), 5.18 (s, 1H), 5.49 (t, *J*=6.7 Hz, 1H), 7.11–7.17 (m, 3H), 7.24–7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.94, −4.92, −4.7, −4.5, 18.0, 18.4, 25.8 (3C), 26.0 (3C), 31.4, 41.4, 52.4, 59.7, 70.0, 72.1, 111.4, 125.7, 126.4, 128.2 (2C), 128.7 (2C), 139.2, 141.0, 146.1; EI-LRMS *m/z* 488 $(M)^+$, 470, 431, 413, 299; EI-HRMS calcd for $C_{28}H_{48}O_3Si_2$ $(M)^+$ 488.3142, found 488.3149.

*4.2.19. (Z)-[2-{(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-methylcyclohexylidene}ethyl]diphenylphosphine oxide (**3a**).* To a solution of NCS (169 mg, 1.23 mmol) in dry CH_2Cl_2 (3 mL) was added dimethylsulfide (0.10 mL, 1.26 mmol) at 0 °C, and stirred at the same temperature for 15 min. To the mixture was added **10a** (251 mg, 0.2 mmol) in dry CH_2Cl_2 (3 mL) at −16 °C and stirred for 1.5 h at the same temperature. The mixture was warmed up to 0 °C, added water at the same temperature, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by short column chromatography on silica gel (hexane/AcOEt/TEA=100/10/1) to give a crude product. To a solution of Ph_2PH (0.21 mL, 1.21 mmol) in dry THF (25 mL) was added ^{n}BuLi (1.53 M hexane solution, 0.58 mL, 0.887 mmol) at 0 °C and stirred for 10 min at the same temperature. To another flask charged with the crude product in dry THF (2 mL) was added the above lithium diphenylphosphide solution at −78 °C and stirred at the same temperature for 10 min. To the mixture was added water at −78 °C and warmed up to 0 °C. The resulting mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (2.1 mL). To the mixture was added 35% H_2O_2 aqueous solution (5.1 mL) at 0 °C. After stirring for 1.5 h at 0 °C, to the mixture was added water at the same temperature and extracted with CH_2Cl_2. The organic layer was washed with 2 N Na_2SO_3 aqueous solution, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=3/2) to give **3a** (213 mg, 77% in three steps) as an amorphous solid: $[\alpha]_D^{25}$ +0.22 (*c* 3.69, $CHCl_3$); IR (neat) 2924, 1458, 1377, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.32 (s, 3H), 0.00 (s, 6H), 0.01 (s, 3H), 0.38 (m, 1H), 1.85 (m, 1H), 2.06 (ddd, *J*=13.6, 5.6, 4.9 Hz, 1H), 2.43 (d, *J*=13.6 Hz, 1H), 3.13 (ddd, *J*=15.8, 14.8, 6.6 Hz, 1H), 3.41 (ddd, *J*=14.8, 13.8, 7.3 Hz, 1H), 3.76 (dd, *J*=11.3, 4.9 Hz, 1H), 4.33 (d, *J*=3.7 Hz, 2H), 4.78 (s, 1H), 5.10 (s, 1H), 5.31 (dd, *J*=7.3, 6.6 Hz, 1H), 7.43–7.54 (m, 6H), 7.67–7.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.8, −4.53, −4.50, 12.3, 18.1, 18.3, 25.9 (6C), 30.9, 31.6, 42.6, 45.4, 72.3, 72.3, 74.3, 111.5, 111.5, 114.3, 114.4, 128.4, 128.5, 130.9, 131.0, 131.6, 131.6, 141.1, 141.2, 145.9, 145.9; EI-LRMS *m/z* 596 $(M)^+$, 539, 449, 263, 210; EI-HRMS calcd for $C_{34}H_{53}O_3PSi_2$ $(M)^+$ 596.3271, found 596.3284.

*4.2.20. (Z)-[2-{(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-(3-(tert-butyldimethylsilanyloxy)propyl)cyclohexylidene}ethyl]diphenylphosphine oxide (**3b**).* In the same procedure for **3a**, **3b** (698 mg, 74%) was obtained from **10b** (715 mg, 1.25 mmol), NCS (340 mg, 2.54 mmol), CH_2Cl_2 (13 mL), dimethylsulfide (0.19 mL, 2.59 mmol), Ph_2PH (0.36 mL, 2.07 mmol), THF (7 mL), ^{n}BuLi (1.53 M hexane solution, 1.0 mL, 1.53 mmol), 35% H_2O_2 aqueous solution (9 mL), and CH_2Cl_2 (3.4 mL). Amorphous solid; $[\alpha]_D^{27}$ +0.16 (*c* 1.92, $CHCl_3$); IR (neat) 2955, 1634, 1255, 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), −0.02 (s, 3H), −0.01 (s, 3H), 0.01 (s, 6H), 0.02 (s, 3H), 0.80 (s, 9H), 0.85 (s, 9H), 0.87 (s, 9H), 1.13 (br s, 1H), 1.45–1.65 (m, 2H), 2.05 (m, 1H), 2.39 (m, 1H), 3.12 (ddd, *J*=16.0, 14.9, 6.8 Hz, 1H), 3.38 (ddd, *J*=14.9, 14.8, 8.8 Hz, 1H), 3.54 (t, *J*=6.1 Hz, 2H), 3.86 (ddd, *J*=4.7, 4.7, 4.7 Hz, 1H), 4.41 (d, *J*=2.3 Hz, 1H), 4.73 (s, 1H), 5.09 (s, 1H), 5.29 (dd, *J*=14.1, 6.8 Hz, 1H), 7.42–7.52 (m, 6H), 7.65–7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2C), −5.0, −4.8, −4.6, −4.5, 18.0, 18.3, 18.4, 21.8, 25.9 (5C), 26.0 (1C), 30.9, 31.3, 31.6, 50.7, 58.0, 63.6, 70.3, 71.3, 72.6, 72.6, 111.1, 113.3, 114.3, 114.4, 128.4, 128.5, 130.9, 130.9, 130.9, 131.0, 131.6, 133.5, 138.5, 141.0. 146.1; EI-LRMS *m/z* 754 $(M)^+$, 697, 622, 565, 490, 433, 201; EI-HRMS calcd for $C_{42}H_{71}O_4PSi_3$ $(M)^+$ 754.4398, found 754.4413.

*4.2.21. (Z)-[2-{(3R,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-(3-(tert-butyldimethylsilanyloxy)propoxy)cyclohexylidene}ethyl]diphenylphosphine oxide (**3c**).* In the same procedure for **3a**, **3c** (1.20 g, 66%) was obtained from **10c** (1.33 g, 2.27 mmol), NCS (701 mg, 5.25 mmol), CH_2Cl_2 (18 mL), dimethylsulfide (0.42 mL, 5.45 mmol), Ph_2PH (0.62 mL, 3.56 mmol), THF (13 mL), ^{n}BuLi (1.53 M hexane solution, 1.0 mL, 1.53 mmol), 35% H_2O_2 aqueous solution (16 mL), and CH_2Cl_2 (6 mL). Amorphous solid; $[\alpha]_D^{27}$ −1.05 (*c* 3.62, $CHCl_3$); IR (neat) 2955, 1644, 1256, 1186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.04 (s, 3H), 0.00 (s, 9H), 0.01 (s, 3H), 0.04 (s, 3H), 0.80 (s, 9H), 0.85 (s, 9H), 0.88 (s, 9H), 1.71 (tt, *J*=6.7, 6.7 Hz, 2H), 2.02 (m, 1H), 2.49 (m, 1H), 3.14 (ddd, *J*=15.5, 14.9, 6.3 Hz, 1H), 3.25 (m, 1H), 3.36 (ddd, *J*=14.9, 14.0, 8.2 Hz, 1H), 3.44–3.52 (m, 4H), 3.92 (ddd, *J*=4.2, 4.2, 4.2 Hz, 1H), 4.37 (s, 1H), 4.76 (s, 1H), 5.16 (s, 1H), 5.32 (dd, *J*=15.5, 8.2 Hz, 1H), 7.41–7.51 (m, 6H), 7.64–7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, −5.2, −4.9, −4.8 (2C), −4.7, 18.1, 18.3, 18.4, 25.8 (3C), 25.9 (3C), 26.0 (3C), 31.0, 31.7, 33.6, 60.3, 68.5, 69.9, 73.3, 84.3, 111.6, 114.7, 114.8, 128.4, 128.4, 128.5, 130.9, 130.9, 131.0, 131.0, 131.6, 133.1, 140.4, 140.6, 144.9, 144.9; EI-LRMS *m/z* 770 $(M)^+$, 713, 581, 523, 449, 201; EI-HRMS calcd for $C_{42}H_{71}O_5PSi_3$ $(M)^+$ 770.4347, found 770.4341.

*4.2.22. (Z)-[2-{(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-butyl-2-methylenecyclohexylidene}ethyl]diphenylphosphine oxide (**3d**).* In the same procedure for **3a**, **3d** (776 mg, 76%) was obtained from **10d** (723 mg, 1.59 mmol), NCS (429 mg, 3.21 mmol), CH_2Cl_2 (17 mL), dimethylsulfide (0.26 mL, 3.54 mmol), Ph_2PH (0.55 mL, 3.16 mmol), THF (5 mL), ^{n}BuLi (1.57 M hexane solution, 1.51 mL, 2.37 mmol), 35% H_2O_2 aqueous solution (10 mL), and CH_2Cl_2 (5 mL). Amorphous solid; $[\alpha]_D^{26}$ −0.39 (*c* 2.08, $CHCl_3$); IR (neat) 2955, 2226, 1254, 1182, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), −0.02 (s, 3H), −0.01 (s, 3H), 0.02 (s, 3H), 0.80 (s, 9H), 0.83–0.88 (m, 3H), 0.88 (s, 9H), 1.10 (m, 1H), 1.23–1.24 (m, 4H), 1.44 (m, 1H), 1.63 (m, 1H), 2.04 (m, 1H), 2.39 (m, 1H), 3.12 (ddd, *J*=16.0, 15.5, 7.0 Hz, 1H), 3.39 (ddd, *J*=15.5, 14.9, 8.3 Hz, 1H), 3.85 (ddd, *J*=9.3, 3.6, 3.6 Hz,

1H), 4.40 (d, J=3.7 Hz, 1H), 4.74 (s, 1H), 5.09 (s, 1H), 5.29 (ddd, J=15.3, 8.3, 7.0 Hz, 1H), 7.42–7.52 (m, 6H), 7.65–7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.3, −5.0, −4.9, 13.6, 17.6, 17.7, 22.5, 24.5, 25.4 (6C), 25.5, 25.6, 50.2, 69.8, 113.8, 113.9, 127.9, 128.0, 130.3, 130.3, 130.4, 130.4, 131.1, 131.8, 132.1, 132.8, 133.1, 140.4, 140.5, 145.7, 145.7; EI-LRMS m/z 638 $(M)^+$, 581, 437, 201; EI-HRMS calcd for $C_{37}H_{59}O_3PSi_2$ $(M)^+$ 638.3740, found 638.3748.

*4.2.23. (Z)-[2-{(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-phenylcyclohexylidene}ethyl]diphenylphosphine oxide (**3e**).* In the same procedure for **3a**, **3e** (77 mg, 39%) was obtained from **10e** (135 mg, 0.28 mmol), NCS (114 mg, 0.85 mmol), CH_2Cl_2 (4 mL), dimethylsulfide (70 μL, 0.94 mmol), Ph_2PH (56 μL, 0.3 mmol), THF (1 mL), ^{n}BuLi (1.57 M hexane solution, 0.1 mL, 0.16 mmol), 35% H_2O_2 aqueous solution (0.16 mL), and CH_2Cl_2 (1 mL). Amorphous solid; $[\alpha]_D^{23}$ +66.2 (c 0.009, $CHCl_3$); IR (neat) 1472, 1437, 1391, 1362 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.46 (s, 3H), −0.22 (s, 3H), −0.16 (s, 3H), −0.04 (s, 3H), 0.61 (s, 9H), 0.79 (s, 9H), 2.24–2.32 (m, 1H), 2.61 (dd, J=13.2, 4.7 Hz, 1H), 2.84 (dd, J=9.2, 3.0 Hz, 1H), 3.04–3.12 (m, 1H), 3.50 (dt, J=14.4, 10.5, Hz, 1H), 4.24 (d, J=3.0 Hz, 1H), 4.36 (dt, J=9.2, 4.7 Hz, 1H), 4.82 (d, J=2.1 Hz, 1H), 5.03 (s, 1H), 5.41 (t, J=5.0 Hz, 1H), 7.13–7.22 (m, 5H), 7.44–7.58 (m, 6H), 7.65–7.70 (m, 2H), 7.76–7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.0, −4.4, −3.9, 14.3, 17.8, 18.1, 25.6 (3C), 25.8, 25.9 (3C), 31.2, 45.5, 58.3, 69.9, 77.0, 77.2, 112.9, 126.2, 127.5, 128.5, 128.6, 129.8, 130.7, 130.8, 131.0, 131.2, 131.7, 131.8, 132.7, 140.3, 140.8, 146.5, 146.5; FABMS m/z 659 $(M+H)^+$, HRFABMS calcd for $C_{39}H_{55}O_3PSi_2$ $(M+H)^+$ 659.3525, found 659.3506.

*4.2.24. (Z)-[2-{(3S,4S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-benzyl-2-methylenecyclohexylidene}ethyl]diphenylphosphine oxide (**3f**).* In the same procedure for **3a**, **3f** (947 mg, 83%) was obtained from **10f** (723 mg, 1.59 mmol), NCS (824 mg, 1.69 mmol), CH_2Cl_2 (17 mL), dimethylsulfide (0.27 mL, 3.68 mmol), Ph_2PH (0.54 mL, 3.10 mmol), THF (13 mL), ^{n}BuLi (1.57 M hexane solution, 1.50 mL, 2.36 mmol), 35% H_2O_2 aqueous solution (5 mL), and CH_2Cl_2 (2 mL). Amorphous solid; $[\alpha]_D^{23}$ −2.02 (c 5.31, $CHCl_3$); IR (neat) 2955, 1638, 1593, 1254, 1173, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.22 (s, 3H), −0.17 (s, 3H), 0.00 (s, 3H), 0.04 (s, 3H), 0.71 (s, 9H), 0.92 (s, 9H), 2.03–2.15 (m, 2H), 2.27 (dd, J=13.1, 11,8 Hz, 1H), 2.53 (d, J=13.9 Hz, 1H), 2.91 (dd, J=13.1, 5.0 Hz, 1H), 3.18 (ddd, J=16.1, 14.9, 6.6 Hz, 1H), 3.38 (ddd, J=14.9, 13.7, 8.0 Hz, 1H), 3.71 (m, 1H), 4.48 (d, J=2.2 Hz, 1H), 4.83 (s, 1H), 5.19 (s, 1H), 5.32 (ddd, J=14.2, 8.0, 6.6 Hz, 1H), 7.07–7.15 (m, 3H), 7.21–7.24 (m, 2H), 7.42–7.52 (m, 6H), 7.67–7.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −5.0, −4.9, −4.5, 18.0, 18.3, 25.8 (3C), 25.9 (3C), 30.9, 31.2, 31.6, 52.5, 68.9, 71.7, 111.0, 114.5, 114.6, 125.6, 128.2 (2C), 128.4 (2C), 128.5 (2C), 128.7 (2C), 130.8, 130.9, 130.9, 131.0, 131.7, 140.8, 140.9, 141.0, 145.6, 145.7; EI-LRMS m/z 672 $(M)^+$, 616, 483, 449; EI-HRMS calcd for $C_{40}H_{57}O_3PSi_2$ $(M)^+$ 672.3584, found 672.3581.

*4.2.25. (2S,3S)-1,4-Bis(benzyloxy)-3-methylbutan-2-ol (**11g**).* To a solution of CuI (398 mg, 2.09 mmol) in Et_2O (5 mL) was added MeLi (1.14 M Et_2O solution, 3.66 mL, 4.17 mmol) at −40 °C and stirred for 40 min at 0 °C. After the mixture was cooled to −78 °C, **6** (396 mg, 1.39 mmol) in Et_2O (2 mL) was added, and the whole mixture was gradually warmed up to 0 °C over 2 h. After stirring for further 1 h at 0 °C, the reaction was quenched by aqueous NH_4Cl at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1 to 8/1) to give **11g** (409 mg, 98%) as a colorless oil.[26b]

*4.2.26. (2S,3S)-1-(Benzyloxy)-3-(benzyloxymethyl)-6-(tert-butyldiphenylsilanyloxy)hexan-2-ol (**11h**).* Allylmagnesium chloride (6.15 mL, 2.0 M THF solution, 12 mmol) was evaporated in a round bottom vessel using vacuum pump to give a residue, which was suspended in toluene (5 mL). To the solution was added **6** (700 mg, 2.46 mmol) in toluene (5 mL) and the mixture was stirred for 3 h at room temperature. The reaction was quenched by aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1 to 8/1) to give a colorless oil (800 mg, 100%). To a solution of the compound obtained above (595 mg, 1.82 mmol) in THF (10 mL) was added 9-BBN (8.02 mL, 0.5 M THF solution, 4 mmol), and the mixture was stirred for 3 h at room temperature. Then, the mixture was cooled to 0 °C, and aqueous 35% H_2O_2 (1 mL) and aqueous 15% NaOH (1 mL) were added to the mixture, which was stirred for 1 h. The reaction was quenched by aqueous $Na_2S_2O_3$ and aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1 to 1/2) to give a colorless oil (630 mg, 100%).To a solution of the compound obtained above (105 mg, 0.305 mmol) in DMF (1.5 mL) were added imidazole (42 mg, 0.61 mmol) and TBDPSCl (95 μL, 0.366 mmol), and the mixture was stirred for 1 h at room temperature. The reaction was quenched by aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=30/1) to give **11h** (169 mg, 95% in three steps) as a colorless oil: $[\alpha]_D^{22}$ +5.1 (c 0.69, $CHCl_3$); IR (neat) 3069, 2930, 2859, 1109, 737, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92–1.96 (m, 1H), 2.22–2.32 (m, 2H), 3.06 (br s, 1H), 3.56–3.66 (m, 4H), 3.93 (dd, J=11.2, 5.6 Hz, 1H), 4.49 (s, 2H), 4.57 (s, 2H), 5.04–5.10 (m, 2H), 5.77–5.84 (m, 1H), 7.29–7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 24.6, 26.9, 30.2, 40.4, 64.0, 70.4, 72.2, 72.9, 73.3, 73.3, 127.5, 127.5, 127.6, 127.6, 128.3, 129.4, 133.9, 135.4, 138.0, 138.0; FABMS m/z 605 $(M+Na)^+$, HRFABMS calcd for $C_{37}H_{46}NaO_4Si$ 605.3063, found 605.3061.

*4.2.27. (4R,5R)-5-(Benzyloxymethyl)-12,12-dimethyl-1,11,11-triphenyl-2,6,10-trioxa-11-silatridecan-4-ol (**11i**).* To a solution of **6** (100 mg, 0.35 mmol) in propylene glycol (1 mL) was added KO^{t}Bu (119 mg, 1.06 mmol) and stirred at 100 °C for 2.5 h. The reaction was quenched by aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1) to give a colorless oil (123 mg, 97%). To a solution of the compound obtained above (120 mg, 0.33 mmol) in DMF (1 mL) were added imidazole (45 mg, 0.66 mmol) and TBDPSCl (104 μL, 0.40 mmol), and the mixture was stirred for 1 h at room temperature. The reaction was quenched by aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1 to 6/1) to give **11i** (189 mg, 92% in two steps) as a colorless oil: $[\alpha]_D^{25}$ +7.7 (c 6.54, $CHCl_3$); IR (neat) 3453, 2930, 2859, 1111, 737, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.78 (m, 2H), 2.60 (d, J=5.1 Hz, 1H), 3.48 (m, 1H), 3.55–3.62 (m, 4H), 3.66–3.75 (m, 4H), 3.92 (m, 1H), 4.49 (s, 2H), 4.50 (d, J=11.2 Hz, 1H), 4.53 (d, J=11.2 Hz, 1H), 7.27–7.40 (m, 16H), 7.64–7.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 19.2, 26.6, 26.9, 33.0, 60.8, 67.3, 69.7, 70.6, 71.1, 73.3, 73.4, 78.8, 127.4, 127.5, 127.5, 127.5, 127.6, 128.2, 128.2, 129.4, 129.4, 133.7, 134.7, 135.2, 135.4, 137.9, 138.0; EI-LRMS m/z 598 $(M)^+$, 575, 507; EI-HRMS calcd for $C_{37}H_{46}O_5Si$ 598.3115, found 598.3109.

*4.2.28. (2S,3S)-4-Bromo-2-methylbutane-1,3-diyl diethanoate (**12g**).* To a solution of **11g** (400 mg, 1.33 mmol) in THF (8 mL) was added Pd on carbon (20 mg), and the mixture was stirred under H_2 atmosphere for 10 h. The reaction was filtered and concentrated to

give a crude product, which was dissolved in CH_2Cl_2 (5 mL). To the solution was added trimethyl orthoacetate (208 μL, 1.73 mmol), and PPTS (3.3 mg, 0.0133 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. The reaction was concentrated, and the residue was dissolved in CH_2Cl_2 (4 mL). To the solution was added acetyl bromide (118 μL, 1.6 mmol), and the mixture was stirred at room temperature for 1 h. The reaction was quenched by aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=6/1 to 4/1) to give **12g** (213 mg, 60% in three steps) as a colorless oil: $[\alpha]_D^{24}$ −29.9 (*c* 1.38, $CHCl_3$); IR (neat) 2975, 1742, 1373, 1240, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J*=7.1 Hz, 3H), 2.05 (s, 3H), 2.12 (s, 3H), 2.26–2.35 (m, 1H), 3.50 (dd, *J*=11.4, 5.3 Hz, 1H), 3.64 (dd, *J*=11.4, 3.7 Hz, 1H), 4.02 (dd, *J*=11.2, 4.8 Hz, 1H), 4.09 (dd, *J*=11.2, 5.4 Hz, 1H), 4.93–4.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 20.9, 20.9, 33.0, 34.9, 65.0, 72.9, 170.1, 170.8; FABMS *m*/*z* 267 $(M+H)^+$, HRFABMS calcd for $C_9H_{15}{}^{79}BrO_4$ 267.0232, found 267.0254.

*4.2.29. (2S,3S)-4-Bromo-2-[3-(tert-butyldiphenylsilanyloxy)propyl] butane-1,3-diyl diethanoate (**12h**).* In the same procedure for **12g**, **11h** (52 mg, 0.089 mmol), Pd on carbon (16 mg), H_2, THF (5 mL) gave a colorless oil (19 mg, 96%). The compound obtained above (37 mg, 0.092 mmol), CH_2Cl_2 (1 mL), trimethyl orthoacetate (33 μL, 0.276 mmol), and then PPTS (1 mg, 0.013 mmol), acetyl bromide (8 μL, 0.11 mmol), and CH_2Cl_2 (1 mL) afforded **12h** (30 mg, 52% in three steps) as a colorless oil: $[\alpha]_D^{22}$ +8.7 (*c* 0.77, $CHCl_3$); IR (neat) 2932, 1744, 1372, 1236, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.3–1.45 (m, 2H), 1.56–1.61 (m, 2H), 2.02 (s, 2H), 2.07 (s, 1H), 2.13 (m, 1H), 3.49 (dd, *J*=11.2, 5.9 Hz, 1H), 3.55 (dd, *J*=11.2, 4.4 Hz, 1H), 3.65 (t, *J*=5.9 Hz, 2H), 4.05 (dd, *J*=11.7, 5.1 Hz, 1H), 4.14 (dd, *J*=11.7, 4.6 Hz, 1H), 5.05 (m, 1H), 7.34–7.43 (m, 6H), 7.62–7.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.8, 20.8, 20.9, 20.9, 24.0, 26.9, 29.6, 32.7, 39.5, 62.5, 63.4, 72.3, 127.5, 129.5, 133.6, 135.4, 169.9, 170.6; FABMS *m*/*z* 573 $(M+Na)^+$, HRFABMS calcd for $C_{27}H_{37}{}^{79}BrNaO_5Si$ 571.1491, found 571.1490.

*4.2.30. (2S,3S)-4-Bromo-2-[3-(tert-butyldiphenylsilanyloxy)propoxy]butane-1,3-diyl diethanoate (**12i**).* In the same procedure for **12g**, **11i** (185 mg, 0.309 mmol), Pd on carbon (24 mg), H_2, MeOH (5 mL) gave a colorless oil (98 mg, 76%). The compound obtained above (585 mg, 1.40 mmol), CH_2Cl_2 (6 mL), trimethyl orthoacetate (508 μL, 4.20 mmol), and then PPTS (3.5 mg, 0.014 mmol), triethylamine (2 μL, 0.014 mmol), acetyl bromide (155 μL, 2.1 mmol), and CH_2Cl_2 (6 mL) afforded **12i** (578 mg, 55% in three steps) as a colorless oil: $[\alpha]_D^{22}$ −3.9 (*c* 0.46, $CHCl_3$); IR (neat) 2930, 2361, 1748, 1238, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.79 (m, 2H), 2.01 (s, 3H), 2.07 (s, 3H), 3.60–3.80 (m, 6H), 4.09 (dd, *J*=12.2, 4.2 Hz, 1H), 4.26 (dd, *J*=12.2, 3.2 Hz, 1H), 4.98 (m, 1H), 7.34–7.41 (m, 6H), 7.63–7.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 19.1, 20.7, 20.8, 26.8, 32.1, 32.8, 60.2, 60.4, 61.6, 67.5, 70.4, 76.4, 127.5, 129.4, 133.6, 135.3, 169.4, 170.4; FABMS *m*/*z* 587 $(M+Na)^+$, HRFABMS calcd for $C_{27}H_{37}{}^{79}BrNaO_6Si$ 587.1441, found 587.1448.

*4.2.31. (S)-2-[(S)-Oxiran-2-yl]propyl benzoate (**13g**).* To a solution of **12g** (700 mg, 2.62 mmol) in MeOH (7 mL) was added K_2CO_3 (1.09 g, 7.86 mmol) at 0 °C and stirred at room temperature for 2.5 h. After the reaction was quenched by aqueous NH_4Cl at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a crude product, which was dissolved in CH_2Cl_2 (11 mL). To the solution was added triethylamine (1.1 mL, 7.86 mmol) and benzoyl chloride (608 μL, 5.24 mmol), and the mixture was stirred at room temperature for 4 h. The reaction was quenched by aqueous $NaHCO_3$ at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give **13g** (432 mg, 80% in two steps) as a colorless oil: $[\alpha]_D^{24}$ −9.0 (*c* 2.85, $CHCl_3$); IR (neat) 2970, 1721, 1275, 1113, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J*=7.1 Hz, 3H), 1.75–1.83 (m, 1H), 2.50 (dd, *J*=4.9, 2.7 Hz, 1H), 2.69 (dd, *J*=4.9, 4.2 Hz, 1H), 2.85–2.90 (m, 1H), 4.30 (d, *J*=5.7 Hz, 2H), 7.35–7.42 (m, 2H), 7.46–7.50 (m, 1H), 8.00–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 35.8, 45.2, 53.6, 66.7, 128.0, 129.2, 129.9, 132.6, 166.0; FABMS *m*/*z* 207 $(M+H)^+$, HRFABMS calcd for $C_{12}H_{15}O_3$ 207.1021, found 207.1028.

*4.2.32. (S)-5-(tert-Butyldiphenylsilanyloxy)-2-[(S)-oxiran-2-yl]pentyl benzoate (**13h**).* In the same procedure for **13g**, **12h** (28 mg, 0.051 mmol), K_2CO_3 (17 mg, 0.122 mmol), MeOH (3 mL) gave a colorless oil (19 mg, 96%). The compound obtained above (270 mg, 0.70 mmol), CH_2Cl_2 (5 mL), triethylamine (0.196 mL, 1.40 mmol), and benzoyl chloride (122 μL, 1.05 mmol) afforded **13h** (339 mg, 95% in two steps) as a colorless oil: $[\alpha]_D^{22}$ −2.9 (*c* 1.08, $CHCl_3$); IR (neat) 2932, 1721, 1273, 1111, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.62–1.71 (m, 5H), 2.58 (m, 1H), 2.83 (dd, *J*=4.6, 4.4 Hz, 1H), 2.95–2.98 (m, 1H), 3.73–3.74 (m, 2H), 4.43–4.50 (m, 2H), 7.39–7.48 (m, 8H), 7.56 (m, 1H), 7.70–7.72 (m, 4H), 8.07–8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 24.7, 26.8, 29.9, 41.1, 46.5, 53.2, 63.6, 65.5, 127.5, 127.8, 128.2, 129.4, 129.8, 130.0, 132.7, 133.6, 133.4, 166.2; FABMS *m*/*z* 489 $(M+H)^+$, HRFABMS calcd for $C_{30}H_{37}O_4Si$ 489.2461, found 489.2448.

*4.2.33. (S)-2-[3-(tert-Butyldiphenylsilanyloxy)propoxy]-2-[(R)-oxiran-2-yl]ethyl benzoate (**13i**).* In the same procedure for **13g**, **12i** (440 mg, 0.778 mmol), K_2CO_3 (269 mg, 1.95 mmol), MeOH (3 mL) gave a colorless oil (309 mg, 99%). The compound obtained above (68 mg, 0.17 mmol), CH_2Cl_2 (2.5 mL), triethylamine (0.047 mL, 0.34 mmol) and benzoyl chloride (30 μL, 2.55 mmol) afforded **13i** (72 mg, 83% in two steps) as a colorless oil: $[\alpha]_D^{22}$ +0.3 (*c* 1.54, $CHCl_3$); IR (neat) 2930, 1725, 1273, 1111, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.86 (m, 2H), 2.80 (dd, *J*=5.4, 2.4 Hz, 1H), 2.83 (dd, *J*=5.4, 3.9 Hz, 1H), 3.10 (m, 1H), 3.54 (m, 1H), 3.70–3.83 (m, 4H), 4.45 (dd, *J*=11.7, 5.9 Hz, 1H), 4.55 (dd, *J*=11.7, 3.9 Hz, 1H), 7.38–7.40 (m, 8H), 7.56 (m, 1H), 7.68–7.71 (m, 4H), 8.07–8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 19.6, 26.9, 33.0, 45.2, 51.0, 60.4, 64.6, 67.4, 77.0, 127.5, 127.5, 127.5, 127.6, 128.3, 129.5, 129.5, 129.6, 129.6, 129.8, 132.9, 133.7, 135.4, 160.1; FABMS *m*/*z* 527 $(M+Na)^+$, HRFABMS calcd for $C_{30}H_{36}NaO_5Si$ 527.2230, found 527.2227.

*4.2.34. (2S,3R)-3-(tert-Butyldimethylsilanyloxy)-2-methylhex-5-yn-1-ol (**14g**).* To a solution of trimethylsilylacetylene (0.823 mL, 5.83 mmol) in THF (5 mL) was added ^{n}BuLi (1.56 M hexane solution, 3.43 mL, 5.36 mmol) at −78 °C and stirred at the same temperature for 30 min. To the mixture were added **13g** (480 mg, 2.33 mmol) in THF (3 mL) and $BF_3{\cdot}Et_2O$ (325 μL, 2.56 mmol) at −78 °C, and the whole mixture was gradually warmed to −30 °C over 2.5 h. After the reaction was quenched by aqueous $NaHCO_3$ at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=15/1 to 10/1) to give a colorless oil (564 mg, 80%). To a solution of the compound obtained above (540 mg, 1.77 mmol) in CH_2Cl_2 (5 mL) were added *N*,*N*-diisopropylethylamine (462 μL, 2.66 mmol) and TBSOTf (508 μL, 2.21 mmol) at 0 °C and stirred at room temperature for 1 h. After the reaction was quenched by aqueous $NaHCO_3$ at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=100/1 to 50/1) to give a colorless oil (672 mg, 90%). To a solution of the compound obtained above (630 mg, 1.50 mmol) in MeOH (5 mL) was added K_2CO_3 (624 mg, 4.50 mmol) at 0 °C and stirred at room temperature for

16 h. After the reaction was quenched by aqueous NH_4Cl at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=20/1 to 15/1) to give **14g** (344 mg, 68% in three steps) as a colorless oil: $[\alpha]_D^{24}$ −30.1 (*c* 1.62, $CHCl_3$); IR (neat) 3314, 2932, 1256, 1084, 1030, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.98 (d, *J*=7.1 Hz, 3H), 1.95–2.00 (m, 2H), 2.39 (ddd, *J*=17.1, 4.9, 2.7 Hz, 1H), 2.43 (ddd, *J*=17.1, 7.3, 2.4 Hz, 1H), 2.66 (br s, 1H), 3.55 (dd, *J*=11.2, 5.1 Hz, 1H), 3.74 (dd, *J*=11.2, 4.2 Hz, 1H), 3.78–3.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.5, 14.5, 17.9, 25.3, 25.7, 38.3, 64.5, 70.4, 75.0, 80.8; FABMS *m*/*z* 244 $(M+H)^+$, HRFABMS calcd for $C_{13}H_{26}O_2Si$ 243.1780, found 243.1780.

*4.2.35. (2S,3R)-3-(tert-Butyldimethylsilanyloxy)-2-[3-(tert-butyldiphenylsilanyloxy)propyl]hex-5-yn-1-ol (**14h**).* In the same procedure for **14g**, **13h** (320 mg, 0.655 mmol), trimethylsilylacetylene (231 μL, 1.64 mmol), THF (5 mL), ^{n}BuLi (1.56 M hexane solution, 0.965 mL, 1.51 mmol), $BF_3\cdot Et_2O$ (91 μL, 0.72 mmol) gave a colorless oil (386 mg. 100%). Then, the compound obtained above (370 mg, 0.63 mmol), CH_2Cl_2 (4 mL), *N*,*N*-diisopropylethylamine (165 μL, 0.945 mmol) and TBSOTf (181 μL, 0.79 mmol) gave a colorless oil (397 mg, 90%). Then, the compound obtained above (380 mg, 0.542 mmol), MeOH (5 mL), K_2CO_3 (225 mg, 1.63 mmol) afforded **14h** (263 mg, 83% in three steps) as a colorless oil: $[\alpha]_D^{22}$ +0.78 (*c* 1.15, $CHCl_3$); IR (neat) 3312, 2932, 1256, 1109, 837, 777, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 1.07 (s, 9H), 1.48–1.55 (m, 1H), 1.61–1.73 (m, 3H), 1.77–1.84 (m, 1H), 1.98 (dd, *J*=2.7, 2.7 Hz, 1H), 2.46 (ddd, *J*=16.8, 4.9, 2.7 Hz, 1H), 2.57 (ddd, *J*=16.8, 8.6, 2.7 Hz, 1H), 2.63 (br s, 1H), 3.64 (dd, *J*=11.5, 4.6 Hz, 1H), 3.70–3.73 (m, 2H), 3.92–4.01 (m, 2H), 7.37–7.43 (m, 6H), 7.68–7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.4, 17.9, 19.2, 25.2, 25.7, 26.9, 30.3, 42.4, 62.0, 63.9, 70.7, 70.7, 74.9, 80.7, 127.5, 129.4, 129.4, 133.9, 133.9, 135.5; FABMS *m*/*z* 525 $(M+H)^+$, HRFABMS calcd for $C_{31}H_{48}O_3Si_2$ 525.3220, found 525.3228.

*4.2.36. (2S,3R)-3-(tert-Butyldimethylsilanyloxy)-2-[3-(tert-butyldiphenylsilanyloxy)propoxy]hex-5-yn-1-ol (**14i**).* In the same procedure for **14g**, **13i** (650 mg, 1.29 mmol), trimethylsilylacetylene (455 μL, 3.22 mmol), THF (13 mL), ^{n}BuLi (1.56 M hexane solution, 1.90 mL, 3.0 mmol), $BF_3\cdot Et_2O$ (180 μL, 1.42 mmol) gave a colorless oil (700 mg, 100%). Then, the compound obtained above (740 mg, 1.29 mmol), CH_2Cl_2 (5 mL), *N*,*N*-diisopropylethylamine (337 μL, 1.94 mmol) and TBSOTf (370 μL, 1.61 mmol) gave a colorless oil (880 mg, 95%). Then, the compound obtained above (860 mg, 1.20 mmol), MeOH (5 mL), K_2CO_3 (497 mg, 3.60 mmol) afforded **14i** (700 mg, 95% in three steps) as a colorless oil: $[\alpha]_D^{22}$ −11.6 (*c* 0.31, $CHCl_3$); IR (neat) 3312, 2930, 2361, 1256, 1111, 837, 777, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.15 (s, 3H), 0.94 (s, 9H), 1.10 (s, 9H), 1.84 (m, 2H), 1.99 (dd, *J*=2.6, 2.6 Hz, 1H), 2.30 (br s, 1H), 2.45 (ddd, *J*=11.2, 5.6, 2.6 Hz, 1H), 2.52 (ddd, *J*=11.2, 4.6, 2.6 Hz, 1H), 3.51 (m, 1H), 3.71–3.83 (m, 6H), 3.92 (m, 1H), 7.38–7.44 (m, 6H), 7.70–7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 19.2, 24.1, 25.8, 26.9, 32.9, 60.7, 67.1, 70.4, 70.4, 80.9, 81.1, 127.5, 129.5, 133.6, 133.6, 135.4; FABMS *m*/*z* 563 $(M+Na)^+$, HRFABMS calcd for $C_{31}H_{48}NaO_4Si_2$ 563.2989, found 563.2994.

*4.2.37. (2R,3R)-3-(tert-Butyldimethylsilanyloxy)-2-methylhex-5-ynal (**15g**).* To a solution of **14g** (310 mg, 1.28 mmol) in DMSO (7 mL) was added triethylamine (2.50 mL, 17.9 mmol) and $SO_3\cdot Py$ (1.43 g, 8.96 mmol) at 0 °C and stirred at room temperature for 4 h. The reaction was quenched by aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=100/1 to 50/1) to give **15g** (237 mg, 77%) as a colorless oil: $[\alpha]_D^{24}$ −48.7 (*c* 1.69, $CHCl_3$); IR (neat) 3312, 2932, 2859, 1711, 1256, 1103, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.09 (d, *J*=7.1 Hz, 3H), 2.00–2.02 (m, 1H), 2.40 (ddd, *J*=16.8, 5.1, 2.9 Hz, 1H), 2.47 (ddd, *J*=16.8, 7.1, 2.7 Hz, 1H), 2.68–2.73 (m, 1H), 3.99–4.04 (m, 1H), 9.79 (d, *J*=2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.4, 10.7, 18.0, 25.5, 25.6, 50.6, 71.3, 72.3, 80.0, 203.9; FABMS *m*/*z* 263 $(M+Na)^+$, HRFABMS calcd for $C_{13}H_{24}NaO_2Si$ 263.1522, found 263.1530.

*4.2.38. (2R,3R)-3-(tert-Butyldimethylsilanyloxy)-2-[3-(tert-butyldiphenylsilanyloxy)propyl]hex-5-ynal (**15h**).* In the same procedure for **15g**, **15h** (216 mg, 99 %) was obtained from **14h** (250 mg, 0.476 mmol), DMSO (3 mL), triethylamine (0.93 mL, 6.66 mmol) and $SO_3\cdot Py$ (531 mg, 3.33 mmol). Colorless oil; $[\alpha]_D^{22}$ −19.1 (*c* 1.38, $CHCl_3$); IR (neat) 3312, 2932, 2859, 1725, 1256, 1111, 837, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.07 (s, 9H), 1.54–1.68 (m, 3H), 1.89–1.97 (m, 1H), 2.02 (dd, *J*=2.7, 2.4 Hz, 1H), 2.41–2.53 (m, 2H), 2.57–2.60 (m, 1H), 3.70 (t, *J*=5.9 Hz, 2H), 4.05–4.10 (m, 1H), 7.38–7.46 (m, 6H), 7.68–7.70 (m, 4H), 9.77 (d, *J*=3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.3, 18.0, 19.2, 22.9, 25.7, 26.0, 26.9, 30.2, 55.7, 63.4, 71.3, 71.3, 72.1, 80.1, 127.5, 129.5, 133.7, 133.7, 135.4, 204.3; FABMS *m*/*z* 545 $(M+Na)^+$, HRFABMS calcd for $C_{31}H_{46}NaO_3Si_2$ 545.2831, found 545.2836.

*4.2.39. (2R,3R)-3-(tert-Butyldimethylsilanyloxy)-2-[3-(tert-butyldiphenylsilyloxy)propoxy]hex-5-ynal (**15i**).* In the same procedure for **15g**, **15i** (114 mg, 95 %) was obtained from **14i** (120 mg, 0.222 mmol), DMSO (3 mL), triethylamine (309 μL, 2.22 mmol) and $SO_3\cdot Py$ (177 mg, 1.11 mmol). Colorless oil; $[\alpha]_D^{22}$ +8.6 (*c* 1.0, $CHCl_3$); IR (neat) 3312, 2930, 2857, 1736, 1256, 1111, 839, 779, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 1.03 (s, 9H), 1.85 (m, 2H), 1.98 (dd, *J*=2.6, 2.6 Hz, 1H), 2.40 (ddd, *J*=13.2, 5.4, 2.6 Hz, 1H), 2.48 (ddd, *J*=13.2, 7.1, 2.6 Hz, 1H), 3.71 (t, *J*=6.1 Hz, 2H), 3.74 (m, 1H), 3.77 (t, *J*=5.9 Hz, 2H), 4.07 (m, 1H), 7.35–7.41 (m, 6H), 7.63–7.66 (m, 4H), 9.64 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 19.3, 23.9, 25.7, 26.9, 32.9, 60.4, 68.0, 71.2, 72.5, 80.2, 85.9, 127.6, 129.5, 129.5, 133.7, 133.7, 135.4, 203.2; FABMS *m*/*z* 561 $(M+Na)^+$, HRFABMS calcd for $C_{31}H_{46}NaO_4Si_2$ 561.2832, found 561.2837.

*4.2.40. (4S,5R)-5-(tert-Butyldimethylsilanyloxy)-4-methyloct-1-en-7-yn-3-ol (**16g**).* To a solution of **15g** (450 mg, 1.87 mmol) in THF (12 mL) was added vinylmagnesium chloride (1.44 M THF solution, 3.9 mL, 5.61 mmol) at −78 °C and the whole mixture was gradually warmed to −30 °C over 1.5 h. The reaction was quenched by aqueous NH_4Cl at 0 °C, and the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=50/1 to 30/1) to give **16gα** (230 mg, 46%) and **16gβ** (235 mg, 47%) as each colorless oil. Compound **16gα**: $[\alpha]_D^{24}$ −24.2 (*c* 0.69, $CHCl_3$); IR (neat) 3310, 2934, 1468, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 0.95 (d, *J*=7.1 Hz, 3H), 1.94–2.01 (m, 2H), 2.46 (ddd, *J*=17.1, 4.9, 2.7 Hz, 1H), 2.57 (ddd, *J*=17.1, 8.3, 2.7 Hz, 1H), 3.90–3.93 (m, 1H), 4.59–4.61 (m, 1H), 5.12–5.15 (m, 1H), 5.25–5.31 (m, 1H), 5.81 (ddd, *J*=17.1, 10.5, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.4, 10.9, 17.9, 25.3, 25.8, 39.9, 70.8, 71.0, 75.6, 80.3, 114.3, 139.5; FABMS *m*/*z* 269 $(M+H)^+$, HRFABMS calcd for $C_{15}H_{28}O_2Si$ 269.1937, found 269.1927. Compound **16gβ**: $[\alpha]_D^{24}$ −33.2 (*c* 0.69, $CHCl_3$); IR (neat) 3310, 2934, 1479, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.86 (d, *J*=7.1 Hz, 3H), 0.90 (s, 9H), 1.93–1.99 (m, 2H), 2.36 (ddd, *J*=16.9, 5.4, 2.7 Hz, 1H), 2.53 (ddd, *J*=16.9, 5.9, 2.4 Hz, 1H), 3.88–3.95 (m, 1H), 4.08 (dd, *J*=7.1, 7.1 Hz, 1H), 5.13–5.16 (m, 1H), 5.23–5.27 (m, 1H), 5.83–5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.3, 13.1, 18.1, 25.1, 25.8, 42.9, 70.3, 74.1, 75.5, 81.5, 115.6,

139.4; FABMS *m/z* 269 $(M+H)^+$, HRFABMS calcd for $C_{15}H_{28}O_2Si$ 269.1937, found 269.1935.

*4.2.41. (4S,5R)-5-(tert-Butyldimethylsilanyloxy)-4-[3-(tert-butyldiphenylsilanyloxy)propyl]oct-1-en-7-yn-3-ol (**16h**).* In the same procedure for **16g**, **16hβ** (123 mg, 58%) and **16hα** (37 mg, 37%) were obtained from **15h** (200 mg, 0.38 mmol), THF (3 mL), vinylmagnesium chloride (1.44 M THF solution, 1.33 mL, 1.90 mmol). Colorless oil (**16hβ**); $[\alpha]_D^{22}$ −9.2 (*c* 1.46, $CHCl_3$); IR (neat) 3320, 2932, 1256, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 1.06 (s, 9H), 1.44–1.55 (m, 2H), 1.77 (m, 1H), 1.65–1.73 (m, 2H), 2.00 (dd, *J*=2.7, 2.4 Hz, 1H), 2.54 (ddd, *J*=16.9, 4.9, 2.4 Hz, 1H), 2.62 (ddd, *J*=16.9, 9.0, 2.7 Hz, 1H), 3.65–3.68 (m, 2H), 4.06–4.11 (m, 1H), 4.69 (m, 1H), 5.15 (m, 1H), 5.36 (m, 1H), 5.77–5.85 (m, 1H), 7.36–7.45 (m, 6H), 7.67–7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.3, 17.9, 19.2, 20.4, 25.5, 25.8, 26.9, 30.9, 44.6, 63.8, 70.8, 71.1, 73.3, 80.3, 114.3, 127.5, 129.4, 133.8, 133.9, 135.5, 139.3; FABMS *m/z* 573 $(M+Na)^+$, HRFABMS calcd for $C_{33}H_{50}O_3NaSi_2$ 573.3196, found 573.3209. Colorless oil (**16hα**); $[\alpha]_D^{22}$ −8.8 (*c* 0.75, $CHCl_3$); IR (neat) 3320, 2932, 1256, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.90 (s, 9H), 1.06 (s, 9H), 1.43–1.53 (m, 2H), 1.65–1.70 (m, 2H), 1.79 (m, 1H), 2.00 (dd, *J*=2.7, 2.7 Hz, 1H), 2.52 (ddd, *J*=16.9, 4.9, 2.7 Hz, 1H), 2.62 (ddd, *J*=16.9, 9.0, 2.7 Hz, 1H), 3.55 (br s, 1H), 3.66–3.69 (m, 2H), 4.10 (m, 1H), 4.69 (m, 1H), 5.15 (m, 1H), 5.36 (m, 1H), 5.78–5.86 (m, 1H), 7.37–7.43 (m, 6H), 7.67–7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.8, 17.9, 19.2, 20.4, 25.5, 25.8, 26.9, 30.9, 44.6, 63.8, 70.7, 70.8, 71.1, 71.1, 73.3, 80.3, 114.3, 114.4, 127.5, 129.4, 133.8, 133.9, 135.5, 139.3; FABMS *m/z* 573 $(M+Na)^+$, HRFABMS calcd for $C_{33}H_{50}NaO_3Si_2$ 573.3196, found: 573.3217.

*4.2.42. (4S,5R)-5-(tert-Butyldimethylsilanyloxy)-4-[3-(tert-butyldiphenylsilanyloxy)propoxy]oct-1-en-7-yn-3-ol (**16i**).* In the same procedure for **16g**, **16iβ** (256 mg, 58%) and **16iα** (67 mg, 15%) were obtained from **15i** (420 mg, 0.78 mmol), THF (5 mL), vinylmagnesium chloride (1.44 M THF solution, 2.71 mL, 3.5 mmol). Colorless oil **16iβ**: $[\alpha]_D^{22}$ −11.2 (*c* 4.92, $CHCl_3$); IR (neat) 3320, 2945, 1261, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.05 (s, 9H), 1.74 (m, 2H), 1.97 (t, *J*=2.7 Hz, 1H), 2.50 (dd, *J*=5.1, 2.7 Hz, 1H), 3.43 (dd, *J*=5.6, 5.4 Hz, 1H), 3.70–3.82 (m, 4H), 3.88 (m, 1H), 5.17 (m, 1H), 5.35 (m, 1H), 5.98 (ddd, *J*=17.3, 10.7, 5.6 Hz, 1H), 7.35–7.42 (m, 6H), 7.65–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.3, 18.1, 19.2, 24.2, 25.9, 26.9, 33.0, 60.7, 68.9, 70.5, 72.2, 73.3, 81.2, 83.7, 116.0, 127.5, 129.5, 133.7, 133.7, 135.5, 135.5, 137.2; FABMS *m/z* 589 $(M+Na)^+$, HRFABMS calcd for $C_{33}H_{50}NaO_4Si_2$ 589.3146, found 589.3146.

*4.2.43. (3R,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-methyloct-1-en-7-yne (**4gα**).* To a solution of **16gα** (270 mg, 1.01 mmol) in CH_2Cl_2 (6 mL) were added *N,N*-diisopropylethylamine (263 μL, 1.52 mmol) and TBSOTf (290 μL, 1.26 mmol) at 0 °C and stirred at room temperature for 1 h. After the reaction was quenched by aqueous $NaHCO_3$ at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=100/1 to 50/1) to give **4gα**[28] (385 mg, 100%) as a colorless oil.

*4.2.44. (3S,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-methyloct-1-en-7-yne (**4gβ**).* In the same procedure for **4gα**, **4gβ**[28] (415 mg, 97%) was obtained from the compounds below, **16gβ** (300 mg, 1.12 mmol), *N,N*-diisopropylethylamine (293 μL, 1.68 mmol), and TBSOTf (321 μL, 1.40 mmol) in CH_2Cl_2 (6 mL).

*4.2.45. (3S,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-[3-(tert-butyldimethylsilanyloxy)propyl]oct-1-en-7-yne (**4hβ**).* In the same procedure for **4gα**, **4hβ** (126 mg, 99%) was obtained from the compounds below, **16hβ** (105 mg, 0.190 mmol), *N,N*-diisopropylethylamine (50 μL, 0.285 mmol), and TBSOTf (55 μL, 0.356 mmol) in CH_2Cl_2 (2.5 mL). Colorless oil; $[\alpha]_D^{22}$ −4.3 (*c* 0.92, $CHCl_3$); IR (neat) 2932, 1256, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 0.92 (s, 9H), 1.07 (s, 9H), 1.35–1.45 (m, 2H), 1.62–1.72 (m, 3H), 1.94 (dd, *J*=2.7, 2.4 Hz, 1H), 2.31 (ddd, *J*=16.8, 7.6, 2.4 Hz, 1H), 2.55 (ddd, *J*=16.8, 4.3, 2.7 Hz, 1H), 3.66 (t, *J*=6.6 Hz, 2H), 4.06 (m, 1H), 4.26 (m, 1H), 5.11 (m, 1H), 5.18 (m, 1H), 5.82–5.89 (m, 1H), 7.37–7.44 (m, 6H), 7.68–7.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.5, −4.2, −4.1, 18.1, 18.2, 19.3, 21.7, 24.3, 26.0, 26.0, 27.0, 31.8, 49.9, 64.4, 69.5, 69.5, 71.0, 73.7, 73.7, 83.0, 114.6, 127.5, 129.4, 129.4, 134.0, 134.1, 135.5, 140.2; FABMS *m/z* 687 $(M+Na)^+$, HRFABMS calcd for $C_{39}H_{64}NaO_3Si_3$ 687.4061, found 687.4084.

*4.2.46. (3S,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-4-[3-(tert-butyldimethylsilanyloxy)propoxy]oct-1-en-7-yne (**4iβ**).* In the same procedure for **4gα**, **4iβ** (273 mg, 99%) was obtained from the compounds below, **16iβ** (230 mg, 0.406 mmol), *N,N*-diisopropylethylamine (106 μL, 0.609 mmol), and TBSOTf (112 μL, 0.487 mmol) in CH_2Cl_2 (5 mL). Colorless oil; $[\alpha]_D^{22}$ −0.07 (*c* 1.38, $CHCl_3$); IR (neat) 2945, 1261, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 1.03 (s, 9H), 1.78 (m, 2H), 1.90 (t, *J*=2.6 Hz, 1H), 2.40 (ddd, J=11.2, 3.7, 2.7 Hz, 1H), 2.48 (ddd, *J*=11.2, 5.6, 2.7 Hz, 1H), 3.36 (dd, *J*=5.1, 4.6 Hz, 1H), 3.72 (m, 2H), 3.80 (m, 1H), 3.84 (m, 1H), 4.25 (m, 1H), 5.09 (m, 1H), 5.21 (m, 1H), 5.83 (ddd, *J*=16.9, 10.5, 6.4 Hz, 1H), 7.34–7.40 (m, 6H), 7.64–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.4, −4.3, −4.2, 18.1, 19.2, 19.3, 23.2, 25.9, 26.0, 26.0, 26.9, 33.5, 61.3, 69.6, 69.8, 70.9, 74.3, 82.1, 85.6, 115.9, 127.5, 127.5, 129.4, 134.0, 135.5, 138.0; FABMS *m/z* 703 $(M+Na)^+$, HRFABMS calcd for $C_{39}H_{64}NaO_4Si_3$ 703.4010, found 703.4014.

*4.2.47. (Z)-[2-{(3S,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-methylcyclohexylidene}ethyl]diphenylphosphine Oxide (**3gα**).* To a solution of **4gα** (340 mg, 0.888 mmol) in dry THF (20 mL) was added ^{n}BuLi (1.57 M hexane solution, 0.85 mL, 1.33 mmol) at −78 °C and stirred for 1 h at the same temperature. To the mixture was added paraformaldehyde (89 mg, 2.66 mmol) at −78 °C and stirred at the same temperature for 1 h. The mixture was warmed up to room temperature over 2 h, and stirred at room temperature for 2 h. To the mixture was added saturated NH_4Cl aqueous solution at 0 °C, and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give a colorless oil (345 mg, 94%). To a solution of the compound obtained above (340 mg, 0.824 mmol) in dry Et_2O (5 mL) was added Red-Al® (65% toluene solution, 0.74 mL, 2.47 mmol) at 0 °C and stirred at room temperature for 4 h. To the mixture was added ethyl acetate (0.5 mL) at 0 °C, and then cooled to −78 °C and added I_2 (627 mg, 2.47 mmol) in THF (1 mL) and stirred at the same temperature for 30 min. The mixture was warmed up to room temperature over 1.5 h and stirred for 10 min. To the mixture was diluted with Et_2O, added 10% $Na_2S_2O_3$ aqueous solution and saturated $NaHCO_3$ aqueous solution at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give a colorless oil (272 mg, 61%). To a solution of $Pd(PPh_3)_4$ (27 mg, 0.023 mmol) in dry MeCN (4 mL) was added the compound obtained above (250 mg, 0.462 mmol) in dry MeCN (1 mL) and Et_3N (0.77 mL, 0.554 mmol) at 0 °C and stirred at 90 °C for 1 h. The mixture was cooled to room temperature, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=12/1) to give a colorless oil (185 mg, 97%). To a solution of NCS (549 mg, 4.11 mmol) in dry CH_2Cl_2 (5 mL) was added

dimethylsulfide (0.30 mL, 4.11 mmol) at 0 °C, and stirred at the same temperature for 15 min. To the mixture was added the compound obtained above (170 mg, 0.411 mmol) in dry CH_2Cl_2 (2 mL) at −16 °C and stirred for 1.5 h at the same temperature. The mixture was warmed up to 0 °C, added water at the same temperature, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by short column chromatography on silica gel (hexane/AcOEt/TEA=100/10/1) to give a crude product of allyl chloride. To a solution of Ph_2PH (0.215 mL, 1.23 mmol) in dry THF (5 mL) was added ^{n}BuLi (1.57 M hexane solution, 0.785 mL, 1.23 mmol) at 0 °C and stirred for 10 min at the same temperature. To another flask charged the crude allyl chloride in dry THF (2 mL) was added the above lithium diphenylphosphide solution at −78 °C and stirred at the same temperature for 10 min. To the mixture was added water at −78 °C and warmed up to 0 °C. The resulting mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (2 mL). To the mixture was added 35% H_2O_2 aqueous solution (2 mL) at 0 °C. After stirring for 1.5 h at 0 °C, to the mixture was added water at the same temperature and extracted with CH_2Cl_2. The organic layer was washed with 2 N Na_2SO_3 aqueous solution, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=3/2) to give **3gα** (216 mg, 49% in four steps) as an amorphous solid: $[\alpha]_D^{24}$ −14.5 (*c* 5.77, $CHCl_3$); IR (neat) 2920, 1466, 1370, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H), −0.05 (s, 3H), −0.02 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 0.88 (s, 9H), 0.91 (d, *J*=7.1 Hz, 3H), 1.70–1.74 (m, 1H), 2.22 (m, 2H), 3.10–3.19 (m, 1H), 3.29–3.38 (m, 1H), 3.97 (m, 2H), 4.72 (m, 1H), 5.09 (m, 1H), 5.25–5.30 (m, 1H), 7.42–7.46 (m, 6H), 7.67–7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.9, −4.4, 13.6, 14.1, 18.1, 22.6, 25.8, 30.9, 31.5, 43.5, 45.7, 70.9, 75.4, 110.9, 114.2, 114.3, 128.3, 128.4, 130.8, 130.9, 131.5, 131.6, 132.1, 133.1, 133.2, 141.3, 141.4, 146.8; FABMS *m*/*z* 597 $(M+H)^+$, HRFABMS calcd for $C_{34}H_{54}O_3PSi_2$ 597.3349, found 597.3372.

*4.2.48. (Z)-[2-{(3R,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-methylcyclohexylidene}ethyl]diphenylphosphine Oxide (**3gβ**).* In the same procedure for **3gα**, **4gβ** (330 mg, 0.862 mmol), ^{n}BuLi (1.57 M hexane solution, 0.82 mL, 1.29 mmol), THF (20 mL), and paraformaldehyde (86 mg, 2.58 mmol) gave a colorless oil (344 mg, 93%). Then, the compound obtained above (330 mg, 0.80 mmol), Et_2O (5 mL), Red-Al® (65% toluene solution, 0.72 mL, 2.40 mmol), ethyl acetate (0.5 mL), I_2 (609 mg, 2.40 mmol), and THF (2 mL) gave a colorless oil (319 mg, 74%). Then, $Pd(PPh_3)_4$ (32 mg, 0.027 mmol), MeCN (5 mL), the compound obtained above (300 mg, 0.555 mmol), and Et_3N (0.093 mL, 0.666 mmol) gave a colorless oil (219 mg, 95%). Then, NCS (645 mg, 4.83 mmol), CH_2Cl_2 (13 mL), dimethylsulfide (0.355 mL, 4.83 mmol), the compound obtained above (200 mg, 0.483 mmol), Ph_2PH (0.252 mL, 1.44 mmol), THF (8 mL), ^{n}BuLi (1.57 M hexane solution, 0.92 mL, 1.44 mmol), and 35% H_2O_2 aqueous solution (2 mL) afforded **3gβ** (250 mg, 57% in four steps) as an amorphous solid; $[\alpha]_D^{24}$ +63.6 (*c* 2.85, $CHCl_3$); IR (neat) 2934, 1468, 1379, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.01 (s, 6H), 0.75 (d, *J*=6.8 Hz, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 2.01–2.10 (m, 2H), 2.22–2.29 (m, 1H), 3.15–3.21 (m, 1H), 3.26–3.32 (m, 1H), 3.51–3.54 (m, 1H), 3.69 (m, 1H), 4.84 (m, 1H), 5.27 (m, 1H), 5.42–5.47 (m, 1H), 7.45–7.54 (m, 6H), 7.65–7.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.9, −4.8, −4.7, 5.0, 18.2, 18.3, 25.9, 29.7, 31.1, 31.8, 40.7, 44.2, 60.2, 70.4, 70.4, 72.9, 72.9, 111.5, 114.9, 115.0, 128.3, 128.4, 128.5, 128.6, 130.9, 131.0, 131.1, 131.2, 131.7, 131.8, 140.5, 140.6, 144.2, 144.2, 169.2; FABMS *m*/*z* 597 $(M+H)^+$, HRFABMS calcd for $C_{34}H_{54}O_3PSi_2$ 597.3349, found 597.3358.

*4.2.49. (Z)-[2-{(3R,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-(3-(tert-butyldimethylsilanyloxy)propyl) cyclohexylidene}ethyl]diphenylphosphine Oxide (**3hβ**).* In the same procedure for **3gα**, **4hβ** (205 mg, 0.308 mmol), ^{n}BuLi (1.57 M hexane solution, 0.29 mL, 0.462 mmol), THF (4 mL), and paraformaldehyde (31 mg, 0.924 mmol) gave a colorless oil (212 mg, 93%). Then, the compound obtained above (103 mg, 0.148 mmol), Et_2O (3 mL), Red-Al® (65% toluene solution, 0.133 mL, 0.444 mmol), ethyl acetate (0.3 mL), I_2 (112 mg, 0.444 mmol), and THF (1 mL) gave a colorless oil (63 mg, 52%). Then, $Pd(PPh_3)_4$ (4.6 mg, 0.00395 mmol), MeCN (4 mL), the compound obtained above (65 mg, 0.079 mmol), and Et_3N (0.013 mL, 0.095 mmol) gave a colorless oil (56 mg, 100%). Then, NCS (92 mg, 0.69 mmol), CH_2Cl_2 (3 mL), dimethylsulfide (0.051 mL, 0.69 mmol), the compound obtained above (48 mg, 0.069 mmol), Ph_2PH (0.038 mL, 0.207 mmol), THF (3 mL), ^{n}BuLi (1.57 M hexane solution, 0.132 mL, 0.207 mmol), and 35% H_2O_2 aqueous solution (0.5 mL) afforded **3hβ** (45 mg, 27% in four steps) as an amorphous solid; $[\alpha]_D^{22}$ +19.1 (*c* 1.92, $CHCl_3$); IR (neat) 2950, 1644, 1250, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.01 (s, 6H), 0.85 (s, 9H), 0.91 (s, 9H), 1.02 (s, 9H), 1.34–1.36 (m, 2H), 1.65–1.80 (m, 2H), 1.86 (m, 1H), 2.09 (dd, *J*=13.2, 4.6 Hz, 1H), 2.23 (m, 1H), 3.13–3.33 (m, 2H), 3.57–3.60 (m, 3H), 3.76 (m, 1H), 4.82 (s, 1H), 5.26 (s, 1H), 5.41–5.47 (m, 1H), 7.32–7.54 (m, 12H), 7.64–7.74 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −5.0, −4.7, −4.7, 18.2, 18.4, 18.4, 19.2, 25.9, 25.9, 26.9, 29.7, 31.2, 31.9, 34.0, 41.6, 49.6, 64.9, 71.0, 73.6, 111.6, 114.9, 114.9, 127.4, 128.3, 128.4, 128.5, 128.6, 129.3, 130.9, 131.0, 131.1, 131.2, 131.7, 131.8, 134.2, 135.5, 140.4, 140.5, 144.6, 144.6; FABMS *m*/*z* 901 $(M+Na)^+$, HRFABMS calcd for $C_{52}H_{75}NaO_4PSi_3$ 901.4608, found 901.4622.

*4.2.50. (Z)-[2-{(3S,4R,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-2-methylene-4-(3-(tert-butyldimethylsilanyloxy)propoxy)cyclohexylidene}ethyl]diphenylphosphine Oxide (**3iβ**).* In the same procedure for **3gα**, **4iβ** (270 mg, 0.396 mmol), ^{n}BuLi (1.57 M hexane solution, 0.38 mL, 0.594 mmol), THF (4.5 mL), and paraformaldehyde (45 mg, 1.19 mmol) gave a colorless oil (255 mg, 90%). Then, the compound obtained above (255 mg, 0.359 mmol), Et_2O (4 mL), Red-Al® (65% toluene solution, 0.323 mL, 1.08 mmol), ethyl acetate (0.4 mL), I_2 (273 mg, 1.08 mmol), and THF (1 mL) gave a colorless oil (142 mg, 47%). Then, $Pd(PPh_3)_4$ (9.2 mg, 0.008 mmol), MeCN (4.5 mL), the compound obtained above (133 mg, 0.158 mmol), and Et_3N (0.027 mL, 0.19 mmol) gave a colorless oil (106 mg, 94%). Then, NCS (107 mg, 0.8 mmol), CH_2Cl_2 (3 mL), dimethylsulfide (0.059 mL, 0.8 mmol), the compound obtained above (57 mg, 0.08 mmol), Ph_2PH (0.042 mL, 0.24 mmol), THF (3.5 mL), ^{n}BuLi (1.57 M hexane solution, 0.153 mL, 0.24 mmol), and 35% H_2O_2 aqueous solution (0.5 mL) afforded **3iβ** (51 mg, 28% in four steps) as an amorphous solid; $[\alpha]_D^{22}$ +32.7 (*c* 0.62, $CHCl_3$); IR (neat) 2945, 1649, 1261, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 3H), −0.01 (s, 3H), 0.03 (s, 6H), 0.84 (s, 9H), 0.89 (s, 9H), 1.00 (s, 9H), 1.80 (m, 2H), 2.04 (dd, *J*=12.7, 3.9 Hz, 1H), 2.53 (m, 1H), 3.13 (m, 1H), 3.30 (m, 1H), 3.41 (m, 2H), 3.59 (m, 1H), 3.68–3.78 (m, 4H), 4.77 (br s, 1H), 5.24 (br s, 1H), 5.47 (m, 1H), 7.30–7.50 (m, 12H), 7.61–7.73 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, −4.6, 18.2, 18.3, 19.2, 25.9, 26.9, 31.2, 31.9, 33.6, 40.6, 61.6, 70.5, 71.5, 73.5, 84.3, 112.0, 115.2, 115.3, 127.4, 128.3, 128.4, 128.5, 128.6, 129.3, 130.9, 131.0, 131.0, 131.1, 131.6, 131.8, 134.0, 135.4, 140.2, 140.3, 143.4; FABMS *m*/*z* 917 $(M+Na)^+$, HRFABMS calcd for $C_{52}H_{75}NaO_5PSi_3$, 917.4557, found 917.4559.

*4.2.51. 14-epi-1α,25-Dihydroxy-2α-methylprevitamin D_3 (**14-epi-pre-1a**).* To a solution of **3a** (166 mg, 0.273 mmol) in THF (2 mL) was added ^{n}BuLi (1.58 M hexane solution, 0.19 mL, 0.30 mmol) at −78 °C and stirred at the same temperature for 15 min. To the mixture was added **2**[17] (72 mg, 0.18 mmol) in THF (1.7 mL) at −78 °C and stirred at the same temperature for 1 h. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After the reaction was quenched by aqueous NH_4Cl at 0 °C, the mixture was extracted with AcOEt, washed with brine, dried over

Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give coupling products (62 mg, 44%) as a colorless oil. Then, to the solution of the products (60 mg, 0.051 mmol) in MeCN (5 mL) was added 10% solution of HF in MeCN (5 mL) at 0 °C and stirred at room temperature for 9 h. The aqueous layer was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1) to give a mixture of **14-*epi*-1a** and **14-*epi*-pre-1a**. The mixture were dissolved in benzene (2 mL) and stirred at 80 °C for 1 h. The solution was cooled to room temperature, and concentrated to give a crude product, which was purified by reversed-phase recycle HPLC (MeCN/H_2O=90/10) for biological assay to give **14-*epi*-pre-1a** (13 mg, 39%) as a colorless oil: $[\alpha]_D^{22}$ −11.6 (*c* 1.61, $CHCl_3$); UV (EtOH) λ_{max} 252.5 nm, λ_{min} 229.5 nm; IR (neat) 3374, 2961, 1456, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.87 (d, *J*=6.4 Hz, 3H), 0.99–1.98 (m, 34H), 2.50 (dd, *J*=16.8, 5.1 Hz, 1H), 3.65 (dt, *J*=10.0, 5.5 Hz, 1H), 3.87 (d, *J*=2.0 Hz, 1H), 5.58 (d, *J*=3.4 Hz, 1H), 5.71 (d, *J*=13.1 Hz, 1H), 5.75 (d, *J*=13.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 17.6, 19.6, 20.9, 21.8, 22.9, 28.6, 29.1, 29.5, 29.6, 33.9, 34.1, 35.7, 38.4, 41.1, 41.7, 44.3, 51.0, 51.8, 68.2, 71.1, 74.5, 125.6, 127.4, 130.4, 130.8, 132.7, 138.7; EI-LRMS *m*/*z* 430 $(M)^+$, 412, 396, 374, 350, 169; EI-HRMS calcd for $C_{28}H_{46}O_3$ 430.3446, found 430.3430.

*4.2.52. 14-epi-1α,25-Dihydroxy-2α-(3-hydroxypropyl)previtamin D$_3$ (**14-epi-pre-1b**).* In the same procedure for **14-*epi*-pre-1a**, **3b** (501 mg, 0.663 mmol), **2** (178 mg 0.452 mmol), ^{n}BuLi (1.53 M hexane solution, 0.46 mL, 0.727 mmol), and THF (13 mL) gave coupling products (219 mg, 52%), and the compound obtained above (14 mg, 0.015 mmol), 10% solution of conc. HF in MeCN (5 mL), MeCN (5 mL), and benzene (2 mL) afforded **14-*epi*-pre-1b** (3.0 mg, 41%) as a colorless oil: $[\alpha]_D^{22}$ −4.63 (*c* 1.23, $CHCl_3$); UV (EtOH) λ_{max} 251.0 nm, λ_{min} 226.5 nm; IR (neat) 3358, 2928, 1458, 1377, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.94 (d, *J*=6.3 Hz, 3H), 1.11–2.05 (m, 34H), 2.52–2.57 (m, 2H), 3.11 (br s, 1H), 3.69 (m, 1H), 4.01 (d, *J*=3.4 Hz, 1H), 5.63 (t, *J*=3.3 Hz, 1H), 5.71 (d, *J*=13.6 Hz, 1H), 5.81 (d, *J*=13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 19.6, 20.6, 21.6, 22.6, 23.0, 28.5, 29.0, 29.3, 29.7, 29.8, 33.8, 34.1, 35.7, 38.9, 41.3, 44.4, 46.8, 50.8, 50.9, 62.7, 67.1, 71.2, 71.5, 125.7, 127.4, 130.3, 131.1, 132.9, 138.9; EI-LRMS *m*/*z* 457 $(M\text{-}OH)^+$, 438, 420, 379, 145, 59; EI-HRMS calcd for $C_{30}H_{49}O_3$ $(M\text{-}OH)^+$ 457.3682, found 457.3686.

*4.2.53. 14-epi-1α,25-Dihydroxy-2α-(3-hydroxypropoxy)previtamin D$_3$ (**14-epi-pre-1c**).* In the same procedure for **14-*epi*-pre-1a**, **3c** (203 mg, 0.256 mmol), **2** (70 mg, 0.178 mmol), ^{n}BuLi (1.58 M hexane solution, 0.18 mL, 0.284 mmol), and THF (3.4 mL) gave coupling products (89 mg, 55%), and the compound obtained above (42 mg, 0.044 mmol), 10% solution of HF in MeCN (5 mL), MeCN (5 mL), and benzene (2 mL) afforded **14-*epi*-pre-1c** (9.0 mg, 42%) as a colorless oil: $[\alpha]_D^{22}$ −2.46 (*c* 33.9, $CHCl_3$); UV (EtOH) λ_{max} 250.5 nm, λ_{min} 227.0 nm; IR (neat) 3385, 2953, 1377, 1215, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 0.95 (d, *J*=6.4 Hz, 3H), 1.02–2.05 (m, 32H), 2.65 (dd, *J*=17.0, 5.7 Hz, 1H), 2.72 (br s, 1H), 3.23 (dd, *J*=10.0, 4.2 Hz, 1H), 3.74 (m, 1H), 3.85 (t, *J*=5.6 Hz, 2H), 3.89–3.96 (m, 2H), 4.22 (d, *J*=4.2 Hz, 1H), 5.65 (t, *J*=3.3 Hz, 1H), 5.79 (d, *J*=13.2 Hz, 1H), 5.81 (d, *J*=13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 19.5, 20.6, 21.7, 23.0, 28.5, 28.9, 29.2, 29.8, 31.9, 33.9, 34.0, 35.8, 36.3, 41.3, 44.3, 51.0, 60.8, 65.7, 68.0, 69.0, 71.1, 83.1, 100.5, 125.9, 127.0, 128.7, 131.1, 133.1, 138.5; EI-LRMS *m*/*z* 490 $(M)^+$, 472, 454, 378, 145, 59; EI-HRMS calcd for $C_{30}H_{50}O_5$ 490.3658, found 490.3662.

*4.2.54. 14-epi-1α,25-Dihydroxy-2α-butylprevitamin D$_3$ (**14-epi-pre-1d**).* In the same procedure for **14-*epi*-pre-1a**, **3d** (280 mg, 0.437 mmol), **2** (115 mg, 0.299 mmol), ^{n}BuLi (1.57 M hexane solution, 0.31 mL, 0.487 mmol), and THF (9 mL) gave coupling products (58 mg, 24%), and the compound obtained above (58 mg, 0.070 mmol), TBAF (1.0 M THF solution, 1.4 mL, 1.40 mmol), and THF (7 mL) afforded **14-*epi*-pre-1d** (32 mg, 96%) as a colorless oil: $[\alpha]_D^{18}$ −17.7 (*c* 1.15, $CHCl_3$); UV (EtOH) λ_{max} 248.0 nm, λ_{min} 234.5 nm; IR (neat) 3376, 2955, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90–0.95 (m, 10H), 1.15 (m, 1H), 1.22–1.86 (m, 30H), 1.96–2.04 (m, 4H), 2.57 (dd, *J*=16.8, 4.9 Hz, 1H), 3.73 (ddd, *J*=9.5, 9.5, 5.1 Hz, 1H), 4.40 (br s, 1H), 5.64 (t, *J*=3.3 Hz, 1H), 5.78 (d, *J*=12.9 Hz, 1H), 5.82 (d, *J*=12.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 17.8, 19.6, 20.9, 21.8, 22.9, 23.2, 25.9, 28.8, 29.1, 29.3, 29.5, 29.6 33.9, 34.1, 35.8, 38.8, 41.1, 44.3, 46.7, 51.1, 51.8, 67.5, 71.1, 71.3, 125.6, 127.4, 130.4, 130.8, 132.8, 138.7; EI-LRMS *m*/*z* 472 $(M)^+$, 436, 418, 267, 155; EI-HRMS calcd for $C_{31}H_{52}O_3$ 472.3916, found 472.3939.

*4.2.55. 14-epi-1α,25-Dihydroxy-2α-phenylprevitamin D$_3$ (**14-epi-pre-1e**).* In the same procedure for **14-epi-pre-1a, 3e** (44.0 mg, 67 μmol), **2** (18 mg, 44 μmol), ^{n}BuLi (1.57 M hexane solution, 50 μL, 80 μmol), and THF (1.2 mL) gave coupling products (3 mg, 9%), and the compound obtained above (3 mg, 0.0035 mmol), TBAF (1.0 M THF solution, 70 μL, 70 μmol), and THF (0.7 mL) afforded **14-epi-pre-1e** (1.0 mg, 81%) as a colorless oil: $[\alpha]_D^{23}$ −37.9 (*c* 0.092, $CHCl_3$); UV (EtOH) λ_{max} 251.0 nm, λ_{min} 229.0 nm; IR (neat) 3374, 1730, 1466, 1375, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.83–2.34 (m, 32H), 2.86 (dd, *J*= 3.4, 11.5 Hz, H), 4.07–4.12 (m, H), 4.43 (ddd, *J*= 5.5, 10.3, 10.3 Hz, H), 5.32 (s, H), 5.71 (s, H), 5.77–5.79 (m, H), 5.83 (d, *J*= 6.6 Hz, 2H), 7.33–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2 (2C), 13.9, 17.6, 22.5, 22.7, 28.9, 29.1, 29.3, 29.4, 29.5, 29.5, 31.7 (3C), 33.7, 40.8, 44.1, 51.0, 55.1, 64.7, 70.8, 73.8, 76.6, 76.7, 77.1, 77.1, 77.2, 122.3, 128.8 (2C), 129.3, 131.0; EI-LRMS *m*/*z* 515 $(M)^+$, EI-HRMS calcd for $C_{33}H_{48}O_3$ 515.3501, found 515.3481.

*4.2.56. 14-epi-1α,25-Dihydroxy-2α-benzylprevitamin D$_3$ (**14-epi-pre-1f**).* In the same procedure for **14-*epi*-pre-1a**, **3f** (330 mg, 0.490 mmol), **2** (129 mg, 0.326 mmol), ^{n}BuLi (1.57 M hexane solution, 0.34 mL, 0.534 mmol), and THF (13 mL) gave coupling products (162 mg, 59%), and the compound obtained above (89 mg, 0.105 mmol), TBAF (1.0 M THF solution, 2.1 mL, 2.1 mmol), and THF (9.6 mL) afforded **14-*epi*-pre-1f** (49 mg, 92%) as a colorless oil: $[\alpha]_D^{23}$ −21.1 (*c* 8.08, $CHCl_3$); UV (EtOH) λ_{max} 251.5 nm, λ_{min} 227.0 nm; IR (neat) 3387, 2951, 1636, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.95 (d, *J*=6.4 Hz, 3H), 1.06–1.56 (m, 21H), 1.78–1.89 (m, 4H), 1.99–2.08 (m, 5H), 2.64 (dd, *J*=16.9, 4.6 Hz, 1H), 2.75 (dd, *J*=13.5, 11.1 Hz, 1H), 3.20 (dd, *J*=13.5, 4.5 Hz, 1H), 3.69 (br s, 1H), 3.87 (ddd, *J*=10.1, 10.1, 5.5 Hz, 1H), 5.63 (t, *J*=3.5 Hz, 1H), 5.78 (d, *J*=12.8 Hz, 1H), 5.81 (d, *J*=12.8 Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 19.5, 20.7, 21.8, 22.9, 28.8, 29.1, 29.3, 29.8, 32.6, 34.0, 35.8, 38.9, 41.2, 44.3, 49.0, 51.2, 51.4, 67.3, 70.7, 71.2, 125.6, 125.8, 127.3, 128.4, 129.1, 130.4, 130.8, 132.9, 138.6, 140.6; EI-LRMS *m*/*z* 506 $(M)^+$, 470, 452, 379, 195, 91; EI-HRMS calcd for $C_{34}H_{50}O_3$ 506.3761, found 506.3760.

*4.2.57. 14-epi-1α,25-Dihydroxy-2β-methylprevitamin D$_3$ (**14-epi-pre-1gα**).* In the same procedure for **14-*epi*-pre-1a**, **3gα** (210 mg, 0.351 mmol), **2** (92 mg, 0.234 mmol), ^{n}BuLi (1.57 M hexane solution, 246 μL, 0.386 mmol), and THF (6 mL) gave coupling products (66 mg, 37%), and the compound obtained above (36 mg, 0.046 mmol), TBAF (0.92 mL, 1.0 M THF solution, 0.92 mmol), and THF (4 mL) afforded **14-*epi*-pre-1gα** (20 mg, 100%) as a colorless oil: $[\alpha]_D^{23}$ −18.4 (*c* 0.038, $CHCl_3$); UV (EtOH) λ_{max} 252.5 nm, λ_{min} 227.0 nm; IR (neat) 3370, 2961, 1456, 1379 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 1.01 (s, 3H), 1.02 (d, *J*=6.3 Hz, 3H), 1.03 (d, *J*=6.9 Hz, 3H), 1.15 (s, 3H), 1.15 (s, 3H), 1.32–1.62 (m, 10H), 1.86 (s, 3H), 1.87–2.04 (m, 3H), 2.07 (m, 2H), 2.15–2.21 (m 2H), 2.48–2.51 (m, 1H), 3.77 (d, *J*=4.4 Hz, 1H), 4.06 (m, 1H), 5.83, (m, 1H), 5.91 (d, *J*=12.1 Hz, 1H), 5.94 (d, *J*=12.1 Hz, 1H); ^{13}C NMR (150 MHz, C_6D_6)

δ 11.8, 14.2, 17.3, 19.9, 21.2, 22.0, 23.2, 28.9, 29.3, 29.8, 29.9, 34.3, 34.5, 35.2, 36.3, 41.5, 42.0, 44.6, 51.4, 52.2, 67.4, 70.4, 75.8, 125.9, 128.4, 128.6, 129.9, 132.7, 139.3; FABMS *m*/*z* 453 $(M+Na)^+$, HRFABMS calcd for $C_{28}H_{46}NaO_3$ 453.3345, found 453.3363.

*4.2.58. 14-epi-1β,25-Dihydroxy-2β-methylprevitamin D₃ (**14-epi-pre-1gβ**).* In the same procedure for **14-*epi*-pre-1a**, **3gβ** (198 mg, 0.331 mmol), **2** (87 mg, 0.221 mmol), ^{n}BuLi (1.57 M hexane solution, 232 μL, 0.364 mmol), and THF (7 mL) gave coupling products (84 mg, 49%), and the compound obtained above (29 mg, 0.0375 mmol), TBAF (0.75 mL, 1.0 M THF solution, 0.75 mmol), and THF (3 mL) afforded **14-*epi*-pre-1gβ** (16 mg, 100%) as a colorless oil: $[\alpha]_D^{23}$ −35.4 (*c* 0.54, $CHCl_3$); UV (EtOH) λ_{max} 252.5 nm, λ_{min} 227.0 nm; IR (neat) 3370, 2961, 1456, 1379 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 1.03 (d, *J*=6.2 Hz, 3H), 1.05 (s, 3H), 1.12 (s, 3H), 1.12 (s, 3H), 1.22 (d, *J*=7.2 Hz, 3H), 1.33–1.55 (m, 13H), 1.87–1.90 (m, 1H), 1.99 (s, 3H), 2.03–2.12 (m, 3H), 2.23–2.28 (m, 2H), 2.33 (m, 1H), 3.64 (m, 1H), 3.69 (m, 1H), 5.84, (m, 1H), 5.95 (s, 1H), 5.95 (s, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 14.5, 18.7, 20.1, 21.4, 21.9, 23.3, 29.0, 29.3, 29.8, 30.2, 34.2, 34.7, 36.4, 37.2, 38.9, 41.4, 44.6, 51.0, 52.9, 70.3, 70.8, 73.3, 126.1, 127.3, 128.5, 132.1, 132.5, 139.4; FABMS *m*/*z* 453 $(M+Na)^+$, HRFABMS calcd for $C_{28}H_{46}NaO_3$ 453.3345, found 453.3332.

*4.2.59. 14-epi-1β,25-Dihydroxy-2β-(3-hydroxypropyl)previtamin D₃ (**14-epi-pre-1hβ**).* >In the same procedure for **14-*epi*-pre-1a**, **3hβ** (45 mg, 0.051 mmol), **2** (13 mg, 0.034 mmol), ^{n}BuLi (1.57 M hexane solution, 0.036 mL, 0.056 mmol), and THF (1.5 mL) gave coupling products (13 mg, 36%), and the compound obtained above (12 mg, 0.0113 mmol), TBAF (0.23 mL, 1.0 M THF solution, 0.23 mmol), and THF (1 mL) afforded **14-*epi*-pre-1hβ** (5.4 mg, 100%) as a colorless oil; $[\alpha]_D^{22}$ +60.9 (*c* 0.023, $CHCl_3$); UV (EtOH) λ_{max} 250.0 nm, λ_{min} 227.0 nm; IR (neat) 3350, 2930, 1458, 1377, 1210 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 0.93 (d, *J*=6.3 Hz, 3H), 1.10 (m, 1H), 1.21 (s, 3H), 1.28 (s, 3H), 1.33–2.06 (m, 21H), 1.82 (s, 3H), 2.28 (m, 1H), 2.49 (m, 1H), 3.67–3.75 (m, 2H), 3.86 (m, 1H), 4.10 (m, 1H), 5.79 (d, *J*=12.2 Hz, 1H), 5.92 (d, *J*=12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 19.7, 21.0, 21.8, 22.9, 25.0, 28.7, 29.1, 29.7, 29.8, 33.8, 34.3, 35.9, 38.5, 41.1, 41.9, 44.4, 50.9, 52.4, 63.1, 69.5, 71.1, 71.4, 77.2, 125.5, 127.3, 127.8, 131.2, 132.3, 138.8; FABMS *m*/*z* 497 $(M+Na)^+$, HRFABMS calcd for $C_{30}H_{50}NaO_4$ 497.3607, found 497.3616.

*4.2.60. 14-epi-1β,25-Dihydroxy-2β-(3-hydroxypropoxy)previtamin D₃ (**14-epi-pre-1iβ**).* In the same procedure for **14-*epi*-pre-1a**, **3iβ** (50 mg, 0.056 mmol), **2** (15 mg, 0.038 mmol), ^{n}BuLi (1.57 M hexane solution, 0.39 mL, 0.061 mmol), and THF (2 mL) gave coupling products (22 mg, 57%), and the compound obtained above (18 mg, 0.0175 mmol), TBAF (0.35 mL, 1.0 M THF solution, 0.35 mmol), and THF (1.5 mL) afforded **14-*epi*-pre-1iβ** (7.4 mg, 86%) as a colorless oil: $[\alpha]_D^{23}$ −10.7 (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} 251.5 nm, λ_{min} 227.5 nm; IR (neat) 3385, 2950, 1377, 1212, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 1.10 (m, 1H), 1.21 (s, 3H), 1.21 (s, 3H), 1.22–1.60 (m, 15H), 1.74–1.78 (m, 1H), 1.78 (s, 3H), 1.87 (m, 3H), 2.02–2.06 (m, 3H), 2.41 (m, 2H), 3.00 (br s, 2H), 3.48 (m, 1H), 3.81–3.91 (m, 4H), 4.13 (m, 2H), 5.62 (m, 1H), 5.80 (d, *J*=12.9 Hz, 1H), 5.84 (d, *J*=12.9 Hz, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 17.3, 19.2, 20.3, 20.6, 22.1, 27.4, 28.1, 28.7, 29.1, 31.3, 31.4, 33.0, 33.4, 35.1, 35.5, 40.6, 43.5, 59.3, 67.6, 69.3, 77.2, 125.5, 126.6, 127.3, 127.8, 131.2, 132.1; EI-LSMS *m*/*z* 490 $(M)^+$, 472, 454, 396, 378, 324; EI-HRMS calcd for $C_{30}H_{50}O_5$ 490.3658, found 490.3667.

4.3. General procedure for VDR binding assay

[26,27-*Methyl*-^{3}H]-1α,25-dihydroxyvitamin D_3 (specific activity 6.623 TBq/mmol, 15,000 dpm, 15.7 pg) and various amounts of 1α,25-dihydroxyvitamin D_3 and the analog to be tested were dissolved in 50 μL of absolute ethanol in 12×75-mm polypropylene tubes. The chick intestinal VDR (0.2 mg) and 1 mg of gelatin in 1 mL of phosphate buffer solution (25 nM KH_2PO_4, 0.1 M KCl, and 1 mM dithiothreitol, pH 7.4) were added to each tube in an ice bath. The assay tubes were incubated in a shaking water bath for 1 h at 25 °C and then chilled in an ice bath. One milliliter of 40% polypropylene glycol 6000 in distilled water was added to each tube, which was mixed vigorously and centrifuged at 2,260×*g* for 60 min at 4 °C. After the supernatant was decanted, the bottom of the tube containing the pellet was cut off into a scintillation vial containing 10 mL of dioxane-based scintillation fluid and the radioactivity was measured with a Beckman liquid scintillation counter (Model LS6500). The relative potency of the analog was calculated from the concentration needed to displace 50% of [26,27-*methyl*-^{3}H]-1α,25-dihydroxyvitamin D_3 from the receptor compared with the activity of 1α,25-dihydroxyvitamin D_3 (assigned a 100% value).[30]

4.4. General procedure for transactivation assay of human osteocalcin promoter

The human osteocalcin gene promoter fragment −838/+10 was cloned into the reporter plasmid pGL3 (Promega) as reported.[31] Human VDR and RXR gene were cloned into expression vector pcDNA3 (Invitrogen). Hos cells maintained in phenol red free DMEM (Invitrogen) containing 10% FCS (Invitrogen). Prior to transfections, the cells were plated in a 96 well plate at the density of 400,000 cells per well in the Opti-MEM (Invitrogen). The cells were transfected with human osteocalcin reporter vector (pGL3-hOc: 100 ng/well), human VDR and RXR expression vector (pcDNA-hVDR, pcDNA-hRXR: 10 ng/well) and phRL-TK (Promega: 25 ng/well) using 0.45 μL of Lipofectamine 2000 reagent (Invitrogen). After incubation at 37 °C for 3 h, the culture media were replaced to phenol red free DMEM containing 10% FCS. The cells were treated with ethanol vehicle or various concentrations of compounds (from 0.1 pM to 100 nM). After incubation at 37 °C for 24 h, the luciferase activity of the cells was quantitated by luminometer (Berthold) using Dual-Glo luciferase assay system (Promega).

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for ten new previtamin D_3 analogs **14-*epi*-pre-1a**–**iβ**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.028.

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