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The 2α-(3-hydroxypropyl) group as an active motif in vitamin D_3 analogues as agonists of the mutant vitamin D receptor (Arg274Leu)

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Abstract—We designed and synthesized 1α- and 1β-hydroxymethyl-2α-(3-hydroxypropyl)-25-hydroxyvitamin D_3 (**2a,b**) and related analogues 2α-(3-hydroxypropyl)-25-hydroxyvitamin D_3 (**3**), Posner's analogues of 1α- and 1β-hydroxymethyl-25-hydroxyvitamin D_3 (**4a,b**), as well as 2α-(3-hydroxypropyl)-1α,25-dihydroxyvitamin D_3 (**5**), to confirm the effect of the 1α-hydroxy group and/or 2α-(3-hydroxypropyl) group of vitamin D_3 analogues with the modified A-ring moiety on the mutant vitamin D receptor, VDR(Arg274Leu). The 2α-(3-hydroxypropyl) group showed better effect on enhancement of the transcriptional activity through the mutant VDR than the 1α- and 1β-hydroxymethyl groups.

1. Introduction

1α,25-Dihydroxyvitamin D_3 (1α,25$(OH)_2D_3$, **1**) has drawn the attention of many researchers in academia and industry, because of its wide variety of biological and pharmacological activities.[1] It is well known that **1** regulates calcium and phosphate homeostasis together with parathyroid hormone (PTH) and calcitonin, and its deficiency causes osteomalacia or rickets. 1α,25$(OH)_2D_3$ has also been shown to influence cell differentiation and growth, and **1** and its analogues have been investigated as drugs for diseases such as cancer, psoriasis, immunodeficiency, and so on. Many of the functions of **1** are mediated through binding to a specific nuclear receptor, the vitamin D receptor (VDR), which is a member of steroid-thyroid hormone receptor superfamily.[2] These receptors act as transcription factors, which activate or suppress gene transcription in response to intra- or extracellular stimuli in a ligand-dependent fashion. X-ray crystal structure analysis[3] shows that **1** is anchored in the ligand binding domain (LBD) of the VDR through hydrogen bonds between hydrophilic amino acid residues and three hydroxy groups of **1**, that is, 1α-OH, 3β-OH, and 25-OH (Fig. 1). It seems reasonable that the substitution of one or more of these amino acids would reduce the affinity of **1** for the VDR. A rare genetic disease called hereditary vitamin D resistant rickets (HVDRR) has been clinically recognized to occur resulting from mutations of VDR.[4] Mutations appear in every part of the receptor, and two mutations that relate to hydrogen bond formation are known so far (His305Gln and Arg274Leu), the latter showing severe rickets. Arg274 forms hydrogen bond with 1α-OH (Fig. 1), and its substitution with hydrophobic Leu leads to detrimental loss of the affinity for **1** (ca. 1/1000 against the wild type receptor).[5] To overcome the low activity of **1** in the mutant receptor, two research groups have reported vitamin D analogues designed for the mutant receptor. Koh et al. reported 1α-O-benzylated analogues in which *O*-benzyl groups were expected to compensate for the loss of affinity by new hydrophobic interactions through the benzyl group and the resulting hydrophobic pocket of the mutant receptor.[6] Posner and co-workers

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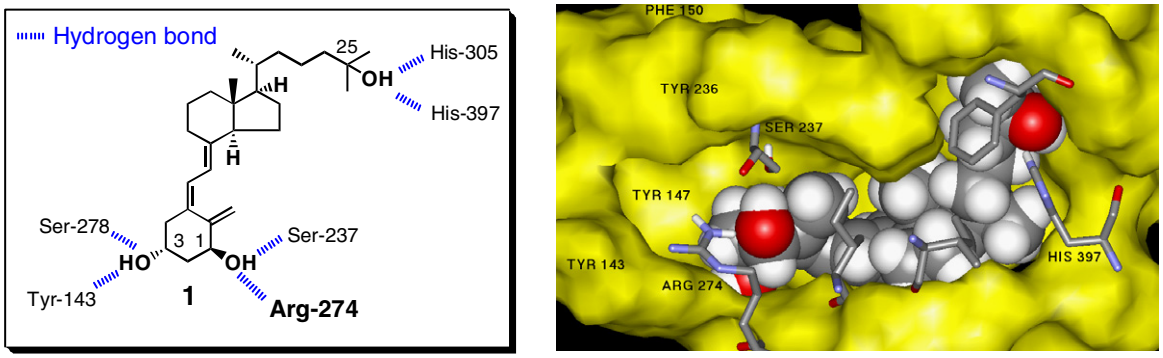


Figure 1. Crystal structure of VDR bound to 1α,25(OH)$_2$D$_3$ (**1**) by D. Moras and co-workers[3].

showed that 1-hydroxymethylated analogue has improved the vitamin D action by the mutant receptor,[7] but this restoration effect was brought about by double modification, because the side chain was also changed. In order to confirm the effect of the 1α-hydroxymethyl group on the mutant receptor, and to increase the activities of the analogues further, we designed analogues that have 2α-(3-hydroxypropyl) group, a functional group has been found in our laboratory to potentiate the vitamin D action,[8,9] with or without a 1α-hydroxymethyl group (Fig. 2). Our group has already reported that 2α-(3-hydroxypropyl)-1α,25(OH)$_2$D$_3$ (**5**) could act as a ligand for a mutant VDR(Arg274Ala), which was an artificial mutant related to the mutant VDR (Arg274Leu).[10] In the LBD of the VDR, there is a water channel connecting the A-ring part of the LBD to the surface of the VDR and forming a network of hydrogen bonds.[3] The 2α-substituent affects the presence and/or the location of the water molecules in the channel, and X-ray crystal structure demonstrated that the terminal hydroxy group of **5** acts as one of the water molecules to form hydrogen bonds with Arg274 and the other water molecule located in the ligand binding pocket (LBP) to organize the network and to enhance the binding affinity for the VDR.[11]

2. Results and discussions

2.1. Synthesis

Retrosynthetic analysis of the vitamin D derivatives, **2a,b** and **4a,b**, is shown in Scheme 1. The strategy was to use the palladium-catalyzed coupling reaction of CD-ring precursor bromoolefin **6** and A-ring synthon enynes reported by Trost et al.[12] The CD-ring precursor **6** could be prepared from vitamin D$_3$,[12] and A-ring enynes were synthesized from D-glucose. Our synthetic procedure reported recently[13] was modified in order to introduce hydroxymethyl group into the 1-position of vitamin D$_3$ framework. As shown in Scheme 2, the known sugar epoxide **7**[14] reacted with allylmagnesium chloride in THF to give allyl substituted compound in good yield. The resulting secondary hydroxy group was silylated, and then the terminal alkene was hydroborated, and oxidative workup furnished primary alcohol, which was protected as pivalate to give **8**. Stereoselective reductive ring opening reaction of benzylidene acetal was carried out by using TFA–Et$_3$SiH in the presence of molecular sieves 3A.[15] Secondary alcohol **9** was oxidized by TPAP-NMO, and then Lombardo methylenation[16] proceeded in good yield to give **10**. Hydroboration of *exo*-methylene group was carried out with BH$_3$·THF, and then oxidative workup gave a diastereomeric mixture of primary alcohols (ratio 1.3:1), which could be separated at this stage by silica gel flash column chromatography. Each isomer was transformed in the following scheme in diastereomerically pure form. The primary hydroxy group was protected as the pivalate (**11a,b**), and benzyl ether was converted to the mesylate (**12a,b**), which was subjected to a nucleophilic bromination reaction. Reductive ring opening of the bromo ether (**13a,b**) gave the primary alcohol (**14a,b**), which upon treatment with TsCl followed by TBAF furnished the epoxide (**15a,b**) in good yield. Addition of lithium acetylide to the epoxide and methanolysis of the pivalate gave the triol, which was pro-

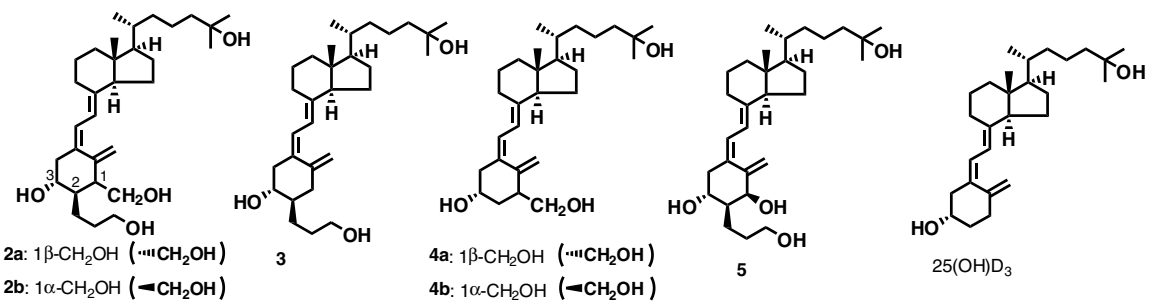
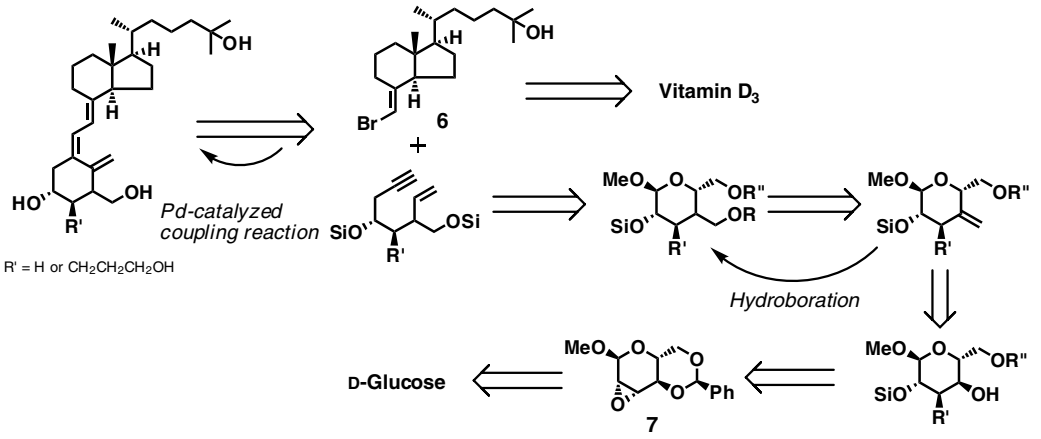
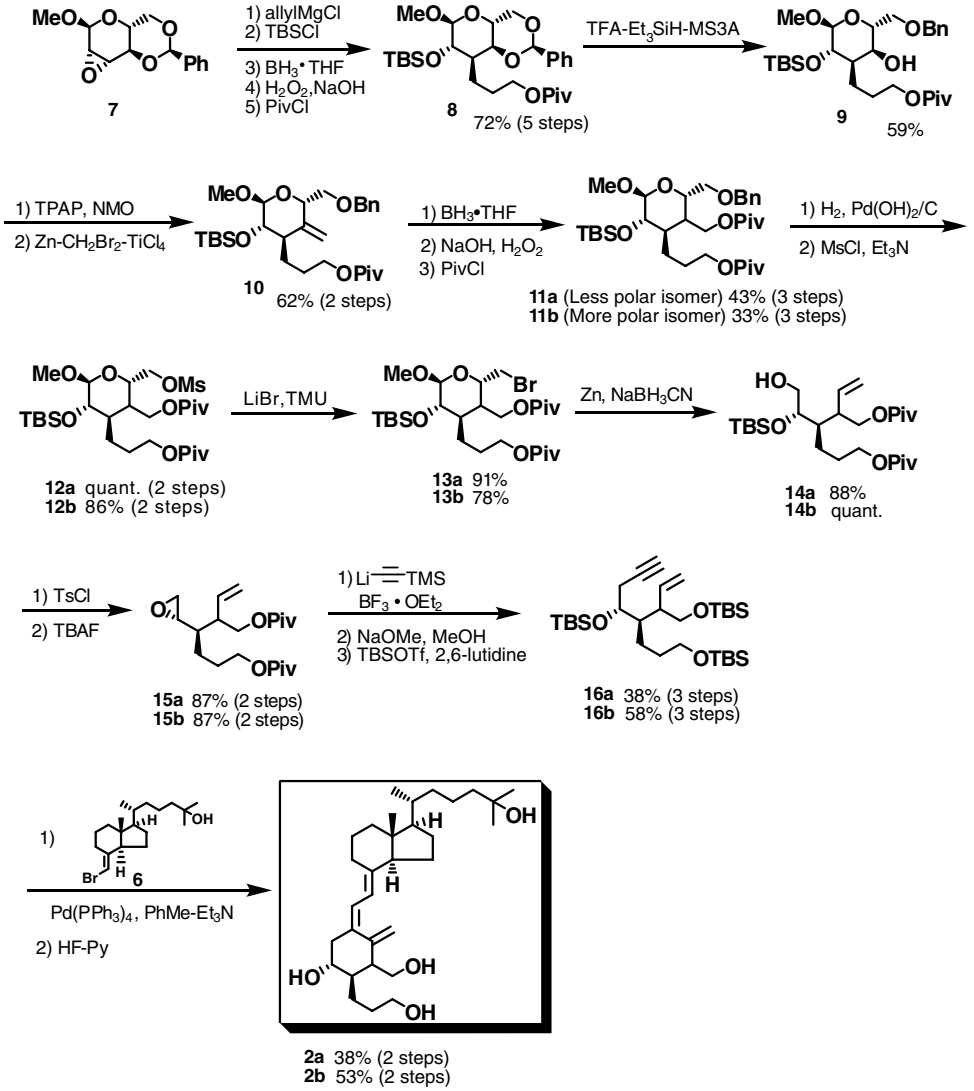


Figure 2. Structures of vitamin D$_3$ analogues tested.



Scheme 1. Retrosynthetic analysis of 1-hydroxymethylated analogues.



Scheme 2. Synthesis of 1α- and 1β-hydroxymethyl-2α-(3-hydroxypropyl)-25-hydroxyvitamin D_3 analogues **2a** and **2b**.

tected as the TBS ether (**16a,b**). Trost coupling reaction of the A-ring enyne (**16a,b**) and the CD-ring bromoolefin **6**, followed by deprotection of the TBS groups, gave the desired analogues (Scheme 2).

The stereochemistry at the 1-position could be determined by 2D NMR (HH-COSY) and NOE experiments for **2b** that was derived from **11b** (more polar isomer). NOE enhancement was observed between 3-H and meth-

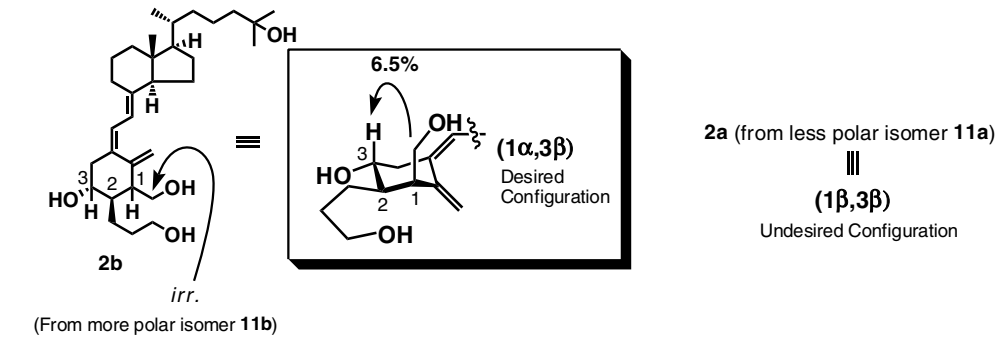
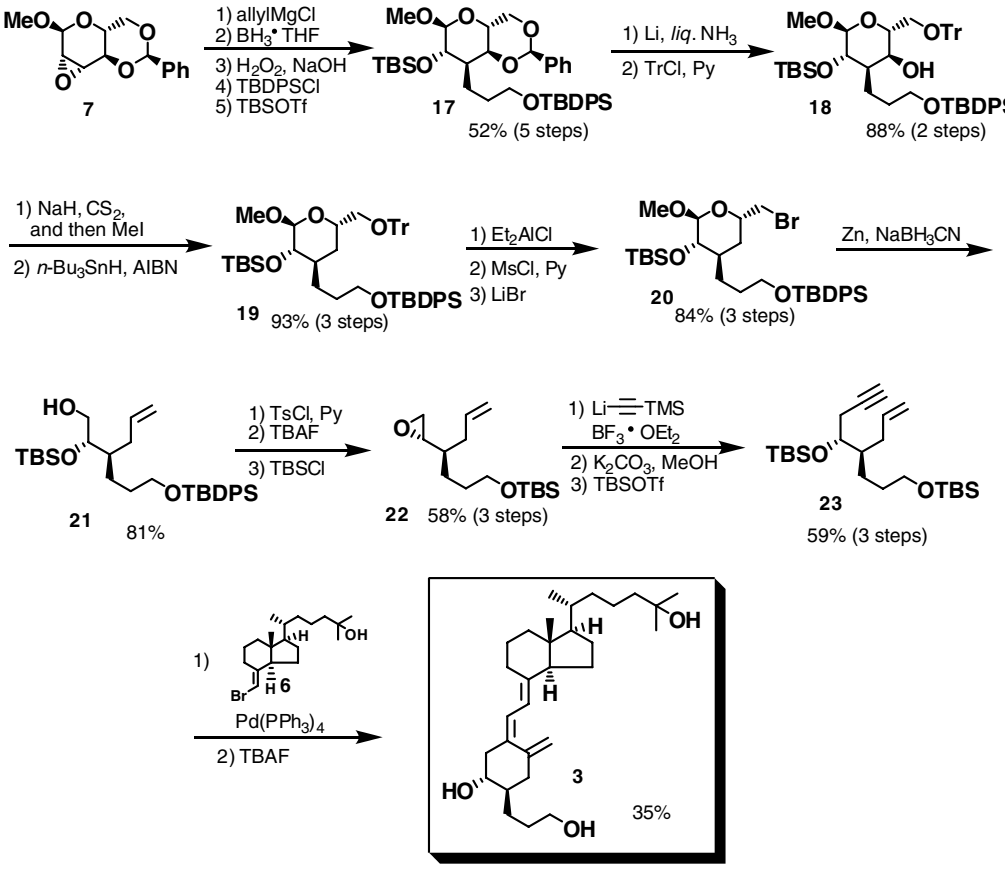


Figure 3. NOE experiments for **2b**.



Scheme 3. Synthesis of 1-unsubstituted analogue **3**.

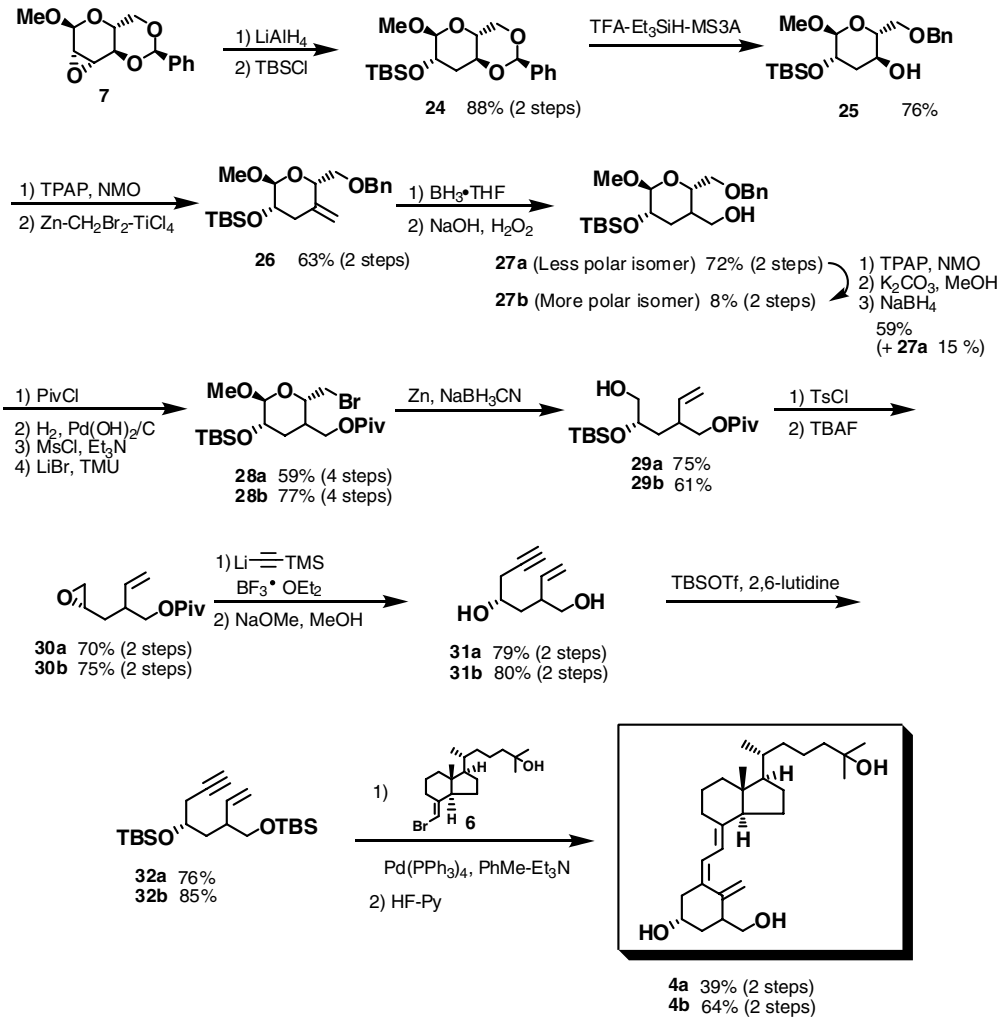
ylene protons (or one of the methylene protons) of the hydroxymethyl group at the 1-position, so this isomer must have the 1α,2α,3β-configuration and, accordingly, the other isomer must have 1β,2α,3β-stereochemistry (Fig. 3).

As a reference compound, 2α-(3-hydroxypropyl)-25-hydroxyvitamin D_3 (**3**), which does not have a 1α-OH group but does have a 2α-(3-hydroxypropyl) group, could also be prepared by the similar procedure as shown in Scheme 3. Deoxygenation at the 1-position could be achieved by way of xanthate formation and *n*-Bu_3SnH reduction.

Another reference compounds, 1-hydroxymethyl-25-hydroxyvitamin D_3 (**4a,b**), could be also prepared substantially by the same manner, except that epoxide ring opening of **7** was carried out with $LiAlH_4$[17] (Scheme 4). At the stage of hydroboration of **26**, the diastereoselectivity was relatively high (ca. 8.4:1) in contrast with the 2α-(3-hydroxypropyl) series. The configuration of the major diastereoisomer could be inverted via oxidation, epimerization, and reduction. Stereochemisty of **4a** and **4b** was similarly determined by NMR experiments (Fig. 4).

2.2. Biological testing

All synthesized analogues were purified by preparative reverse phase HPLC. Reporter assays were carried out utilizing luciferase activity. The fusion protein was used for assays, which consist of DNA-binding domain of Gal4



Scheme 4. Synthesis of 2-unsubstituted analogues **4a** and **4b**.

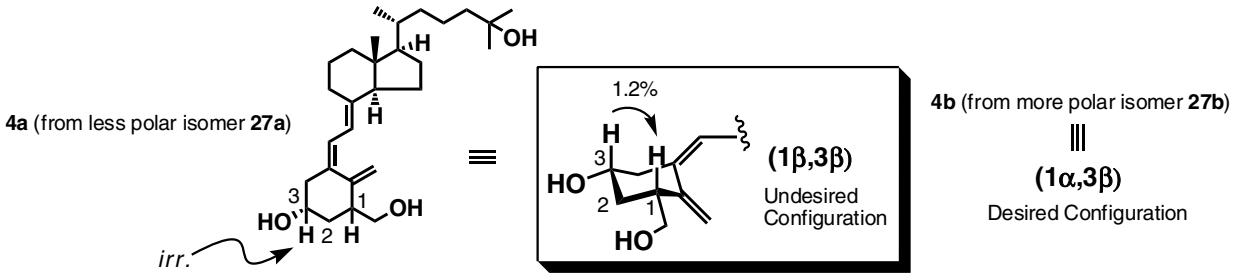


Figure 4. Determination of the stereochemistry of 2-unsubstituted analogues.

(transcription factor protein of *Saccharomyces cerevisiae*) and human VDR LBD.[18] Site-directed mutagenesis was conducted to construct the LBD of Arg274Leu, and reporter assays were carried out by using both wild type and mutant VDR. Other than the analogues synthesized above, 2α-(3-hydroxypropyl)-1α,25(OH)$_2$D$_3$ (**5**)[8b] and 25-hydroxyvitamin D$_3$ (25(OH)D$_3$) were also assayed in order to compare the effects of 1- and 2α-substituents.

As shown in Figure 5, when assays were performed on the wild type VDR, the 1-hydroxymethylated analogues (**2a,b** and **4a,b**) were found to be rather less effective than the natural hormone **1**, irrespective of the presence of the 2α-(3-hydroxypropyl) group (Table 1). The results could be expected because of steric hindrance of the 1-hydroxymethyl group. When the effect of the 2α-(3-hydroxypropyl) group was compared in the series of 1-hydroxymethylated analogues (**2a,b** and **4a,b**), the transcriptional activities were lower at 10^{-8} M by the introduction of 2α-(3-hydroxypropyl) group in both the 1α- and 1β-hydroxymethyl analogues (Table 2). The A-ring of **4a,b** might be located at the different

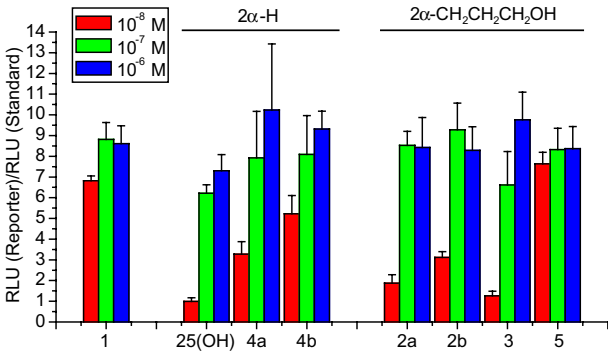


Figure 5. Reporter assays for wild type VDR ($n = 3$, means ± SD).

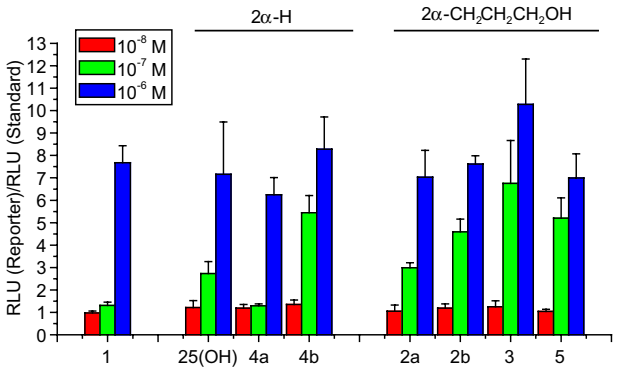


Figure 6. Reporter assays for mutant VDR(Arg274Leu) ($n = 3$, means ± SD).

position from the A-ring of **1** in the LBD, and the 2α-(3-hydroxypropyl) group of **4a,b** does not work as a positive motif for binding to the wild type VDR. Comparing the activities of **5** with its 1-deoxy analogue, **3**, the transcriptional activity of **3** was lower at 10^{-8} M, similar to the case in the 2-unsubstituted series (i.e., **1** and 25(OH)D_3), previously reported in SAR studies.[1] This confirms that the presence of the 1α-OH group is very important for vitamin D action even in the presence of the 2α-(3-hydroxypropyl) group.

When the mutant receptor (Arg274Leu) was assayed (Fig. 6), the replacement of the 1α-hydroxy group of **1** to the 1α-hydroxymethyl group (**4b**) appears to increase its transcriptional activities. While the introduction of the 1β-hydroxymethyl group (**4a**) showed little effect (Table 1). In contrast, in the 2α-substituted series, the effect of the substituent at the 1-position appeared not to be so dramatic (compare **2b**, **3**, and **5** in Figure 6 and Table 1), which may imply that an attractive interaction between the terminal OH group of the 2α-(3-hydroxypropyl) group and sites in the mutant receptor plays the dominant role, and accordingly, this substituent could represent an active motif for the mutant receptor as the 1α-OH group does for the wild type.

The recovery of the affinity by another attractive interaction was the theme of the paper published recently.[19]

The fact that the hydrogen bond between the 1α-OH group of **1** and Arg274 in the wild type receptor LBD plays an important role for vitamin D action has been supported by an X-ray diffraction study,[3] and alanine scanning mutational analysis[20] has also demonstrated the importance of the hydrogen bond. Destruction of this hydrogen bond would result in reduction of the affinity between the analogues and the mutant receptor. We planned to create a hydrophobic interaction between an alternative substituent at the 1-position and the hydrophobic cavity formed by the mutation. This approach has been formally applied by Koh's group, who synthesized and assayed 1-*O*-benzyl analogues of **1**.[6a] Posner and co-workers have reported on 1α-hydroxymethyl analogues with reduced calcemic action,[7,21] an interesting feature among the vitamin D derivatives that retain non-classical activity. We chose to model our target compounds initially on Posner's compounds and to examine the effect of a 2α-substituent on affinity to the mutant VDR. In the case of the 2-unsubstituted series, the 1α-hydroxymethyl analogue was most effective (Table 1). However, in the case of the 2α-substituted series, modification at the 1-position was not critical, that is, the activities of 1α-hydroxymethylated **2b**, 1α-unsubstituted **3**, and 1α-hydroxylated **5** were similar (Table 1). We assumed that this averaging effect of the activities of the 1-substituted analogues

Table 1. Summary of the effects of the 1α-substituent of the vitamin D_3 derivatives on the transcriptional activities mediated by wild type/mutant VDR

2α-Substituent	Wild type VDR	Mutant VDR
–$(CH_2)_3OH$	H ∼ 1β-CH_2OH ⩽ 1α-CH_2OH < 1α-OH **3** ∼ **2a** ⩽ **2b** < **5**	1β-CH_2OH < 1α-CH_2OH ∼ H ∼ 1α-OH **2a** < **2b** ∼ **3** ∼ **5**
–H	H < 1β-CH_2OH < 1α-CH_2OH < 1α-OH 25(OH)D_3 < **4a** < **4b** < **1**	1α-OH ∼ 1β-CH_2OH < H < 1α-CH_2OH **1** ∼ **4a** < 25(OH)D_3 < **4b**

Table 2. Summary of the effects of the 2α-substituent of the vitamin D_3 analogues on the transcriptional activities mediated by wild type/mutant VDR

1-Substituent	Wild type VDR	Mutant VDR
α-CH_2OH	H (**4b**) ⩾ 2α-$(CH_2)_3OH$ (**2b**)	H (**4b**) ∼ 2α-$(CH_2)_3OH$ (**2b**)
β-CH_2OH	H (**4a**) ⩾ 2α-$(CH_2)_3OH$ (**2a**)	H (**4a**) < 2α-$(CH_2)_3OH$ (**2a**)
α-OH	H (**1**) < 2α-$(CH_2)_3OH$ (**5**)	H (**1**) < 2α-$(CH_2)_3OH$ (**5**)
H	H (25(OH)D_3) ∼ 2α-$(CH_2)_3OH$ (**3**)	H (25(OH)D_3) < 2α-$(CH_2)_3OH$ (**3**)

would result from insufficiencies in promoting attractive interaction by hydrophobic interaction induced by the 1-substitution. In the absence of the 2α-(3-hydroxypropyl) group, subtle steric differences around the 1-position would be effectively recognized by the mutant receptor.[22]

As noted above, the 1α-OH group of **1** forms hydrogen bond with Arg274 of the wild type VDR, and this hydrogen bond plays an important role in the complexation of the vitamin D analogues with the receptor. This strong hydrogen bond defines the conformation of the A-ring of the vitamin D analogues in an appropriate manner, in the β-form, to form the strong complex. In the mutant VDR in which the polar Arg274 is absent, the hydrogen bond would not be formed, and the conformation of the A-ring might not necessarily be the same as that of the wild type VDR complex. This conformational change would modify the projection of the 2α-(3-hydroxypropyl) group, which could be one of the reasons for the differences of the activities of **2b** and **4b** (between in the presence and in the absence of 2α-(3-hydroxypropyl) group). That might be the case for 1-deoxy derivatives 25(OH)D_3 and **3**, in which the conformational preference might be small because of the steric effects of small substituent (H). The effect of the 1α-hydroxymethyl group would be compounded onto the conformational changes of the A-ring moiety. Hydrophobic interactions could be an important factor for complexation, but a hydrogen bond between the OH group of the 1α-hydroxymethyl group and the Ile271 would assist the conformational changes. These conformational changes are supported by molecular modeling studies (Figs. 7a and b). In the latter case, **2b**, OH group of the 2α-(3-hydroxypropyl) group could no longer form a hydrogen bond. These complex substitution effects may explain the activities of the analogues toward the mutant receptor. It is not easy task to compensate for the stronger hydrogen bond by hydrophobic interactions, but this could be overcome by introducing much larger hydrophobic substituent which fits more appropriately into the hydrophobic pocket.

In conclusion, we have synthesized and assayed 1- and 2α-doubly modified vitamin D analogues for the mutant VDR(Arg274Leu), and found that the 2α-(3-hydroxypropyl) group, rather than the 1-modification, had a larger enhancing effect on transcriptional activity. We suggest that the 2α-(3-hydroxypropyl) group could be a universal active motif of vitamin D derivatives as agonists for the mutant VDR. Further research is now in progress in order to optimize the ligands for the mutant receptor by introducing larger and more hydrophobic substituents at the 1-position.

3. Experimental

Melting points were determined with a Yanagimoto micromelting point apparatus without correction. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were measured on a JASCO FT/IR-800 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL AL-400 NMR (400 MHz) or ECP-600 NMR (600 MHz) with Me_4Si as an internal standard. ^{13}C NMR spectra taken in $CDCl_3$ (δ 77.0) were referenced to the residual solvents. Low- and high-resolution mass spectra were recorded on a JEOL JMX-SX 102A spectrometer. FAB mass spectra were measured using *m*-nitrobenzyl alcohol matrix. Elemental analyses were conducted with a Perkin-Elmer PE 2400II CHNS/O analyzer. Column chromatography was performed on silica gel 60N (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).

Sugar epoxide **7** was synthesized according to the literature procedure.[13,14]

3.1. Synthesis of 1α- and 1β-hydroxymethyl-2α-hydroxypropylated analogues (2a,b)

3.1.1. Methyl 3-*C*-Allyl-4,6-*O*-benzylidene-2-*O*-*tert*-butyldimethylsilyl-3-deoxy-α-D-altropyranoside. A mixture of C-allylated starting alcohol[8e] (derived from the sugar epoxide **7**, 5.47 g, 17.9 mmol), imidazole (6.08 g, 89.3 mmol), TBSCl (10.0 g, 66.3 mmol) in DMF (15 mL) was stirred at room temperature for 13 h. The mixture was diluted with Et_2O (50 mL) and washed with

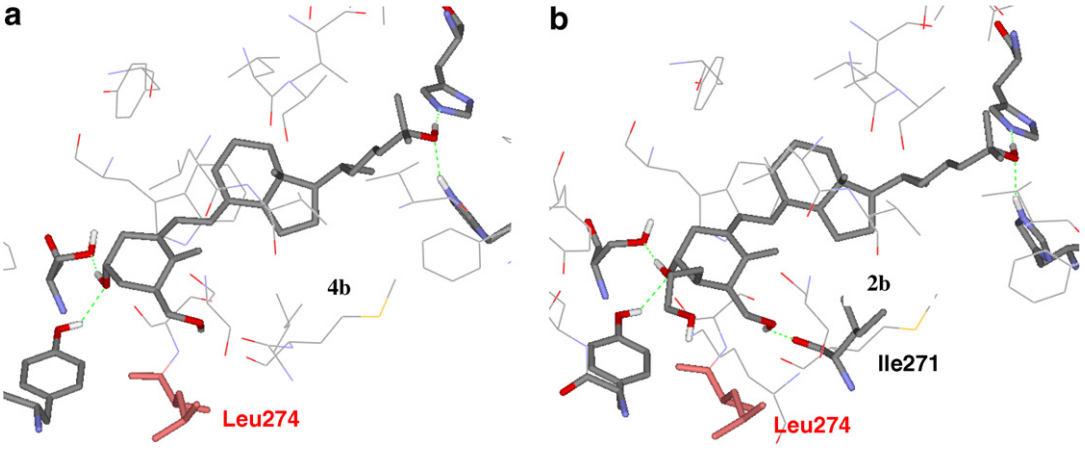


Figure 7. Computer-generated models of the complexes between the mutant VDR(Arg274Leu) and **4b** (a), or **2b** (b).

water (2× 50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (25:1)) gave the TBS ether (7.37 g, 98%) as a colorless oil.

$[\alpha]_D^{17}$ +40.5° (*c* 1.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 2.11 (1H, m), 2.44–2.58 (2H, m), 3.36 (3H, s), 3.78 (1H, dd, J = 10.0, 10.0 Hz), 3.91 (1H, s), 3.93 (1H, ddd, J = 4.9, 10.0, 10.0 Hz), 4.13 (1H, dd, J = 5.8, 10.0 Hz), 4.26 (1H, dd, J = 4.9, 10.0 Hz), 4.46 (1H, s), 5.04–5.15 (2H, m), 5.61 (1H, s), 5.82 (1H, dddd, J = 6.5, 7.9, 10.3, 16.8 Hz), 7.32–7.40 (3H, m), 7.46–7.52 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.8, 18.1, 25.9, 28.8, 43.1, 55.1, 59.4, 69.7, 69.8, 76.2, 102.0, 102.9, 116.8, 126.2, 128.2, 129.0, 137.2, 137.8. IR (neat, cm^{-1}) 2930, 1642, 1468, 1258, 1102, 1051, 853, 776, 698. LRMS (EI(+)) *m/z* 420 (M^+), 419 (M^+-1), 389 ([M−OMe]$^+$), 363 ([M−*t*-Bu]$^+$), 331 ([M−*t*-Bu−MeOH]$^+$), 271, 257, 225 (bp), 141. HRMS (EI(+)) calcd for $C_{23}H_{36}O_5Si$ (M^+) 420.2332, found 420.2320.

3.1.2. Methyl 4,6-*O*-benzylidene-2-*O*-*tert*-butyldimethylsilyl-3-deoxy-3-*C*-(3-hydroxypropyl)-α-D-altropyranoside. To a solution of olefin prepared as above (7.37 g, 17.5 mmol) in THF (10 mL) was added BH_3·THF (1 M in THF, 35 mL, 35 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h. Aqueous 1 N NaOH solution (25 mL) was added dropwise, followed by 30% aqueous H_2O_2 solution (25 mL). The mixture was stirred at 0 °C for 3 h and poured into 10% aqueous $Na_2S_2O_3$ solution (50 mL). The mixture was extracted with AcOEt (2× 50 mL) and organic layers were combined, washed with 10% aqueous $Na_2S_2O_3$ solution (50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (20:1 to 2:1)) gave the alcohol (5.71 g, 77%) as a colorless oil.

$[\alpha]_D^{19}$ +44.7° (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.09 (3H, s), 0.09 (3H, s), 0.92 (9H, s), 1.54–1.65 (1H, m), 1.66–1.85 (3H, m), 2.03–2.10 (1H, m), 3.35 (3H, s), 3.65 (2H, t, J = 6.8 Hz), 3.77 (1H, dd, J = 10.0, 10.0 Hz), 3.91 (1H, s), 3.94 (1H, ddd, J = 5.1, 10.0, 10.0 Hz), 4.12 (1H, dd, J = 5.1, 10.0 Hz), 4.26 (1H, dd, J = 5.1, 10.0 Hz), 4.45 (1H, s), 5.59 (1H, s), 7.32–7.40 (3H, m), 7.46–7.51 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.9, −4.8, 18.1, 20.6, 25.9, 31.6, 43.4, 55.1, 59.4, 63.0, 69.7, 70.8, 76.6, 102.0, 102.6, 126.2, 128.2, 129.0, 137.7. IR (neat, cm^{-1}) 3441, 2930, 1466, 1385, 1258, 1107, 1046, 841, 777, 698. LRMS (EI(+)) *m/z* 438 (M^+), 437 (M^+-1), 407 ([M−OMe]$^+$), 381 ([M−*t*-Bu]$^+$), 349 ([M−*t*-Bu−MeOH]$^+$), 275, 243, 159 (bp). HRMS (EI(+)) calcd for $C_{23}H_{38}O_6Si$ (M^+) 438.2438, found 438.2435.

3.1.3. Methyl 4,6-*O*-Benzylidene-2-*O*-*tert*-butyldimethylsilyl-3-deoxy-3-*C*-(3-pivaloyloxypropyl)-α-D-altropyranoside (8). To a solution of alcohol prepared as above (5.57 g, 13.1 mmol) in pyridine (50 mL) was added PivCl (1.9 mL, 15.4 mmol) and stirred at 0 °C, and gradually raised up to room temperature for 24 h. The mixture was cooled to 0 °C, and additional PivCl (1.9 mL, 15.4 mmol) was added, which was stirred at 0 °C, and gradually raised up to room temperature for 3.5 h. The solvent was removed under reduced pressure, and the residue was partitioned between Et_2O (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). Layers were separated, and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (10:1)) gave the pivalate **8** (6.51 g, 95%) as a colorless oil.

$[\alpha]_D^{21}$ +45.8° (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.08 (3H, s), 0.09 (3H, s), 0.92 (9H, s), 1.19 (9H, s), 1.46–1.72 (1H, m), 1.72–1.90 (3H, m), 2.00–2.09 (1H, m), 3.34 (3H, s), 3.77 (1H, dd, J = 10.1, 10.1 Hz), 3.87 (1H, m), 3.92 (1H, ddd, J = 5.0, 10.1, 10.1 Hz), 4.02–4.18 (3H, m), 4.25 (1H, dd, J = 5.0, 10.1 Hz), 4.45 (1H, s), 5.59 (1H, s), 7.32–7.39 (3H, m), 7.44–7.51 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.5, −4.5, 18.4, 21.4, 26.2, 27.5, 28.1, 39.1, 43.8, 55.3, 59.7, 64.7, 70.0, 71.0, 76.7, 102.2, 103.0, 116.8, 126.5, 128.5, 129.2, 138.1, 178.7. IR (neat, cm^{-1}) 2932, 1730, 1464, 1285, 1156, 1105, 1049, 853, 841, 777. LRMS (EI(+)) *m/z* 522 (M^+), 521 ([M−H]$^+$), 491 ([M−MeO]$^+$), 465 ([M−*t*-Bu]$^+$), 447, 433 ([M−*t*-Bu−MeOH]$^+$), 363, 341, 159 (bp). HRMS (EI(+)) calcd for $C_{28}H_{46}O_7Si$ (M^+) 522.3013, found 522.3021.

3.1.4. Methyl 6-*O*-Benzyl-2-*O*-*tert*-butyldimethylsilyl-3-deoxy-3-*C*-(3-pivaloyloxypropyl)-α-D-altropyranoside (9). Under an Ar atmosphere, to a cooled (0 °C) mixture of benzylidene acetal **8** (6.51 g, 12.5 mmol), Et_3SiH (15 mL, 93.9 mmol), MS3A (12.4 g) in CH_2Cl_2 (75 mL) was added TFA (7.2 mL, 93.5 mmol) and stirred at room temperature for 6 h. Another Et_3SiH (15 mL, 9.39 mmol) and TFA (7.2 mL, 93.5 mmol) were added, and stirred at room temperature for 2 h. The mixture was cooled in ice-water bath, the reaction was quenched by slow addition of saturated aqueous Na_2CO_3 solution (100 mL), and the mixture was stirred at room temperature for 30 min. The mixture was filtered through Celite, washed with CH_2Cl_2 and water, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2× 30 mL), and organic layers were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (5:1 to 1:1)) gave desired alcohol **9** (3.86 g, 59%) as a colorless oil.

$[\alpha]_D^{17}$ +21.1° (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.20 (9H, s), 1.54–1.83 (5H, m), 2.41 (1H, br s), 3.35 (3H, s), 3.63 (1H, dd, J = 6.0, 9.6 Hz), 3.68 (1H, dd, J = 2.4, 6.0 Hz), 3.73 (1H, dd, J = 4.8, 9.6 Hz), 3.82 (1H, m), 4.03 (1H, dd, J = 4.4, 7.2 Hz), 4.03–4.12 (2H, m), 4.41 (1H, d, J = 2.4 Hz), 4.57 (1H, d, J = 12.0 Hz), 4.63 (1H, d, J = 12.0 Hz), 7.26–7.39 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.6, 18.1, 21.3, 25.9, 27.1, 27.3, 38.8, 43.3, 55.2, 64.6, 67.8, 69.9, 71.4, 71.5, 73.7, 103.5, 127.7, 127.8, 128.4, 137.7, 178.5. IR (neat, cm^{-1}) 3486, 2930, 1729, 1472, 1287, 1252, 1159, 1111, 1051, 837,

777. LRMS (EI(+)) *m/z* 493 ([M−MeO]$^+$), 492 ([M−MeOH]$^+$), 475 ([M−MeO−H_2O]$^+$), 449 ([M−*t*-Bu−H_2O]$^+$), 435 ([M−*t*-Bu−MeOH]$^+$), 417 ([M−*t*-Bu−H_2O−MeOH]$^+$), 341, 243, 159 (bp), 91 (C_7H_7). HRMS (EI(+)) calcd for $C_{27}H_{45}O_6Si$ ([M−MeO]$^+$) 493.2985, found 493.2974.

3.1.5. 3-[(2*R*,4*S*,5*S*,6*S*)-2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-3-oxotetrahydropyran-4-yl]propyl pivalate. Under an Ar atmosphere, a mixture of alcohol **9** (3.86 g, 7.36 mmol), NMO (1.33 g, 7.51 mmol), TPAP (256.7 mg, 0.73 mmol) in CH_2Cl_2 (75 mL) was stirred at room temperature for 2.5 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/AcOEt (10:1)) to give the ketone (3.29 g, 86%) as a colorless oil.

$[\alpha]_D^{16}$ +96.5° (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.07 (3H, s), 0.09 (3H, s), 0.90 (9H, s), 1.19 (9H, s), 1.50–1.84 (4H, m), 2.83 (1H, ddd, *J* = 3.3, 7.5, 10.6 Hz), 3.40 (3H, s), 3.50 (1H, dd, *J* = 2.8, 10.6 Hz), 3.77 (1H, dd, *J* = 2.8, 10.4 Hz), 3.83 (1H, dd, *J* = 4.4, 10.4 Hz), 3.98–4.09 (3H, m), 4.52 (1H, d, *J* = 12.0 Hz), 4.59 (1H, d, *J* = 12.0 Hz), 4.77 (1H, d, *J* = 2.8 Hz), 7.24–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.0, −4.5, 18.0, 21.2, 25.8, 26.6, 27.3, 38.7, 52.5, 55.4, 64.6, 69.6, 73.6, 75.0, 75.5, 105.7, 127.5, 127.6, 128.3, 137.7, 178.4, 210.4. IR (neat, cm^{-1}) 2957, 1730, 1474, 1456, 1159, 1113, 1042, 837, 777. LRMS (EI(+)) *m/z* 522 (M$^+$), 465 ([M−*t*-Bu]$^+$), 433 ([M−*t*-Bu−MeOH]$^+$), 386, 363, 343, 255, 159, 91 (C_7H_7, bp). HRMS (EI(+)) calcd for $C_{28}H_{46}O_7Si$ (M$^+$) 522.3013, found 522.3013.

3.1.6. 3-[(2*S*,4*R*,5*S*,6*S*)-2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-3-methylenetetrahydropyran-4-yl]propyl pivalate (10). Under an Ar atmosphere, to a cold (−40 °C) mixture of Zn dust (activated by sequential treatment of 1 N HCl aq, water, EtOH, and Et_2O, and then dried in vacuo, 5.88 g, 88.7 mmol), CH_2Br_2 (2.1 mL, 29.9 mmol) in THF (50 mL) was added $TiCl_4$ (2.3 mL, 21.0 mmol) dropwise and stirred at 5 °C (in a cold room) for 3 d. The mixture was diluted with CH_2Cl_2 (20 mL) and ketone prepared as above (3.14 g, 6.00 mmol) in CH_2Cl_2 (25 mL) was added. After stirred at room temperature for 9.5 h, the mixture was poured into a mixture of Et_2O (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL) and vigorously stirred for several minutes. The mixture was filtered through Celite, washed with CH_2Cl_2 and water, and the layers were separated. The organic layer was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (10:1)) gave olefin **10** (2.27 g, 73%) as a colorless oil.

$[\alpha]_D^{18}$ +42.2° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (6H, s), 0.89 (9H, s), 1.20 (9H, s), 1.48–1.65 (2H, m), 1.65–1.82 (2H, m), 2.28 (1H, m), 3.32 (1H, dd, *J* = 1.8, 8.0 Hz), 3.39 (3H, s), 3.63 (1H, dd, *J* = 4.6, 10.2 Hz), 3.67 (1H, dd, *J* = 6.6, 10.2 Hz), 4.04 (2H, t, *J* = 6.0 Hz), 4.39 (1H, apparent t, *J* = 5.4 Hz), 4.57 (1H, d, *J* = 1.8 Hz), 4.58 (1H, d, *J* = 12.6 Hz), 4.64 (1H, d, *J* = 12.6 Hz), 4.90 (1H, s), 4.98 (1H, s), 7.25–7.36 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.9, −4.5, 18.1, 24.2, 25.9, 26.5, 27.3, 38.8, 44.9, 55.4, 64.5, 70.7, 72.4, 73.4, 77.2, 105.0, 109.7, 127.5, 127.5, 128.2, 138.2, 144.2, 178.5. IR (neat, cm^{-1}) 2930, 1730, 1462, 1285, 1254, 1157, 1113, 1051, 837, 777. LRMS (EI(+)) *m/z* 520 (M$^+$), 505 ([M−Me]$^+$), 489 ([M−OMe]$^+$), 473 ([M−Me−MeOH]$^+$), 463 ([M−*t*-Bu]$^+$), 431 ([M−*t*-Bu−MeOH]$^+$), 399 ([M−$BnOCH_2$]$^+$), 352, 341, 159, 91 (C_7H_7, bp). HRMS (EI(+)) calcd for $C_{29}H_{48}O_6Si$ (M$^+$) 520.3220, found 520.3204.

3.1.7. Hydroboration of 10 followed by re-protection as pivalate. Under an Ar atmosphere, to a cold (0 °C) solution of olefin **10** (2.27 g, 4.36 mmol) in THF (15 mL) was added BH_3·THF (1 M in THF, 13 mL, 13 mmol). Reaction temperature was gradually raised up to room temperature, and the mixture was stirred for 9.5 h. The mixture was cooled to 0 °C, and 3 M NaOAc (10 mL) and 30% H_2O_2 (10 mL) were added. After stirred at room temperature overnight, the reaction was quenched by the addition of 10% aqueous $Na_2S_2O_3$ solution (50 mL) at 0 °C. The mixture was extracted with AcOEt (2× 25 mL) and the organic layers were combined, washed with 10% aqueous $Na_2S_2O_3$ solution (25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in pyridine (20 mL) and PivCl (2 mL, 16.9 mmol) was added. After stirred at room temperature for 11 h, the solvent was removed under reduced pressure. The residue was diluted with water (20 mL) and extracted with AcOEt (2× 20 mL). The organic layers were combined, washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (20:1)) gave **11a** (less polar isomer, 1.16 g, 43%) and **11b** (more polar isomer, 904.1 mg, 33%) as colorless oils, respectively.

3.1.8. 3-[(2*S*,3*S*,4*R*,5*S*,6*S*)-2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-3-pivaloyloxymethyltetrahydropyran-4-yl]propyl pivalate (11a). $[\alpha]_D^{19}$ +23.2° (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (6H, s), 0.89 (9H, s), 1.15 (9H, s), 1.20 (9H, s), 1.50–1.81 (6H, m), 3.37 (3H, s), 3.48 (1H, s), 3.56 (1H, dd, *J* = 2.8, 10.5 Hz), 3.64 (1H, dd, *J* = 8.5, 10.5 Hz), 4.06 (2H, apparent dt, *J* = 3.2, 6.2 Hz), 4.18 (1H, dt, *J* = 8.5, 2.8 Hz), 4.22 (1H, dd, *J* = 5.6, 11.3 Hz), 4.44 (1H, dd, *J* = 7.8, 11.3 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.52 (1H, s), 4.67 (1H, d, *J* = 12.0 Hz), 7.24–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.9, −4.9, 18.0, 25.8, 27.2, 27.5, 37.9, 38.6, 38.8, 41.6, 54.7, 64.0, 65.0, 65.1, 69.6, 72.2, 73.4, 102.7, 127.4, 127.4, 128.2, 138.3, 178.0, 178.3. IR (neat, cm^{-1}) 2934, 1730, 1478, 1285, 1156, 1119, 1034, 857, 839, 777. LRMS (EI(+)) *m/z* 591 ([M−OMe]$^+$), 590 ([M−MeOH]$^+$), 533 ([M−*t*-Bu−MeOH]$^+$), 431, 341, 243, 221, 159 (bp), 91 (C_7H_7). HRMS (EI(+)) calcd for $C_{33}H_{55}O_7Si$ ([M−OMe]$^+$) 591.3717, found 591.3721.

3.1.9. 3-[(2*S*,3*R*,4*R*,5*S*,6*S*)-2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-3-pivaloyloxymethyltetrahydropyran-4-yl]propyl pivalate (11b). $[\alpha]_D^{20}$ +26.0° (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.16 (9H, s), 1.19 (9H, s),

1.58–1.94 (5H, m), 2.46 (1H, m), 3.35 (3H, s), 3.55–3.64 (3H, s), 3.87 (1H, m), 3.97–4.11 (4H, m), 4.47 (1H, d, $J = 2.4$ Hz), 4.57 (1H, d, $J = 10.2$ Hz), 4.62 (1H, d, $J = 10.2$ Hz), 7.25–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.5, 18.1, 22.3, 25.9, 27.2, 27.2, 27.3, 34.6, 38.8, 40.0, 55.1, 62.5, 64.5, 67.6, 69.8, 71.4, 73.4, 103.3, 127.5, 128.3, 138.2, 178.1, 178.4. IR (neat, cm^{-1}) 2932, 1730, 1480, 1460, 1285, 1156, 1107, 1053, 839, 776. LRMS (EI(+)) *m/z* 591 ([M−OMe]$^+$), 590 ([M−MeOH]$^+$), 533 ([M−*t*-Bu−MeOH]$^+$), 489, 463, 431, 341, 243, 159 (bp), 91 (C_7H_7). HRMS (EI(+)) calcd for $C_{33}H_{55}O_7Si$ ([M−OMe]$^+$) 591.3717, found 591.3707.

3.2. Synthesis of 12a,b

A mixture of **11a** (1.16 g, 1.86 mmol), $Pd(OH)_2$/C (20% dry basis, 58.6 mg) in EtOH (5 mL) was stirred under H_2 atmosphere at room temperature for 4 h. The catalyst was filtered off and concentrated. The residue was dried by azeotroping with PhMe and diluted with CH_2Cl_2 (5 mL). The solution was cooled to 0 °C, and Et_3N (310 μL, 2.22 mmol) and MsCl (145 μL, 1.83 mmol) were added. After stirred at 0 °C, for 40 min, another Et_3N (100 μL, 0.72 mmol) and MsCl (50 μL, 0.65 mmol) were added and stirred at the same temperature for further 30 min. The reaction was quenched by the addition of water (10 mL) and extracted with AcOEt (2× 10 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give mesylate **12a** (1.15 g, quant.) as a colorless oil.

3.2.1. 3-[(2*S*,3*S*,4*R*,5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-methanesulfonyloxymethyl-6-methoxy-3-pivaloyloxymethyltetrahydropyran-4-yl]propyl pivalate (12a). $[\alpha]_D^{22}$ +39.6° (*c* 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.07 (6H, s), 0.91 (9H, s), 1.19 (9H, s), 1.21 (9H, s), 1.48–1.60 (1H, m), 1.60–1.84 (5H, m), 3.05 (3H, s), 3.35 (3H, s), 3.49 (1H, br s), 4.05 (1H, dt, $J = 10.9$, 6.2 Hz), 4.09 (1H, dt, $J = 10.9$, 6.2 Hz), 4.17 (1H, dd, $J = 4.0$, 11.8 Hz), 4.24 (1H, m), 4.29 (1H, dd, $J = 2.8$, 11.2 Hz), 4.34 (1H, dd, $J = 9.2$, 11.2 Hz), 4.49 (1H, s), 4.52 (1H, dd, $J = 8.8$, 11.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.0, −4.8, 18.0, 25.8, 27.2, 27.3, 27.5, 37.5, 37.9, 38.7, 38.8, 42.3, 55.0, 63.9, 64.0, 65.0, 68.9, 71.9, 102.8, 177.9, 178.3. IR (neat, cm^{-1}) 2936, 1730, 1472, 1362, 1285, 1179, 1157, 839. LRMS (EI(+)) *m/z* 579 ([M−OMe]$^+$), 578 ([M−MeOH]$^+$), 521 ([M−*t*-Bu−MeOH]$^+$), 477, 451, 419, 159 (bp). HRMS (EI(+)) calcd for $C_{27}H_{51}O_9SSi$ ([M−OMe]$^+$) 579.3023, found 579.3044.

Compound **12b** was also synthesized similarly (86%) as a colorless oil.

3.2.2. 3-[(2*S*,3*R*,4*R*,5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-methanesulfonyloxymethyl-6-methoxy-3-pivaloyloxymethyltetrahydropyran-4-yl]propyl pivalate (12b). $[\alpha]_D^{23}$ +38.9° (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (6H, s), 0.88 (9H, s), 1.20 (9H, s), 1.20 (9H, s), 1.15–1.32 (1H, m), 1.50–1.57 (1H, m), 1.71–1.94 (3H, m), 2.50 (1H, m), 3.10 (3H, s), 3.34 (3H, s), 3.67 (1H, dd, $J = 2.0$, 3.6 Hz), 3.92 (1H, ddd, $J = 2.5$, 5.7, 9.5 Hz), 3.97–4.10 (4H, m), 4.25 (1H, dd, $J = 5.5$, 11.6 Hz), 4.47 (1H, d, $J = 2.0$ Hz), 4.49 (1H, dd, $J = 2.5$, 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.7, 18.0, 22.0, 25.8, 27.2, 27.2, 33.6, 37.9, 38.7, 38.8, 40.5, 55.3, 62.6, 64.2, 66.3, 68.7, 70.9, 103.0, 177.9, 178.3. IR (neat, cm^{-1}) 2936, 1730, 1482, 1362, 1254, 1177, 1154, 837, 777. LRMS (EI(+)) *m/z* 579 ([M−OMe]$^+$), 578 ([M−MeOH]$^+$), 521 ([M−*t*-Bu−MeOH]$^+$), 477, 451, 419, 159 (bp). HRMS (EI(+)) calcd for $C_{27}H_{51}O_9SSi$ ([M−OMe]$^+$) 579.3023, found 579.3044.

3.3. Synthesis of bromide 13a,b

Under an Ar atmosphere, a mixture of mesylate **12a** (1.15 g, 1.88 mmol), LiBr (1.06 g, 12.2 mmol) in TMU (1,1,3,3-tetramethylurea, 9 mL) was stirred at 80 °C for 6.5 h. After cooled to room temperature, the mixture was diluted with water (20 mL) and extracted with Et_2O (2× 20 mL). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (20:1)) gave bromide **13a** (1.01 g, 91%) as a colorless oil.

3.3.1. 3-[(2*S*,3*S*,4*R*,5*S*,6*S*)-2-Bromomethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-3-pivaloyloxymethyltetrahydropyran-4-yl]propyl pivalate (13a). $[\alpha]_D^{22}$ +48.1° (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (6H, s), 0.90 (9H, s), 1.19 (9H, s), 1.21 (9H, s), 1.44–1.87 (6H, m), 3.42 (3H, s), 3.46 (1H, dd, $J = 4.0$, 10.7 Hz), 3.47 (1H, m), 3.54 (1H, dd, $J = 9.3$, 10.7 Hz), 4.06 (1H, dt, $J = 10.7$, 6.3 Hz), 4.09 (1H, dt, $J = 10.7$, 6.3 Hz), 4.17 (1H, apparent dt, $J = 9.3$, 3.0 Hz), 4.22 (1H, dd, $J = 4.4$, 11.7 Hz), 4.48 (1H, dd, $J = 8.4$, 11.7 Hz), 4.52 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.0, −4.9, 18.0, 25.8, 27.2, 27.3, 27.4, 27.5, 34.3, 38.6, 38.8, 39.5, 42.4, 55.2, 63.9, 64.9, 66.7, 69.2, 103.3, 178.0, 178.3. IR (neat, cm^{-1}) 2932, 1730, 1480, 1283, 1157, 1034, 839, 776. LRMS (EI(+)) *m/z* 563 ([M(^{79}Br)−OMe]$^+$), 537 ([M(^{79}Br)−*t*-Bu]$^+$), 505 ([M−*t*-Bu−MeOH]$^+$), 461, 435, 353, 159 (bp). HRMS (EI(+)) calcd for $C_{26}H_{48}{}^{79}BrO_6Si$ ([M(^{79}Br)−OMe]$^+$) 563.2404, found 563.2397.

Compound **13b** was also synthesized similarly (78% yield) as a colorless oil.

3.3.2. 3-[(2*S*,3*R*,4*R*,5*S*,6*S*)-2-Bromomethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-3-pivaloyloxymethyltetrahydropyran-4-yl]propyl pivalate (13b). $[\alpha]_D^{23}$ +32.9° (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.20 (9H, s), 1.20 (9H, s), 1.12–1.32 (1H, m), 1.53–1.66 (1H, m), 1.69–1.96 (3H, m), 2.45 (1H, m), 3.39 (3H, s), 3.45 (1H, dd, $J = 7.3$, 11.0 Hz), 3.60 (1H, dd, $J = 3.0$, 11.0 Hz), 3.62 (1H, dd, $J = 2.6$, 4.4 Hz), 3.90 (1H, ddd, $J = 3.0$, 7.3, 8.7 Hz), 3.99 (1H, dd, $J = 7.2$, 11.6 Hz), 4.02–4.12 (3H, m), 4.48 (1H, d, $J = 2.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.5, 18.1, 22.4, 25.8, 27.1, 27.2, 27.2, 35.0, 36.4, 38.8, 40.6, 55.3, 62.8, 64.3, 68.1, 69.2, 103.2, 178.0, 178.4. IR (neat, cm^{-1}) 2932, 1732, 1480, 1285, 1157, 1111, 1036, 837, 776. LRMS (EI(+)) *m/z* 594 (M(^{79}Br)$^+$), 563 ([M(^{79}Br)−OMe]$^+$), 537 ([M(^{79}Br)−*t*-Bu]$^+$), 505 ([M−*t*-Bu−MeOH]$^+$), 461, 435, 353, 159

(bp). HRMS (EI(+)) calcd for $C_{27}H_{51}{}^{79}BrO_7Si$ ($M(^{79}Br)^+$) 594.2587, found 594.2609.

3.3.3. Reductive ring opening by Zn–$NaBH_3CN$. A mixture of bromide **13a** (1.01 g, 1.70 mmol), Zn dust (2.59 g, 39.6 mmol), $NaBH_3CN$ (802.7 mg, 12.8 mmol) in 1-propanol (6 mL)–H_2O (0.6 mL) was stirred at 95 °C for 4 h. After cooled to room temperature, saturated aqueous NH_4Cl solution (20 mL) was added, and the excess Zn dust was removed by decantation. The liquid was extracted with AcOEt (2× 20 mL) and the organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (15:2)) gave the alcohol **14a** (730.9 mg, 88%) as a colorless oil.

3.3.4. (4*R*,5*S*)-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-hydroxyethyl]-5-(pivaloyloxymethyl)-hept-6-enyl pivalate (14a). $[\alpha]_D^{19}$ −4.5° (*c* 1.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.08 (3H, s), 0.09 (3H, s), 0.90 (9H, s), 1.18 (9H, s), 1.19 (9H, s), 1.32–1.45 (1H, m), 1.46–1.58 (1H, m), 1.60–1.80 (4H, m), 2.55 (1H, m), 3.52 (1H, dd, *J* = 5.4, 11.2 Hz), 3.62 (1H, dd, *J* = 5.4, 11.2 Hz), 3.88 (1H, dt, *J* = 3.5, 5.4 Hz), 4.02 (1H, dt, *J* = 10.8, 6.4 Hz), 4.05 (1H, dt, *J* = 10.8, 6.4 Hz), 4.08 (1H, dd, *J* = 7.6, 11.0 Hz), 4.15 (1H, dd, *J* = 5.2, 11.0 Hz), 5.04–5.16 (2H, m), 5.72 (1H, ddd, *J* = 8.6, 10.4, 17.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.3, −3.9, 18.2, 23.5, 26.0, 27.3, 28.0, 38.8, 38.8, 41.5, 44.4, 64.4, 65.1, 65.2, 73.8, 117.2, 138.1, 178.3, 178.5. IR (neat, cm^{-1}) 3521, 2934, 1730, 1480, 1287, 1159, 1049, 837, 776. LRMS (EI(+)) *m*/*z* 455 ($[M-CH_2OH]^+$), 429 ($[M-t\text{-}Bu]^+$), 353, 159 (bp). HRMS (EI(+)) calcd for $C_{25}H_{47}O_5Si$ ($[M-CH_2OH]^+$) 455.3193, found 455.3174.

Compound **14b** was also synthesized similarly (quant.) as a colorless oil.

3.3.5. (4*R*,5*R*)-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-hydroxyethyl]-5-(pivaloyloxymethyl)-hept-6-enyl pivalate (14b). $[\alpha]_D^{20}$ +13.8° (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.10 (6H, s), 0.91 (9H, s), 1.18 (9H, s), 1.19 (9H, s), 1.30–1.52 (2H, m), 1.67–1.80 (4H, m), 2.59 (1H, m), 3.55 (1H, dd, *J* = 4.0, 11.2 Hz), 3.67 (1H, dd, *J* = 6.0, 11.2 Hz), 3.81 (1H, m), 4.00 (1H, dt, *J* = 11.1, 6.6 Hz), 4.03 (1H, dt, *J* = 11.1, 6.6 Hz), 4.05 (1H, dd, *J* = 8.4, 11.1 Hz), 4.12 (1H, dd, *J* = 5.4, 11.1 Hz), 5.04–5.11 (2H, m), 5.13 (1H, dd, *J* = 1.8, 10.1 Hz), 5.63 (1H, ddd, *J* = 9.3, 10.1, 16.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.4, −4.2, 18.2, 23.8, 25.9, 27.3, 28.3, 38.3, 38.8, 41.5, 44.2, 64.0, 64.3, 65.6, 74.5, 118.1, 137.0, 178.2, 178.4. IR (neat, cm^{-1}) 3542, 2934, 1730, 1482, 1287, 1256, 1161, 1049, 837, 777. LRMS (EI(+)) *m*/*z* 455 ($[M-CH_2OH]^+$), 429 ($[M-t\text{-}Bu]^+$), 353, 327, 159, 117 (bp). HRMS (EI(+)) calcd for $C_{25}H_{47}O_5Si$ ($[M-CH_2OH]^+$) 455.3193, found 455.3199.

3.3.6. Tosylation of the alcohol 14a,b followed by base treatment. Under an Ar atmosphere, a mixture of alcohol **14a** (730.6 mg, 1.50 mmol), Et_3N (630 μL, 4.52 mmol), DMAP (170.4 mg, 1.39 mmol), TsCl (422.4 mg, 2.22 mmol) in CH_2Cl_2 (7.5 mL) was stirred at room temperature for 13 h. The reaction mixture was quenched by the addition of water (20 mL), extracted with AcOEt (30 mL), and the organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (10:1)) gave the tosylate (914.4 mg, 95%) as a colorless oil.

3.3.7. (4*R*,5*S*)-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(4-toluenesulfonyloxy)ethyl]-5-(pivaloyloxymethyl)hept-6-enyl pivalate. $[\alpha]_D^{22}$ −3.8° (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.00 (3H, s), 0.02 (3H, s), 0.83 (9H, s), 1.17 (9H, s), 1.18 (9H, s), 1.26–1.37 (1H, m), 1.40–1.73 (4H, m), 2.40–2.51 (1H, m), 2.46 (3H, s), 3.90 (1H, dd, *J* = 6.2, 9.8 Hz), 3.92–4.01 (4H, m), 4.03 (1H, dd, *J* = 6.8, 11.2 Hz), 4.08 (1H, dd, *J* = 4.8, 11.2 Hz), 5.01–5.08 (1H, m), 5.10 (1H, dd, *J* = 1.6, 10.4 Hz), 5.60 (1H, ddd, *J* = 9.0, 10.4, 17.2 Hz), 7.37 (2H, m), 7.78 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.6, −4.0, 18.1, 21.7, 23.0, 25.9, 27.2, 27.7, 38.7, 38.8, 41.3, 44.5, 64.3, 65.3, 70.8, 71.3, 117.7, 127.9, 129.8, 132.8, 137.8, 144.9, 178.1, 178.3. IR (neat, cm^{-1}) 2930, 1730, 1480, 1370, 1285, 1179, 1159, 1049, 982, 833. LRMS (EI(+)) *m*/*z* 625 ($[M-Me]^+$), 583 ($[M-t\text{-}Bu]^+$), 411, 353, 329, 309, 229, 159, 133 (bp). HRMS (EI(+)) calcd for $C_{32}H_{53}O_8SSi$ ($[M-Me]^+$) 625.3230, found 625.3249.

Under an Ar atmosphere, to a solution of the tosylate prepared above (914.4 mg, 1.43 mmol) in THF (7 mL) was added TBAF (1 M in THF, 3.6 mL, 3.6 mmol) and stirred at 0 °C for 6 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (20 mL), and the mixture was extracted with AcOEt (2× 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (10:1)) gave the epoxide **15a** (462.1 mg, 91%) as a colorless oil.

3.3.8. (4*R*,5*S*)-4-[(*S*)-Oxiranyl]-5-(pivaloyloxymethyl)-hept-6-enyl pivalate (15a). $[\alpha]_D^{18}$ −20.5° (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.18 (9H, s), 1.20 (9H, s), 1.18–1.30 (1H, m), 1.52–1.69 (2H, m), 1.70–1.82 (2H, m), 2.49 (1H, dd, *J* = 3.6, 4.4 Hz), 2.58 (1H, m), 2.74–2.81 (2H, m), 4.01–4.11 (3H, m), 4.15 (1H, dd, *J* = 7.6, 11.0 Hz), 5.10–5.20 (2H, m), 5.70 (1H, ddd, *J* = 9.3, 10.3, 17.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 26.2, 27.0, 27.2, 27.2, 38.7, 38.7, 42.2, 45.1, 47.0, 53.6, 64.2, 64.8, 118.3, 135.1, 178.0, 178.3. IR (neat, cm^{-1}) 2975, 1730, 1482, 1285, 1159, 1038, 924. LRMS (EI(+)) *m*/*z* 354 (M^+), 324 ($[M-CH_2O]^+$), 311, 252, 167, 150, 120, 85, 57 (*t*-Bu, bp). HRMS (EI(+)) calcd for $C_{20}H_{34}O_5$ (M^+) 354.2406, found 354.2399.

Synthesis of the epoxide from **14b** was also carried out similarly (87% for two steps).

3.3.9. (4*R*,5*R*)-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(4-toluenesulfonyloxy)ethyl]-5-(pivaloyloxymethyl)hept-6-enyl pivalate. A colorless oil, $[\alpha]_D^{22}$ +14.8° (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.00 (3H, s), 0.01 (3H, s), 0.81 (9H, s), 1.13 (9H, s), 1.15 (9H, s), 1.22–1.32 (1H, m), 1.32–1.44 (1H, m), 1.48–1.66 (3H, m),

2.42 (3H, s), 2.52 (1H, m), 3.88–3.96 (6H, m), 3.99 (1H, dd, J = 5.6, 11.2 Hz), 5.00 (1H, dd, J = 1.5, 17.1 Hz), 5.06 (1H, dd, J = 1.5, 10.2 Hz), 5.54 (1H, ddd, J = 9.6, 10.2, 17.1 Hz), 7.31 (2H, m), 7.74 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.3, 18.0, 21.6, 23.2, 25.7, 27.2, 27.7, 38.7, 42.1, 43.7, 64.0, 65.2, 71.3, 71.3, 118.3, 127.8, 129.7, 132.7, 136.8, 144.8, 178.0, 178.2. IR (neat, cm^{-1}) 2934, 1730, 1480, 1368, 1285, 1179, 1157, 980, 837, 779. LRMS (EI(+)) m/z 625 ($[M-Me]^+$), 583 ($[M-t\text{-}Bu]^+$), 411, 353, 329, 309, 229 (bp), 159, 133. HRMS (EI(+)) calcd for $C_{32}H_{53}O_8SSi$ ($[M-Me]^+$) 625.3230, found 625.3236.

3.3.10. (4*R*,5*R*)-4-[(*S*)-Oxiranyl]-5-(pivaloyloxymethyl)-hept-6-enyl pivalate (15b). A colorless oil, $[\alpha]_D^{19}$ +6.6° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.18 (9H, s), 1.20 (9H, s), 1.14–1.29 (1H, m), 1.46–1.58 (1H, m), 1.71–1.80 (2H, m), 1.82–1.95 (1H, m), 2.48 (1H, dd, J = 3.0, 4.6 Hz), 2.53 (1H, m), 2.76–2.84 (2H, m), 4.06 (2H, t, J = 6.4 Hz), 4.08 (1H, dd, J = 6.8, 11.1 Hz), 4.14 (1H, dd, J = 5.6, 11.1 Hz), 5.09–5.19 (2H, m), 5.67 (1H, ddd, J = 9.1, 10.3, 16.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 26.1, 26.5, 27.2, 27.2, 38.7, 38.8, 42.3, 45.5, 46.5, 54.6, 64.2, 64.7, 118.0, 136.2, 178.1, 178.3. IR (neat, cm^{-1}) 2975, 1730, 1482, 1285, 1157, 1036, 922. LRMS (EI(+)) m/z 354 (M^+), 324 ($[M-CH_2O]^+$), 311, 252, 150, 137, 120, 57 (t-Bu, bp). HRMS (EI(+)) calcd for $C_{20}H_{34}O_5$ (M^+) 354.2406, found 354.2426.

3.3.11. Ethynylation followed by protection. Under an Ar atmosphere, to a cooled (−78 °C) solution of epoxide **15a** (435.9 mg, 1.23 mmol) in THF (6 mL) was added a solution of lithium TMS-acetylide (0.44 M in THF–hexane, prepared from TMS-acetylene and n-BuLi, 8.4 mL, 3.70 mmol) and $BF_3{\cdot}OEt_2$ (234 μL, 185 mmol), and the mixture was stirred at the same temperature for 6 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (30 mL), and the mixture was extracted with AcOEt (2× 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The crude residue was dissolved in MeOH (5 mL) and NaOMe (28% in MeOH, 1.2 mL, 6.2 mmol) was added. The mixture was stirred at 0 °C for 5 min, warmed at 40 °C, and stirred for 11.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with AcOEt (20 mL). The organic layer was washed with water (10 mL), and the aqueous layers were combined, saturated with NaCl, and extracted with AcOEt (5× 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (AcOEt) gave the triol (151.2 mg, 58% for two steps) as a colorless oil.

3.3.12. (4*R*,5*R*)-4-[(*S*)-1-(Hydroxymethyl)allyl]oct-7-yne-1,5-diol. $[\alpha]_D^{20}$ −21.3° (c 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.38–1.47 (1H, m), 1.53–1.76 (3H, m), 1.76–1.82 (1H, m), 2.06 (1H, t, J = 2.8 Hz), 2.39 (1H, ddd, J = 2.8, 6.5, 16.7 Hz), 2.46 (1H, m), 2.51 (1H, ddd, J = 2.8, 7.5, 16.7 Hz), 2.76 (3H, br s), 3.64 (1H, dd, J = 6.6, 10.6 Hz), 3.64 (2H, t, J = 6.6 Hz), 3.72 (1H, dd, J = 7.0, 10.6 Hz), 3.96 (1H, ddd, J = 2.1, 6.5, 7.5 Hz), 5.01–5.21 (2H, m), 5.80 (1H, ddd, J = 8.7, 10.5, 17.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 21.3, 25.7, 31.8, 43.0, 49.2, 62.8, 63.1, 70.6, 72.0, 81.4, 117.4, 138.5. IR (neat, cm^{-1}) 3357, 3303, 3079, 2938, 2118, 1640, 1424, 1375, 1258, 1048, 916. LRMS (EI(+)) m/z 212 (M^+), 211 ($[M-H]^+$), 55 (bp). HRMS (EI(+)) calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1405.

Under an Ar atmosphere, to a cooled (−78 °C) solution of the triol prepared as above (151.2 mg, 0.712 mmol) and 2,6-lutidine (747 μL, 6.41 mmol) was added TBSOTf (736 μL, 3.20 mmol) and stirred at the same temperature for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL), and the mixture was extracted with AcOEt (20 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (50:1)) gave the TBS ether **16a** (257.3 mg, 65%) as a colorless oil.

3.3.13. (3*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)-4-[3-(*tert*-butyldimethylsilyloxy)propyl]oct-1-en-7-yne (16a). $[\alpha]_D^{21}$ −14.0° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.02 (6H, s), 0.04 (3H, s), 0.04 (6H, s), 0.06 (3H, s), 0.87 (9H, s), 0.88 (9H, s), 0.89 (9H, s), 1.24–1.37 (1H, m), 1.48–1.74 (3H, m), 1.87 (1H, m), 1.95 (1H, t, J = 2.7 Hz), 2.27 (1H, m), 2.35 (1H, ddd, J = 2.7, 5.8, 16.8 Hz), 2.40 (1H, ddd, J = 2.7, 7.9, 16.8 Hz), 3.59 (2H, t, J = 6.4 Hz), 3.65 (2H, dd, J = 5.6, 10.1 Hz), 3.68 (1H, dd, J = 5.0, 10.1 Hz), 4.00 (1H, ddd, J = 2.0, 5.8, 7.9 Hz), 4.99–5.10 (2H, m), 5.76 (1H, ddd, J = 9.1, 10.5, 17.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.2, −5.2, −5.2, −4.3, −3.7, 18.2, 18.3, 18.4, 22.6, 26.0, 26.1, 32.3, 41.9, 48.1, 63.6, 64.9, 70.1, 72.0, 81.8, 116.0, 140.4. IR (neat, cm^{-1}) 3316, 3075, 2930, 1472, 1254, 1102, 837, 776. LRMS (EI(+)) m/z 554 (M^+), 539 ($[M-Me]^+$), 515 ($[M-C_3H_3]^+$), 497 ($[M-t\text{-}Bu]^+$), 457 ($[M-t\text{-}Bu-H-C_3H_3]^+$), 422 ($[M-TBSOH]^+$), 407 ($[M-TBSOH-Me]^+$), 383 ($[M-TBSOH-C_3H_3]^+$), 365 ($[M-TBSOH-t\text{-}Bu]^+$), 291, 251, 233, 183, 147, 73 (bp). HRMS (EI(+)) calcd for $C_{30}H_{62}O_3Si_3$ (M^+) 554.4007, found 554.3995.

The synthesis of **16b** was also carried out similarly (58% for three steps).

3.3.14. (4*R*,5*R*)-4-[(*R*)-1-(Hydroxymethyl)allyl]oct-7-yne-1,5-diol. A colorless oil, $[\alpha]_D^{21}$ +3.8° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.46–1.73 (4H, m), 1.84 (1H, m), 2.07 (1H, t, J = 2.7 Hz), 2.40 (1H, ddd, J = 2.7, 6.2, 12.7 Hz), 2.45 (1H, m), 2.49 (1H, ddd, J = 2.7, 7.4, 12.7 Hz), 3.40 (3H, br s), 3.65 (2H, m), 3.68 (1H, dd, J = 5.6, 11.2 Hz), 3.73 (1H, dd, J = 5.2, 11.2 Hz), 3.96 (1H, ddd, J = 3.2, 6.2, 7.4 Hz), 5.15–5.22 (2H, m), 5.83 (1H, ddd, J = 8.1, 9.9, 17.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 22.2, 24.8, 31.3, 43.4, 46.2, 62.5, 62.6, 70.2, 70.6, 81.4, 117.3, 137.8. IR (neat, cm^{-1}) 3332, 3301, 3077, 2936, 2118, 1640, 1424, 1256, 1053, 918. LRMS (EI(+)) m/z 212 (M^+), 211 ($[M-H]^+$), 57 (bp). HRMS (EI(+)) calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1414.

3.3.15. (3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)-4-[3-(*tert*-butyldimethylsilyloxy)propyl]oct-1-en-7-yne (16b). A colorless oil, $[\alpha]_D^{21}$ +12.6° (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.02 (6H, s), 0.04 (6H, s), 0.06 (3H, s), 0.10 (3H, s), 0.88 (9H, s), 0.89 (18H, s), 1.24–1.46 (2H, m), 1.47–1.67 (2H, m), 1.86 (1H, m), 1.92 (1H, t, *J* = 2.7 Hz), 2.37 (2H, dd, *J* = 2.7, 6.2 Hz), 2.42 (1H, m), 3.55 (1H, dd, *J* = 4.8, 9.8 Hz), 3.65 (2H, t, *J* = 6.4 Hz), 3.62 (1H, dd, *J* = 5.4, 9.8 Hz), 3.95 (1H, dt, *J* = 3.9, 6.2 Hz), 5.01–5.09 (2H, m), 5.73 (1H, ddd, *J* = 9.4, 9.4, 17.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.3, −5.2, −5.2, −4.5, −4.0, 18.2, 18.4, 18.4, 23.0, 25.0, 26.0, 26.0, 26.0, 32.3, 42.2, 47.0, 63.6, 65.0, 70.0, 72.5, 82.3, 116.6, 139.0. IR (neat, cm^{-1}) 3316, 3071, 2930, 1472, 1254, 1100, 835, 776. LRMS (EI(+)) *m*/*z* 554 (M^+), 539 ([M−Me]$^+$), 515 ([M−C_3H_3]$^+$), 497 ([M−*t*-Bu]$^+$), 457 ([M−*t*-Bu−H−C_3H_3]$^+$), 422 ([M−TBSOH]$^+$), 407 ([M−TBSOH−Me]$^+$), 383 ([M−TBSOH−C_3H_3]$^+$), 365 ([M−TBSOH−*t*-Bu]$^+$), 291, 251, 233, 183, 147, 73 (bp). HRMS (EI(+)) calcd for $C_{30}H_{62}O_3Si_3$ (M^+) 554.4007, found 554.4001.

3.4. Synthesis of 1β-(hydroxymethyl)-2α-(3-hydroxypropyl)-25-hydroxyvitamin D_3 (2a)

Under an Ar atmosphere, a mixture of A-ring enyne **16a** (52.8 mg, 95.1 μmol), CD-ring bromoolefin **6**[12] (38.8 mg, 0.109 mmol), $Pd(PPh_3)_4$ (56.6 mg, 49.0 μmol) in PhMe (300 μL)-Et_3N (300 μL) was stirred at 90 °C for 2 h. After cooled to room temperature, the mixture was diluted with AcOEt, filtered through Celite, washed with AcOEt, and the filtrate was concentrated. The residue was partially purified with silica gel column chromatography (hexane/AcOEt (50:1)). The residue was diluted with THF (500 μL), and HF·pyridine (100 μL) was added. After stirred at room temperature for 1 h, the reaction was quenched by the addition of water (1 mL), and the mixture was extracted with AcOEt (2× 2 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (AcOEt) gave the product (17.5 mg, 38%) as a white powder.

$[\alpha]_D^{22}$ −81.8° (*c* 0.2, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$, ppm) δ 0.55 (3H, s), 0.94 (3H, d, *J* = 6.6 Hz), 1.02–1.10 (1H, m), 1.22 (6H, s), 1.17–1.72 (22H, m), 1.83–1.92 (2H, m), 1.95–2.03 (2H, m), 2.28 (1H, dd, *J* = 3.6, 14.4 Hz), 2.38 (1H, dt, *J* = 1.2, 5.4 Hz), 2.65 (1H, d, *J* = 14.4 Hz), 2.82 (1H, dd, *J* = 4.2, 12.0 Hz), 3.66 (2H, t, *J* = 6.3 Hz), 3.70 (1H, dd, *J* = 6.0, 11.1 Hz), 3.73 (1H, dd, *J* = 6.0, 11.1 Hz), 3.85 (1H, apparent q, *J* = 3.2 Hz), 5.05 (1H, d, *J* = 3.0 Hz), 5.16 (1H, d, *J* = 3.0 Hz), 6.02 (1H, d, *J* = 11.4 Hz), 6.30 (1H, d, *J* = 11.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 11.9, 18.8, 20.8, 22.3, 23.7, 27.6, 28.7, 29.2, 29.2, 29.4, 30.7, 36.1, 36.4, 40.5, 41.2, 44.1, 44.4, 46.0, 50.7, 56.3, 56.6, 62.8, 66.8, 71.1, 71.2, 116.1, 116.8, 123.6. IR (film, cm^{-1}) 3360, 2942, 1653, 1470, 1377, 1042, 756. LRMS (EI(+)) *m*/*z* 488 (M^+), 470 ([M−H_2O]$^+$), 458 ([M−CH_2O]$^+$), 452 ([M−2×H_2O]$^+$), 440 ([M−CH_2O−H_2O]$^+$), 421 ([M−2×H_2O−CH_2OH]$^+$), 363, 59 (bp). HRMS (EI(+)) calcd for $C_{31}H_{52}O_4$ (M^+) 488.3866, found 488.3850.

3.4.1. The 1α-hydroxymethylated analogue (2b) was also prepared similarly (53%) as a white powder. $[\alpha]_D^{24}$ +41.3° (*c* 1.5, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$, ppm) δ 0.51 (3H, s), 0.93 (3H, d, *J* = 6.6 Hz), 1.01–1.09 (1H, m), 1.21 (9H, s), 1.17–1.64 (11H, m), 1.64–1.76 (4H, m), 1.81–2.03 (7H, m), 2.25 (1H, dd, *J* = 9.1, 13.3 Hz), 2.59 (2H, br s), 2.64 (1H, dd, *J* = 4.5, 13.3 Hz), 2.62–2.69 (1H, m), 2.78–2.84 (1H, m), 3.51 (1H, dd, *J* = 9.1, 10.6 Hz), 3.64–3.70 (2H, m), 3.71 (1H, apparent dt, *J* = 4.5, 8.4 Hz), 4.99 (1H, d, *J* = 1.9 Hz), 5.09 (1H, d, *J* = 1.9 Hz), 5.95 (1H, d, *J* = 11.3 Hz), 6.31 (1H, d, *J* = 11.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 11.9, 18.8, 20.8, 22.2, 23.5, 23.9, 27.7, 29.1, 29.2, 29.3, 30.0, 36.1, 36.4, 40.5, 44.4, 44.9, 45.7, 45.9, 47.6, 56.3, 56.5, 60.3, 62.5, 70.8, 71.1, 114.3, 116.7, 123.1, 134.4, 143.4, 145.6. IR (film, cm^{-1}) 3355, 2944, 1649, 1466, 1377, 1032, 909, 735. LRMS (EI(+)) *m*/*z* 488 (M^+), 470 ([M−H_2O]$^+$), 452 ([M−2×H_2O]$^+$), 434 ([M−3×H_2O]$^+$), 422 ([M−H_2O−CH_2OH−OH]$^+$), 157, 55 (bp). HRMS (EI(+)) calcd for $C_{31}H_{52}O_4$ (M^+) 488.3866, found 488.3865.

3.5. Synthesis of 2α-(3-hydroxypropyl)-1-unsubstituted analogue (3)

3.5.1. Methyl 4,6-*O*-Benzylidene-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3-deoxy-α-D-altropyranoside. Under an Ar atmosphere, to a cold (0 °C) solution of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-(3-hydroxypropyl)-α-D-altropyranoside (prepared from sugar epoxide **7** as in the case of **2a**,**b**, 2.2 g, 6.78 mmol) in CH_2Cl_2 (68 mL) were added Et_3N (2.6 mL, 18.7 mmol), TBDPSCl (2.1 mL, 8.1 mmol), and DMAP (82 mg, 0.68 mmol), and stirred at room temperature overnight. The reaction mixture was cooled (0 °C), and saturated aqueous NH_4Cl solution (100 mL) was added. The mixture was extracted with AcOEt (300 mL), and the organic layer was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (9:1 to 5:1)) gave the TBDPS ether (3.58 g, 94%) as a colorless oil.

$[\alpha]_D^{22}$ +57.8° (*c* 1.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.05 (9H, s), 1.56–1.65 (1H, m), 1.70–1.77 (1H, m), 1.80–1.87 (2H, m), 3.35 (3H, s), 3.69 (2H, t, *J* = 6.4 Hz), 3.77 (1H, t, *J* = 10.0 Hz), 3.91 (1H, br s), 3.98 (1H, ddd, *J* = 4.7, 10.0, 14.9 Hz), 4.09 (1H, dd, *J* = 4.7, 10.0 Hz), 4.28 (1H, dd, *J* = 4.9, 10.3 Hz), 4.58 (1H, s), 5.58 (1H, s), 7.33–7.43 (9H, m), 7.47–7.49 (2H, m), 7.66–7.69 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 19.3, 20.9, 26.9, 31.4, 42.7, 55.2, 59.5, 64.0, 69.6, 70.3, 102.0, 102.2, 126.2, 127.5, 128.2, 128.8, 129.4, 134.0, 135.5, 135.5, 137.7. IR (neat, cm^{-1}) 3331, 2932, 2892, 2859, 1612, 1590, 1138, 1107, 1053, 1028, 700. LRMS (EI(+)) *m*/*z* 562 (M^+), 473 ([M−*t*-Bu−MeOH]$^+$), 367, 295. HRMS (EI(+)) calcd for $C_{33}H_{42}O_6Si$ (M^+) 562.2751, found 562.2754.

3.5.2. Methyl 4,6-*O*-Benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3-deoxy-α-D-altropyranoside (17). Under an Ar atmosphere, to a cold (0 °C) solution of the TBDPS ether prepared as above (3.5 g, 6.21 mmol) in CH_2Cl_2 (62 mL) were added

2,6-lutidine (2.2 mL, 18.6 mmol) and TBSOTf (2.2 mL, 9.3 mmol), and stirred at 0 °C for 30 min. The reaction was quenched by the addition of water (50 mL) and extracted with AcOEt (300 mL). The organic extract was washed with water (50 mL), saturated aqueous NH_4Cl solution (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (50:1)) gave the product (4.06 g, 96%) as a colorless oil.

$[\alpha]_D^{22}$ +33.4° (*c* 3.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.07 (6H, s), 0.91 (9H, s), 1.04 (9H, s), 1.58–1.62 (1H, m), 1.69–1.84 (3H, m), 2.02–2.04 (1H, m), 3.32 (3H, s), 3.68 (2H, t, J = 6.1 Hz), 3.76 (1H, dd, J = 10.0, 10.3 Hz), 3.87 (1H, m), 3.92 (1H, ddd, J = 5.0, 10.0, 14.9 Hz), 4.10 (1H, dd, J = 5.0, 10.3 Hz), 4.25 (1H, dd, J = 5.0, 10.1 Hz), 4.44 (1H, s), 5.59 (1H, s), 7.33–7.41 (9H, m), 7.47–7.49 (2H, m), 7.66–7.68 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.9, −4.8, 18.1, 19.3, 21.0, 25.9, 26.9, 31.6, 43.6, 55.0, 59.4, 64.1, 69.7, 70.7, 101.9, 102.7, 126.2, 127.5, 128.2, 128.8, 129.4, 134.1, 135.5, 135.5, 137.9. IR (neat, cm^{-1}) 2953, 2930, 2859, 1591, 1543, 1140, 1107, 1049, 1028, 1012, 700. LRMS (EI(+)) *m*/*z* 437 ([M−TBDPS]$^+$), 421([M−OTBDPS]$^+$), 363, 199, 183. HRMS calcd for $C_{23}H_{37}O_6Si$ ([M−TBDPS]$^+$) 437.2356, found 437.2386.

3.5.3. Methyl 2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3-deoxy-α-D-altropyranoside. Li metal (83 mg, 2.59 mmol) was dissolved in liquid NH_3 (30 mL) at −78 °C, and to this was added a solution of **17** (500 mg, 0.74 mmol) in THF (9 mL). After stirred at the same temperature for 15 min, solid NH_4Cl was added. Excess NH_3 was volatized, and the residue was partitioned between CH_2Cl_2 (300 mL) and water (30 mL). The layers were separated, and the organic layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (9:1 to 4:1)) gave the diol (411 mg, 95%) as a colorless oil.

$[\alpha]_D^{22}$ +34.6° (*c* 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (6H, s), 0.88 (9H, s), 1.05 (9H, s), 1.56–1.71 (4H, m), 1.73–1.77 (1H, m), 2.04–2.07 (1H, m), 3.34 (3H, s), 3.67–3.71 (4H, m), 3.75 (1H, dd, J = 5.4, 11.2 Hz), 3.81 (1H, dd, J = 3.9, 11.2 Hz), 4.02 (1H, br s), 4.42 (1H, d, J = 1.7 Hz), 7.26–7.44 (6H, m), 7.66–7.68 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.7, 18.1, 19.2, 20.8, 25.9, 26.9, 30.9, 44.1, 55.1, 63.7, 64.2, 66.4, 70.9, 71.6, 103.6, 127.5, 129.5, 133.8, 135.5. IR (neat, cm^{-1}) 3430, 3073, 2955, 2930, 2899, 2859, 1472, 1427, 704. LRMS (EI(+)) *m*/*z* 349 ([M−TBDPS]$^+$), 289, 199, 181. HRMS calcd for $C_{16}H_{33}O_6Si$ ([M−TBDPS]$^+$) 349.2046, found 349.2041.

3.5.4. Methyl 2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3-deoxy-6-*O*-(triphenylmethyl)-α-D-altropyranoside (18). To a solution of the diol prepared as above (322 mg, 0.54 mmol) in DMF (3 mL) were added TrCl (452 mg, 1.62 mmol) and DMAP (198 mg, 1.62 mmol), and stirred at 75 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between Et_2O (15 mL) and water (15 mL). The layers were separated, and the organic layer was washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (20:1)) gave the product **18** (403 mg, 93%) as a colorless oil.

$[\alpha]_D^{22}$ +12.0° (*c* 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (6H, s), 0.89 (9H, s), 1.04 (9H, s), 1.50–1.62 (3H, m), 1.67–1.75 (2H, m), 2.23 (1H, br s), 3.30–3.37 (5H, m), 3.63–3.67 (3H, m), 3.74 (1H, dd, J = 5.3, 12.0 Hz), 3.95 (1H, br s), 4.39 (1H, d, J = 2.7 Hz), 7.17–7.40 (15H, m), 7.46–7.48 (6H, m), 7.66–7.68 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.7, −4.5, 18.1, 19.2, 21.2, 25.9, 26.9, 30.9, 43.3, 55.1, 64.3, 64.9, 67.5, 71.1, 71.7, 103.7, 127.0, 127.5, 127.8, 127.8, 128.6, 129.4, 133.9, 135.5, 143.7. IR (neat, cm^{-1}) 3456, 3069, 3032, 2934, 2893, 2859, 1597, 1489, 1472, 1449, 1109, 1046, 767, 704. LRMS (FAB(+), NBA) *m*/*z* 853 ([M+Na]$^+$). HRMS (FAB(+), NBA) calcd for $C_{51}H_{66}O_6Si_2Na$ ([M+Na]$^+$) 853.4249, found 853.4272.

3.5.5. *O*-[(2*R*,3*S*,4*R*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-{3-(*tert*-butyldiphenylsilyloxy)propyl}-6-methoxy-2-{(triphenylmethyloxy)methyl}tetrahydropyran-3-yl] *S*-methyl dithiocarbonate. Under an Ar atmosphere, to a solution of **18** (108 mg, 0.13 mmol) in Et_2O (500 μL) were added CS_2 (23 μL, 0.39 mmol) and NaH (60% in oil, 260 mg, 6.5 mmol), and stirred at room temperature for 1 h. MeI (80 μL, 1.3 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, diluted with Et_2O (100 mL), and washed with saturated aqueous NH_4Cl solution (10 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (30:1)) gave the xanthate (111 mg, 93%) as a white amorphous solid.

$[\alpha]_D^{21}$ +43.5° (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.08 (6H, s), 0.92 (9H, s), 1.02 (9H, s), 1.32–1.58 (3H, m), 1.77–1.86 (1H, m), 2.17–2.23 (1H, m), 2.39 (3H, s), 3.23 (1H, dd, J = 5.5, 10.0 Hz), 3.36 (1H, dd, J = 3.5, 10.0 Hz), 3.39 (3H, s), 3.60 (2H, t, J = 6.1 Hz), 3.70 (1H, dd, J = 3.4, 6.9 Hz), 4.01 (1H, dt, J = 3.5, 5.5 Hz), 4.49 (1H, d, J = 3.4 Hz), 6.08 (1H, dt, J = 4.4, 6.4 Hz), 7.19–7.23 (3H, m), 7.25–7.29 (6H, m), 7.32–7.39 (6H, m), 7.47–7.49 (6H, m), 7.62–7.65 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.5, 18.1, 18.1, 18.7, 19.2, 22.1, 25.9, 26.8, 30.7, 41.8, 55.3, 63.3, 64.0, 71.8, 78.1, 86.6, 103.3, 126.9, 127.6, 127.8, 128.8, 129.5, 134.0, 135.6, 143.9, 214.3. IR (film, cm^{-1}) 2953, 2930, 2885, 2867, 1651, 1581, 1462, 1447, 1428, 1109, 1059, 750, 700. LRMS (FAB(+), NBA) *m*/*z* 943 ([M+Na]$^+$). HRMS (FAB(+), NBA) calcd for $C_{53}H_{68}O_6Si_2S_2Na$ ([M+Na]$^+$) 943.3894, found 943.3902.

3.5.6. Methyl 2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3,4-dideoxy-6-*O*-(triphenylmethyl)-α-D-altropyranoside (19). To a solution of xanthate prepared as above (347 mg, 0.38 mmol) in benzene (1.3 mL) were added *n*-Bu_3SnH (511 μL, 1.9 mmol) and AIBN (37 mg, 0.23 mmol), and stirred at 80 °C for 7 h. The reaction mixture was cooled to room tempera-

ture, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt (50:1)) gave the product **19** (309 mg, quant.) as a colorless oil.

$[\alpha]_D^{21}$ +7.0° (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.03 (6H, s), 0.87 (9H, s), 1.04 (9H, s), 1.14–1.20 (1H, m), 1.30–1.39 (2H, m), 1.42–1.62 (2H, m), 1.64–1.80 (2H, m), 3.01 (1H, dd, *J* = 4.5, 9.6 Hz), 3.23 (1H, dd, *J* = 6.5, 9.6 Hz), 3.35 (1H, dd, *J* = 2.7, 5.3 Hz), 3.37 (3H, s), 3.63 (2H, t, *J* = 6.3 Hz), 3.86–3.93 (1H, m), 4.41 (1H, d, *J* = 2.7 Hz), 7.20–7.24 (3H, m), 7.26–7.30 (6H, m), 7.33–7.39 (6H, m), 7.47–7.49 (6H, m), 7.64–7.67 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.7, −4.5, 18.2, 19.3, 25.9, 26.9, 27.1, 30.6, 37.6, 54.9, 64.1, 65.4, 66.7, 72.1, 86.4, 103.2, 126.8, 127.5, 127.7, 128.7, 129.4, 134.0, 135.5, 135.5, 144.1. IR (neat, cm^{-1}) 2928, 2896, 2859, 1491, 1462, 1448, 1427, 1111, 1046, 775, 706. LRMS (FAB(+), NBA) *m*/*z* 838 ($[M+Na]^+$). HRMS (FAB(+), NBA) calcd for $C_{51}H_{66}O_5Si_2Na$ ($[M+Na]^+$) 837.4346, found 837.4357.

3.5.7. Methyl 2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3,4-dideoxy-α-D-altro-pyranoside. Under an Ar atmosphere, to a cooled (−15 °C) solution of **19** (309 mg, 0.38 mmol) in CH_2Cl_2 (3.8 mL) was added Et_2AlCl (0.9 M in hexane, 989 μL, 0.92 mmol) and stirred at the same temperature for 5 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL), and the mixture was extracted with Et_2O (200 mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (5:1)) gave the product (202 mg, 93%) as a colorless oil.

$[\alpha]_D^{22}$ +17.2° (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.03 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.05 (9H, s), 1.14 (1H, dt, *J* = 3.8, 13.2 Hz), 1.44–1.75 (5H, m), 1.82–1.88 (1H, m), 2.01 (1H, br s), 3.33 (3H, s), 3.43 (1H, dd, *J* = 2.1, 4.2 Hz), 3.57 (2H, br t, *J* = 4.5 Hz), 3.65 (2H, t, *J* = 6.3 Hz), 3.83–3.89 (1H, m), 4.45 (1H, d, *J* = 2.1 Hz), 7.35–7.43 (6H, m), 7.65–7.67 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.6, 18.2, 19.3, 25.9, 26.2, 27.0, 30.8, 37.6, 54.9, 64.0, 65.7, 66.0, 71.2, 103.1, 127.5, 129.4, 134.0, 135.5, 135.5. IR (neat, cm^{-1}) 3476, 2930, 2897, 2859, 1653, 1557, 1541, 1111, 1044, 702. LRMS (EI(+)) *m*/*z* 541 ($[M-OCH_3]^+$), 397, 321, 295. HRMS calcd for $C_{31}H_{49}O_4Si_2$ ($[M-OCH_3]^+$) 541.3169, found 541.3168.

3.5.8. Methyl 2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3,4-dideoxy-6-*O*-(methanesulfonyl)-α-D-altropyranoside. Under an Ar atmosphere, to a cold (0 °C) solution of the alcohol prepared as above (200 mg, 0.35 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (397 μL, 1.05 mmol), and MsCl (81 μL, 1.05 mmol) and stirred at the same temperature for 5 min. The reaction was quenched by the addition of water (10 mL), and the mixture was extracted with AcOEt (200 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (4:1)) gave the mesylate (220 mg, 97%) as a colorless oil.

$[\alpha]_D^{22}$ +22.1° (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 1.05 (9H, s), 1.19–1.22 (1H, m), 1.46–1.57 (3H, m), 1.69–1.75 (1H, m), 1.89–1.94 (1H, m), 3.07 (3H, s), 3.32 (3H, s), 3.43 (3H, br s), 3.98–4.04 (1H, m), 4.19 (1H, dd, *J* = 6.5, 11.0 Hz), 4.27 (1H, dd, *J* = 2.9, 11.0 Hz), 4.44 (1H, s), 7.36–7.43 (6H, m), 7.65–7.67 (4H, m). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ −4.8, −4.7, 18.1, 19.3, 25.8, 25.9, 26.7, 26.9, 30.8, 37.8, 55.1, 63.4, 63.9, 70.4, 72.5, 103.0, 127.5, 129.4, 133.9, 135.5. IR (neat, cm^{-1}) 2953, 2932, 2903, 2859, 1472, 1429, 1176, 1113, 1049, 704. LRMS (EI(+)) *m*/*z* 593 (M^+-t-Bu), 531, 277, 153, 73. HRMS (EI(+)) calcd for $C_{29}H_{45}O_7Si_2S$ ($[M-t$-Bu$]^+$) 593.2424, found 593.2424.

3.5.9. Methyl 6-Bromo-2-*O*-(*tert*-butyldimethylsilyl)-3-*C*-{3-(*tert*-butyldiphenylsilyloxy)propyl}-3,4,6-trideoxy-α-D-altropyranoside (20). Under an Ar atmosphere, to a solution of the mesylate prepared as above (75.5 mg, 0.12 mmol) in 2-butanone (1.2 mL) was added LiBr (52 mg, 0.60 mmol) and stirred at reflux for 7 h. After cooled to room temperature, water (3 mL) was added, and the mixture was extracted with AcOEt (30 mL). The organic layer was washed with brine (3 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (9:1)) gave the bromide 20 (67.2 mg, 91%) as a colorless oil.

$[\alpha]_D^{22}$ +19.4° (*c* 4.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.02 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.05 (9H, s), 1.35 (1H, dt, *J* = 3.8, 13.3 Hz), 1.41–1.61 (3H, m), 1.62–1.74 (2H, m), 1.81–1.88 (1H, m), 3.34 (1H, dd, *J* = 4.6, 10.5 Hz), 3.37 (3H, s), 3.38–3.43 (2H, m), 3.66 (2H, t, *J* = 6.3 Hz), 3.91–3.98 (1H, m), 4.46 (1H, d, *J* = 2.2 Hz), 7.36–7.44 (6H, m), 7.65–7.68 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.6, 18.2, 19.3, 25.9, 25.9, 26.7, 26.7, 29.2, 30.7, 35.8, 38.3, 55.1, 63.9, 65.7, 70.9, 103.2, 127.5, 129.4, 133.9, 135.5, 135.5. IR (neat, cm^{-1}) 2953, 2955, 2934, 2892, 2855, 1684, 1651, 1458, 1115, 1035, 702. LRMS (EI(+)) *m*/*z* 603 ($[M-OMe]^+$), 545 ($[M-t$-Bu$-$MeOH$]^+$), 289, 197. HRMS (EI(+)) calcd for $C_{31}H_{48}O_3{}^{79}BrSi_2$ ($[M-OMe]^+$) 603.2325, found 603.2325.

3.5.10. (2*S*,3*R*)-2-{(*tert*-Butyldimethylsilyl)oxy}-3-(*tert*-butyldiphenylsilyloxy)hex-5-en-1-ol (21). Under an Ar atmosphere, to a solution of **20** (136 mg, 0.21 mmol) in *n*-propanol (3 mL) was added water (500 μL) and warmed to 110 °C. Zn dust (activated by sequential treatment with dil. HCl aq, water, EtOH, and Et_2O, 696 mg, 10.7 mmol) and $NaBH_3CN$ (402 mg, 6.4 mmol) were added and stirred at the same temperature for 20 min. Another Zn dust (696 mg, 10.7 mmol) and $NaBH_3CN$ (402 mg, 6.4 mmol) were added and stirred at the same temperature for 20 min. The mixture was cooled to room temperature, and insoluble materials were filtered off through Celite, and washed with AcOEt and water. The organic layer of the filtrate was washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography

(hexane/AcOEt (15:1)) gave the alcohol **21** (92 mg, 81%) as a colorless oil.

$[\alpha]_D^{21}$ −0.9° (*c* 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.07 (3H, s), 0.09 (3H, s), 0.90 (9H, s), 1.04 (9H, s), 1.31–1.43 (2H, m), 1.53–1.62 (2H, m), 1.72 (1H, t, J = 6.3 Hz), 1.90 (1H, dt, J = 7.4, 13.8 Hz), 2.31 (1H, dt, J = 7.4, 13.8 Hz), 3.54 (2H, t, J = 5.6 Hz), 3.63 (2H, t, J = 6.3 Hz), 3.74–3.77 (1H, m), 4.98 (1H, d, J = 10.0 Hz), 5.00 (1H, d, J = 17.1 Hz), 5.73 (1H, ddt, J = 7.1, 10.0, 17.1 Hz), 7.35–7.44 (6H, m), 7.65–7.67 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.4, −4.4, 18.2, 19.3, 25.8, 25.9, 26.9, 30.7, 36.2, 34.3, 41.6, 63.7, 64.1, 115.9, 127.5, 129.5, 133.9, 135.5, 137.6. IR (neat, cm^{-1}) 3443, 3073, 2932, 2894, 2857, 1640, 1472, 1428, 1113, 1007, 704. LRMS (EI(+)) *m*/*z* 508 ($[M-H_2O]^+$), 495 ($[M-OMe]^+$), 467, 199. HRMS (EI(+)) calcd for $C_{31}H_{48}O_2Si_2$ ($[M-H_2O]^+$) 508.3187, found 508.3190.

3.5.11. 4-{(1*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(*p*-toluenesulfonyloxy)}ethyl-7-(*tert*-butyldiphenylsilyloxy) hept-1-ene. Under an Ar atmosphere, to a solution of **21** (95 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added TsCl (38 mg, 0.20 mmol), Et_3N (62 μL, 0.45 mmol), and DMAP (44 mg, 0.36 mmol), and stirred at room temperature for 4 h. The reaction mixture was diluted with AcOEt (30 mL) and washed with water (3 mL) and brine (3 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (15:1)) gave the tosylate (112 mg, 91%) as a colorless oil.

$[\alpha]_D^{21}$ +7.6° (*c* 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.01 (6H, s), 0.84 (9H, s), 1.03 (9H, s), 1.22–1.54 (5H, m), 1.90 (1H, dt, J = 7.0, 14.1 Hz), 2.16 (1H, dt, J = 7.0, 14.1 Hz), 2.42 (3H, s), 3.56 (1H, dd, J = 5.2, 10.0 Hz), 3.61 (1H, dd, J = 6.2, 10.0 Hz), 3.88 (2H, t, J = 6.3 Hz), 3.93–3.96 (1H, m), 4.95–4.99 (2H, m), 5.61–5.71 (1H, m), 7.31 (2H, d, J = 8.2 Hz), 7.36–7.45 (6H, m), 7.64–7.66 (4H, m), 7.77 (2H, d, J = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.2, 18.1, 19.2, 21.7, 25.2, 25.8, 26.9, 30.6, 34.3, 41.7, 63.9, 71.4, 71.7, 116.2, 127.5, 127.9, 129.5, 129.7, 133.9, 135.5, 137.1, 144.6. IR (neat, cm^{-1}): 2995, 2924, 2911, 2861, 1599, 1364, 1179, 1111, 704. LRMS (EI(+)) *m*/*z* 623 ($[M-t\text{-Bu}]^+$), 451, 427, 229. HRMS (EI(+)) calcd for $C_{34}H_{47}O_5Si_2S$ ($[M-t\text{-Bu}]^+$) 623.2682, found 623.2687.

3.5.12. (4*R*)-4-[(*S*)-Oxiranyl]hept-6-en-1-ol. Under an Ar atmosphere, to a solution of the tosylate prepared as above (92 mg, 0.14 mmol) in THF (1.4 mL) was added TBAF (1 M in THF, 1 mL, 1 mmol) and stirred at room temperature for 1.5 h. The mixture was diluted with AcOEt (20 mL) and washed with saturated aqueous NH_4Cl solution (2 mL), brine (2 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (5:1 to 1:1)) gave the epoxide (16 mg, 75%) as a colorless oil.

$[\alpha]_D^{21}$ +6.4° (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.21–1.30 (1H, m), 1.53–1.59 (1H, m), 1.65–1.74 (2H, m), 2.09–2.17 (2H, m), 2.49 (1H, dd, J = 3.2, 4.6 Hz), 2.72–3.63 (2H, m), 3.63 (1H, dd, J = 2.8, 6.4 Hz), 3.67 (1H, dd, J = 2.8, 6.4 Hz), 5.02 (1H, br d, J = 10.5 Hz), 5.06 (1H, br d, J = 17.8 Hz), 5.78 (1H, ddt, J = 7.2, 10.4, 17.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 29.1, 30.0, 36.2, 41.3, 46.6, 56.0, 63.2, 116.5, 135.9. IR (neat, cm^{-1}) 1601, 1584, 1453. LRMS (EI(+)) *m*/*z* 156 (M^+), 125 ($[M-CH_2OH]^+$), 107. HRMS (EI(+)) calcd for $C_9H_{16}O_2$ (M^+), 156.1150, found 156.1152.

3.5.13. (4*R*,5*S*)-4-{3-(*tert*-Butyldimethylsilyloxy)propyl}-5,6-epoxyhex-1-ene (22). Under an Ar atmosphere, to a solution of the epoxy alcohol prepared as above (47.6 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (86 mL, 0.62 mmol), TBSCl (93 mg, 0.62 mmol), and DMAP (38 mg, 0.31 mmol), and stirred at room temperature for 1 h. DMAP (38 mg, 0.31 mmol) was added and stirred at room temperature for 1 h. The mixture was diluted with AcOEt (50 mL), washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (15:1)) gave the product **22** (71.6 mg, 85%) as a colorless oil.

$[\alpha]_D^{21}$ −0.6° (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (6H, s), 0.89 (9H, s), 1.20–1.25 (1H, m), 1.47–1.53 (2H, m), 1.58–1.67(2H, m), 2.10 (1H, dd, J = 7.1, 14.0 Hz), 2.17 (1H, dd, J = 7.1, 14.0 Hz), 2.49 (1H, dd, J = 3.4, 4.4 Hz), 2.71–2.75 (2H, m), 3.61 (2H, t, J = 6.3 Hz), 5.01 (1H, br d, J = 11.2 Hz), 5.05 (1H, br d, J = 19.0 Hz), 5.78 (1H, ddt, J = 7.1, 10.3, 17.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.2, 0.1, 18.4, 26.0, 28.7, 32.1, 36.0, 46.5, 55.9, 63.2, 116.3, 136.1. IR (neat, cm^{-1}) 2953, 2930, 2901, 2859, 1640, 1255, 1101. LRMS (EI(+)) *m*/*z* 213 ($[M-t\text{-Bu}]^+$), 183, 101. HRMS (EI(+)) calcd for $C_{11}H_{21}O_2Si$ ($[M-t\text{-Bu}]^+$) 213.1311, found 213.1287.

3.5.14. (4*R*,5*R*)-5-{3-(*tert*-Butyldimethylsilyloxy)propyl}-1-(trimethylsilyl)oct-7-en-1-yn-4-ol. Under an Ar atmosphere, to a cooled (−78 °C) solution of TMS acetylene (49 μL, 0.35 mmol) in THF (2 mL) was added *n*-BuLi (1.5 M in hexane, 189 μL, 0.3 mmol) and stirred at the same temperature for 10 min. To the resulting lithium acetylide solution was added a solution of **22** (27.2 mg, 0.10 mmol) in THF (2 mL) via cannula, and then $BF_3{\cdot}OEt_2$ (14 mL, 0.11 mmol) was added. The mixture was stirred at the same temperature for 25 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL), and the mixture was extracted with AcOEt (100 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (20:1)) gave enyne (26.3 mg, 71%) as a colorless oil.

$[\alpha]_D^{23}$ +0.9° (*c* 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.04 (6H, s), 0.15 (9H, s), 0.89 (9H, s), 1.31–1.40 (1H, m), 1.42–1.67 (4H, m), 2.04 (1H, dt, J = 7.1, 14.0 Hz), 2.22 (1H, dt, J = 7.1, 14.0 Hz), 2.40 (1H, dd, J = 7.3, 16.8 Hz), 2.45 (1H, dd, J = 5.4, 16.8 Hz), 3.59 (2H, t, J = 6.4 Hz), 3.72–3.77 (1H, m), 5.02 (1H, br d, J = 10.1 Hz), 5.06 (1H, br d, J = 17.4 Hz), 5.78 (1H,

ddt, J = 7.1, 10.1, 17.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.3, 0.0, 18.2, 24.5, 25.9, 26.0, 30.3, 34.5, 41.9, 63.2, 71.3, 87.3, 103.4, 116.2, 136.7. IR (neat, cm^{-1}) 2957, 2932, 2903, 2859, 2176, 1252, 1009, 845. LRMS (EI(+)) m/z 368 (M^+), 311 ([M−t-Bu]$^+$), 293 ([M−t-Bu−H_2O]$^+$), 219. HRMS (EI(+)) calcd for $C_{20}H_{40}O_2Si_2$ (M^+) 368.2567, found 368.2559.

3.5.15. (4*R*,5*R*)-5-{3-(*tert*-Butyldimethylsilyloxy)propyl}-oct-7-en-1-yn-4-ol. The enyne alcohol prepared as above (26.3 mg, 0.071 mmol) was dissolved in MeOH (500 mL) and to the solution was added K_2CO_3 (14.7 mg, 0.107 mmol). After stirred at room temperature for 3.5 h, the reaction mixture was diluted with saturated aqueous NH_4Cl solution (3 mL), and the mixture was extracted with AcOEt (30 mL). The organic layer was washed with brine (3 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (PhMe/AcOEt (15:1)) gave the product (17.5 mg, 83%) as a colorless oil.

$[\alpha]_D^{22}$ −5.0° (c 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (6H, s), 0.89 (9H, s), 1.36–1.42 (1H, m), 1.44–1.54 (2H, m), 1.59–1.68 (2H, m), 2.02–2.10 (3H, m), 2.23 (1H, dt, J = 6.9, 14.0 Hz), 2.40 (1H, t, J = 2.7 Hz), 2.41 (1H, dd, J = 1.1, 2.7 Hz), 3.60 (2H, t, J = 6.3 Hz), 3.75–3.80 (1H, m), 5.04 (1H, br d, J = 10.0 Hz), 5.07 (1H, br d, J = 17.1 Hz), 5.79 (1H, ddt, J = 7.1, 10.0, 17.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.2, 18.4, 24.6, 24.7, 26.0, 26.0, 30.3, 34.7, 42.0, 63.3, 70.6, 71.6, 81.3, 116.3, 136.7. IR (neat, cm^{-1}) 3422, 3306, 2934, 2859, 2116, 1638, 1256, 1098, 837, 700. LRMS (EI(+)) m/z 239 ([M−t-Bu]$^+$), 221([M−t-Bu−H_2O]$^+$), 147, 105. HRMS (EI(+)) calcd for $C_{13}H_{23}O_2Si$ ([M−t-Bu]$^+$) 239.1467, found 239.1465.

3.5.16. (4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-{3-(*tert*-butyldimethylsilyloxy)propyl}oct-1-en-7-yne (23). Under an Ar atmosphere, to a cold (0 °C) solution of the alcohol prepared as above (17.5 mg, 0.059 mmol) in CH_2Cl_2 (600 mL) were added 2,6-lutidine (20 μL, 0.177 mmol) and TBSOTf (20 μL, 0.089 mmol), and stirred at the same temperature for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (3 mL), and the mixture was extracted with AcOEt (30 mL). The organic layer was washed with brine (3 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (100:1)) gave the product **23** (24 mg, quant.) as a colorless oil.

$[\alpha]_D^{21}$ −6.5° (c 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (6H, s), 0.06 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 0.89 (9H, s), 1.24–1.73 (6H, m), 1.99 (1H, dt, J = 7.0, 14.0 Hz), 2.21 (1H, dt, J = 7.0, 14.0 Hz), 2.29 (1H, ddd, J = 2.7, 6.4, 16.8 Hz), 2.36 (1H, ddd, J = 2.7, 6.4, 16.8 Hz), 3.59 (2H, t, J = 6.3 Hz), 3.87 (1H, ddd, J = 3.2, 6.4, 6.4 Hz), 5.03 (2H, dd, J = 10.1, 17.1 Hz), 5.77 (1H, ddt, J = 7.0, 10.1, 17.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.2, −4.6, −4.1, 18.1, 18.4, 24.4, 24.9, 25.9, 26.0, 31.0, 34.7, 42.5, 63.5, 69.8, 72.3, 82.1, 115.7, 137.7. IR (neat, cm^{-1}) 2957, 2930, 2890, 2857, 2161, 1507, 1254, 1099, 837, 708, 671. LRMS (EI(+)) m/z 410 (M^+), 353 ([M−t-Bu]$^+$), 221, 147. HRMS (EI(+)) calcd for $C_{23}H_{46}O_2Si_2$ (M^+) 410.3019, found 410.3028.

3.5.17. 2α-(3-Hydroxypropyl)-25-hydroxyvitamin D_3 (3). Under an Ar atmosphere, a mixture of A-ring enyne **23** (4.4 mg, 10.7 μmol), CD-ring bromoolefin **6**[12] (20.0 mg, 56.0 μmol), $Pd(PPh_3)_4$ (6.3 mg, 5.5 μmol), PhMe (500 μL), and Et_3N (1.0 mL) was stirred at 110 °C for 2 h. After cooled to room temperature, the mixture was diluted with Et_2O and filtered through Celite. The filtrate was diluted with AcOEt (20 mL), and washed with water (2× 1 mL), brine (1 mL), dried ($MgSO_4$), and concentrated. The residue was partially purified through silica gel pad (eluent: hexane/AcOEt (20:1)) to remove polar materials and dissolved in THF (50 μL). The TBAF solution (1 M in THF, 110 μL, 0.11 mmol) was added, and stirred at room temperature for 2 h. The mixture was partitioned between AcOEt (20 mL) and water (1 mL), and the organic layer was washed with water (1 mL) and brine (1 mL), dried ($MgSO_4$), and concentrated. Purification by preparative TLC (AcOEt) gave the product (1.7 mg, 35% for 2 steps) as a while amorphous.

$[\alpha]_D^{18}$ +27.0° (c 0.04, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 0.54 (3H, s), 0.93 (3H, d, J = 6.6 Hz), 1.03–1.08 (1H, m), 1.19–1.20 (1H, m), 1.21 (6H, s), 1.23–1.33 (5H, m), 1.36–1.49 (9H, m), 1.51–1.73 (8H, m), 1.84–1.93 (2H, m), 1.96–2.02 (2H, m), 2.25 (1H, dd, J = 8.8, 13.1 Hz), 2.47 (1H, dd, J = 4.5, 13.7 Hz), 2.61 (1H, dd, J = 4.0, 13.1 Hz), 2.82 (1H, dd, J = 3.5, 12.1 Hz), 3.55–3.59 (1H, m), 3.67 (2H, br s), 4.83 (1H, s), 5.04 (1H, s), 6.02 (1H, d, J = 11.3 Hz), 6.22 (1H, d, J = 11.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 12.0, 18.8, 20.8, 22.2, 23.5, 27.7, 27.8, 29.0, 29.2, 29.4, 29.8, 36.1, 36.4, 37.9, 40.5, 44.4, 44.4, 44.6, 45.9, 56.4, 56.3, 56.5, 63.1, 71.2, 73.5, 113.0, 117.4, 121.9, 135.2, 142.4, 144.1. IR (film, cm^{-1}) 3374, 2951, 2928, 2897, 2851, 1674, 1615, 1555, 1458, 1053. LRMS (EI(+)) m/z 458 (M^+), 440 ([M−H_2O]$^+$), 341, 311. HRMS (EI(+)) calcd for $C_{30}H_{50}O_3$ (M^+) 458.3760, found 458.3758.

3.6. Synthesis of 1α- and 1β-hydroxymethyl-2-unsubstituted analogues (4a, 4b)

3.6.1. (2*R*,3*S*,5*S*,6*S*)-2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxytetrahydropyran-3-ol (25). Under an Ar atmosphere, to a suspension of **24**[17] (93.1 mg, 0.245 mmol), MS3A (241.1 mg), and Et_3SiH (195 μL, 1.22 mmol) in CH_2Cl_2 (2.5 mL) was added TFA (95 μL, 1.23 mmol) and stirred at 0 °C, and gradually raised up to room temperature for 6 h. The reaction was quenched by the addition of saturated aqueous Na_2CO_3 solution (5 mL), and the mixture was filtered through Celite pad and the solid was washed with CH_2Cl_2 and water. Layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (5:1)) gave the products **25** (69.6 mg, 76%,) as a colorless oil.

$[\alpha]_D^{18}$ +35.6° (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.78 (1H, ddd, *J* = 2.5, 11.2, 12.8 Hz), 1.95 (1H, ddd, *J* = 3.4, 4.6, 12.8 Hz), 2.63 (1H, br s), 3.37 (3H, s), 3.62–3.74 (2H, m), 3.78 (1H, dd, *J* = 4.8, 9.2 Hz), 3.83 (1H, m), 3.97 (1H, ddd, *J* = 4.6, 9.0, 11.2 Hz), 4.39 (1H, s), 4.57 (1H, d, *J* = 11.8 Hz), 4.64 (1H, d, *J* = 11.8 Hz), 7.26–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.8, 18.1, 25.8, 35.0, 54.7, 65.5, 68.4, 70.8, 72.2, 73.7, 100.3, 127.6, 127.7, 128.4, 137.7. IR (neat, cm^{-1}) 3445, 2930, 1464, 1256, 1132, 837, 735. LRMS (EI(+)) *m*/*z* 382 (M^+), 363 ([M−H_2O−H]$^+$), 351 ([M−OMe]$^+$), 333 ([M−H_2O−OMe]$^+$), 325 ([M−*t*-Bu]$^+$), 307 ([M−H_2O−*t*-Bu]$^+$), 293 ([M−*t*-Bu−MeOH]$^+$), 275, 257, 225, 203, 185, 159, 101, 91 (C_7H_7, bp). HRMS (EI(+)) calcd for $C_{20}H_{34}O_5Si$ (M^+) 382.2176, found 382.2175.

3.6.2. (2*R*,5*S*,6*S*)-2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxytetrahydropyran-3-one. A mixture of alcohol **25** (3.02 g, 7.89 mmol), MS4A (6.49 g), NMO (1.36 g, 11.6 mmol), TPAP (136.4 mg, 0.388 mmol) in CH_2Cl_2 (75 mL) was stirred at room temperature for 0.5 h. The mixture was filtered through Celite, washed with CH_2Cl_2, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (hexane/AcOEt (15:1)) gave the ketone (2.64 g, 88%) as a colorless oil.

$[\alpha]_D^{19}$ +98.3° (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 2.56 (1H, dd, *J* = 6.1, 15.1 Hz), 2.74 (1H, dd, *J* = 4.4, 15.1 Hz), 3.49 (3H, s), 3.77 (1H, dd, *J* = 5.9, 10.8 Hz), 3.99 (1H, dd, *J* = 2.9, 10.8 Hz), 4.06 (1H, ddd, *J* = 3.0, 4.4, 6.1 Hz), 4.18 (1H, dd, *J* = 2.9, 5.9 Hz), 4.57 (1H, d, *J* = 12.2 Hz), 4.62 (1H, d, *J* = 12.2 Hz), 4.72 (1H, d, *J* = 3.0 Hz), 7.24–7.36 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.8, 18.0, 25.7, 44.4, 55.6, 68.8, 70.5, 73.5, 75.0, 101.9, 127.5, 127.5, 128.2, 138.0, 206.5. IR (neat, cm^{-1}) 2930, 1732, 1254, 1109, 837. LRMS (EI(+)) *m*/*z* 380 (M^+), 349 ([M−OMe]$^+$), 323 ([M−*t*-Bu]$^+$), 291 ([M−*t*-Bu−MeOH]$^+$), 215, 201, 159, 145, 115, 101, 91 (C_7H_7), 89 (bp). HRMS (EI(+)) calcd for $C_{20}H_{32}O_5Si$ (M^+) 380.2019, found 380.2008.

3.6.3. (2*S*,3*S*,6*S*)-6-Benzyloxymethyl-3-(*tert*-butyldimethylsilyloxy)-2-methoxy-5-methylenetetrahydropyran (26). Under an Ar atmosphere, to a cold (−40 °C) mixture of activated Zn dust (3.75 g, 57.4 mmol), CH_2Br_2 (1.2 mL, 17.1 mmol) in THF (40 mL) was added $TiCl_4$ (1.3 mL, 11.9 mmol), and the mixture was stirred at 5 °C (cold room) for 4 d. The mixture was diluted with CH_2Cl_2 (20 mL), and a solution of ketone prepared as above (2.64 g, 6.94 mmol) in CH_2Cl_2 (25 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into a mixture of Et_2O (100 mL)–saturated aqueous $NaHCO_3$ solution (100 mL) and stirred vigorously for several minutes. Resulting mixture was filtered through Celite, washed with Et_2O and water, and the layers of the filtrate were separated. The organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (15:1)) gave the *exo*-methylene compound **26** (2.16 g, 82%) as a colorless oil.

$[\alpha]_D^{16}$ +73.1° (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 2.25 (1H, dd, *J* = 6.2, 13.5 Hz), 2.54 (1H, dd, *J* = 4.4, 13.5 Hz), 3.43 (3H, s), 3.70 (1H, dd, *J* = 6.6, 14.2 Hz), 3.70–3.74 (1H, m), 3.75 (1H, dd, *J* = 4.6, 14.2 Hz), 4.37 (1H, apparent t, *J* = 5.4 Hz), 4.53 (1H, d, *J* = 2.4 Hz), 4.58 (1H, d, *J* = 12.2 Hz), 4.64 (1H, d, *J* = 12.2 Hz), 4.83 (1H, s), 4.86 (1H, t, *J* = 2.0 Hz), 7.24–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.7, 18.2, 25.8, 37.5, 55.2, 70.0, 70.7, 71.1, 73.3, 102.6, 109.9, 127.4, 127.5, 128.2, 138.2, 141.3. IR (neat, cm^{-1}) 2930, 1655, 1472, 1256, 1183, 1100, 837. LRMS (EI(+)) *m*/*z* 378 (M^+), 347 ([M−OMe]$^+$), 321 ([M−*t*-Bu]$^+$), 289 ([M−*t*-Bu−MeOH]$^+$), 257 ([M−BnOCH_2]$^+$), 210, 199, 153, 91 (C_7H_7, bp). HRMS (EI(+)) calcd for $C_{21}H_{34}O_4Si$ (M^+) 378.2226, found 378.2221.

3.6.4. Hydroboration of the *exo*-methylene compound (26). Under an Ar atmosphere, to a cold (0 °C) solution of *exo*-methylene compound **26** (2.16 g, 5.71 mmol) in THF (20 mL) was added BH_3·THF (1 M in THF, 11 mL, 11 mmol), and the mixture was stirred at the same temperature for 1.5 h. 1 N NaOH solution (10 mL) and 30% H_2O_2 solution (10 mL) were added, and the solution was stirred the same temperature for 1.5 h. The reaction was quenched by the addition of 10% aqueous $Na_2S_2O_3$ solution (50 mL), and the mixture was extracted with AcOEt (3× 250 mL). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ solution (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (8:1)) gave **27a** (less polar isomer, 1.64 g, 72%) and **27b** (more polar isomer, 185.7 mg, 8%) as colorless oils, respectively.

3.6.5. (2*S*,3*S*,5*S*,6*S*)-[2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxytetrahydropyran-3-yl]methanol (27a). $[\alpha]_D^{20}$ +24.4° (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.10 (6H, s), 0.91 (9H, s), 1.70 (1H, m), 1.83 (1H, m), 2.14 (1H, ddd, *J* = 3.3, 5.9, 14.5 Hz), 3.38 (3H, s), 3.66 (1H, dt, *J* = 1.3, 3.3 Hz), 3.75 (1H, dd, *J* = 6.1, 10.1 Hz), 3.74–3.83 (2H, m), 4.15 (1H, dt, *J* = 3.2, 6.1 Hz), 4.48 (1H, s), 4.56 (1H, d, *J* = 11.8 Hz), 4.63 (1H, d, *J* = 11.8 Hz), 7.25–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.0, −4.9, 18.1, 25.8, 30.9, 35.2, 54.6, 62.9, 66.5, 68.3, 71.0, 73.5, 101.2, 127.6, 128.3, 138.0. IR (KBr, cm^{-1}) 3472, 2928, 1468, 1258, 1123, 1030, 862, 700. LRMS (EI(+)) *m*/*z* 396 (M^+), 379 ([M−OH]$^+$), 365 ([M−MeO]$^+$), 321 ([M−*t*-Bu−H_2O]$^+$), 307 ([M−*t*-Bu−MeOH]$^+$), 289 ([M−BnO]$^+$), 231, 101, 91 (C_7H_7, bp). HRMS (EI(+)) calcd for $C_{21}H_{36}O_5Si$ (M^+) 396.2332, found 396.2347.

3.6.6. (2*S*,3*R*,5*S*,6*S*)-[2-Benzyloxymethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxytetrahydropyran-3-yl]methanol (27b). $[\alpha]_D^{21}$ +34.3° (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.05 (6H, s), 0.89 (9H, s), 1.52 (1H, m), 1.68 (1H, ddd, *J* = 2.7, 13.1, 13.1 Hz), 2.16 (1H,

m), 2.75 (1H, br s), 3.36 (3H, s), 3.46 (1H, dd, $J = 6.6$, 11.7 Hz), 3.49 (1H, dd, $J = 4.0$, 11.7 Hz), 3.62–3.80 (4H, m), 4.43 (1H, s), 4.57 (1H, d, $J = 11.6$ Hz), 4.65 (1H, d, $J = 11.8$ Hz), 7.26–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.7, 18.1, 25.9, 30.1, 35.9, 54.6, 65.1, 66.8, 71.1, 72.8, 73.6, 100.8, 127.7, 127.8, 128.4, 137.5. IR (neat, cm^{-1}) 3476, 2930, 1464, 1256, 1190, 1129, 1055, 1019, 835. LRMS (EI(+)) *m/z* 396 (M^+), 365 ([M−MeO]$^+$), 347 ([M−OH−MeOH]$^+$), 339 ([M−*t*-Bu]$^+$), 321 ([M−*t*-Bu−H_2O]$^+$), 307 ([M−*t*-Bu−MeOH]$^+$), 289 ([M−BnO]$^+$), 243, 101, 91 (C_7H_7, bp). HRMS (EI(+)) calcd for $C_{21}H_{36}O_5Si$ (M^+) 396.2332, found 396.2349.

3.6.7. Epimerization of 27a to 27b. A solution of **27a** (1.11 g, 2.80 mmol), NMO (485.2 mg, 4.14 mmol), and TPAP (57.8 mg, 0.164 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 6 h. NMO (297.2 mg, 2.54 mmol) and TPAP (19.2 mg, 54.6 μmol) were added, and the mixture was stirred at room temperature for another 4 h. TPAP (41.4 mg, 0.118 mmol) was added, and the mixture was further stirred at the same temperature for 12 h. NMO (241.3 mg, 2.06 mmol) was added, and the mixture was further stirred at the same temperature for 6 h. The mixture was washed with 10% aqueous $Na_2S_2O_3$ solution (50 mL), and aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with 0.1 N HCl solution (50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (20 mL), and K_2CO_3 (408 mg, 2.95 mmol) was added. The mixture was stirred at room temperature for 20 min, and $NaBH_4$ (175.0 mg, 4.62 mmol) was added. The mixture was further stirred at the same temperature for 10 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (50 mL), and the mixture was extracted with AcOEt (2× 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (8:1)) gave the epimerized **27b** (650.2 mg, 59%), accompanied by the starting material **27a** (15%).

3.6.8. (2*S*,3*S*,5*S*,6*S*)-2-Bromomethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxytetrahydropyran-3-ylmethyl pivalate (28a). A solution of alcohol **27a** (709.3 mg, 1.79 mmol), PivCl (330 μL, 2.68 mmol) in pyridine (9 mL) was added at room temperature for 2.5 h. The solvent was removed under reduced pressure, and the residue was partitioned between AcOEt (30 mL) and water (30 mL). The organic layer was washed with 1 N HCl solution (20 mL) and water (20 mL), and the aqueous layers were combined and extracted with AcOEt (20 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated to give crude pivalate. The residue was dissolved in EtOH (5 mL), and $Pd(OH)_2$/C (20% dry basis, 27.0 mg) was added. The mixture was stirred under H_2 atmosphere at room temperature for 1 h. Insoluble materials were filtered off and the filtrate was concentrated. The residue was re-dissolved in EtOH (5 mL) and treated with $Pd(OH)_2$/C (20% dry basis, 40.5 mg) under H_2 atmosphere for 3.5 h. Insoluble material was filtered off, and the residue in EtOH (5 mL) was further treated with $Pd(OH)_2$/C (20% dry basis, 128.3 mg) under H_2 atmosphere for 3.5 h. Insoluble material was filtered off, concentrated, and the crude alcohol was dissolved in CH_2Cl_2 (10 mL). Under an Ar atmosphere, the solution was cooled to 0 °C, and Et_3N (750 μL, 5.38 mmol) and MsCl (210 μL, 2.71 mmol) were added. The mixture was stirred at the same temperature for 1 h, and the reaction was quenched by the addition of water (10 mL). Resulting mixture was extracted with AcOEt (2× 30 mL), and the organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give crude mesylate. The crude mesylate was dissolved in TMU (10 mL), and LiBr (489.9 mg, 5.64 mmol) was added. The mixture was stirred under an Ar atmosphere at 80 °C for 7 h. After cooled to room temperature, the mixture was diluted with water (10 mL) and extracted with Et_2O (2× 20 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (25:1 to 4:1 to 2:1)) gave the bromide **28a** (476.4 mg, 59% for four steps) as a colorless oil.

$[\alpha]_D^{22}$ +58.6° (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (3H, s), 0.07 (3H, s), 0.91 (9H, s), 1.19 (9H, s), 1.72 (1H, m), 2.00–2.10 (2H, m), 3.46 (3H, s), 3.40–3.55 (2H, m), 3.61 (1H, m), 4.15 (1H, ddd, $J = 1.8$, 4.0, 9.0 Hz), 4.23 (1H, dd, $J = 3.2$, 11.9 Hz), 4.46 (1H, dd, $J = 8.6$, 11.9 Hz), 4.49 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.0, −4.8, 18.0, 25.8, 27.3, 30.7, 34.1, 35.4, 38.6, 55.0, 64.7, 66.1, 70.3, 102.0, 178.0. IR (neat, cm^{-1}) 2932, 1730, 1466, 1283, 1152, 1129, 1061, 1029, 837, 810, 777. LRMS (EI(+)) *m/z* 421 ([M(^{79}Br)−MeO]$^+$), 395 ([M(^{79}Br)−*t*-Bu]$^+$), 363 ([M(^{79}Br)−*t*-Bu−MeOH]$^+$), 293, 261, 211 (bp), 159. HRMS (EI(+)) calcd for $C_{18}H_{34}{}^{79}BrO_4Si$ ([M−MeO]$^+$) 421.1410, found 421.1418.

Compound **28b** could be prepared according to essentially the same manner (77% for four steps) as a colorless oil.

3.6.9. (2*S*,3*R*,5*S*,6*S*)-2-Bromomethyl-5-(*tert*-butyldimethylsilyloxy)-6-methoxytetrahydropyran-3-ylmethyl pivalate (28b). $[\alpha]_D^{22}$ +51.8° (*c* 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.06 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 1.21 (9H, s), 1.63 (1H, ddd, $J = 3.2$, 3.2, 13.2 Hz), 1.80 (1H, ddd, $J = 2.7$, 13.2, 13.2 Hz), 2.37 (1H, m), 3.41 (3H, s), 3.50 (1H, dd, $J = 7.0$, 11.0 Hz), 3.67 (1H, dd, $J = 2.1$, 11.0 Hz), 3.70–3.78 (2H, m), 3.89 (1H, dd, $J = 5.2$, 11.7 Hz), 4.03 (1H, dd, $J = 4.6$, 11.7 Hz), 4.49 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.7, 18.1, 25.8, 27.2, 30.1, 32.9, 34.9, 38.9, 54.8, 65.1, 66.4, 70.3, 100.7, 178.1. IR (neat, cm^{-1}) 2932, 1732, 1474, 1285, 1256, 1144, 1113, 1032, 837, 776. LRMS (EI(+)) *m/z* 421 ([M(^{79}Br)−MeO]$^+$), 395 ([M(^{79}Br)−*t*-Bu]$^+$), 363 ([M(^{79}Br)−*t*-Bu−MeOH]$^+$), 319, 293 (bp), 211, 159. HRMS (EI(+)) calcd for $C_{18}H_{34}{}^{79}BrO_4Si$ ([M−MeO]$^+$) 421.1410, found 421.1412.

3.6.10. (*R*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-hydroxypropyl]but-3-enyl pivalate (29a). A mixture of the bromide **28a** (595.3 mg, 1.31 mmol), activated Zn dust (2.18 g, 33.3 mmol), and $NaBH_3CN$ (615.5 mg, 9.79 mmol) in *n*-PrOH (5 mL)–H_2O (0.5 mL) was stirred at 80 °C for 6 h and then 100 °C for 6 h. After cooled to room temperature, the mixture was diluted with saturated aqueous NH_4Cl solution (20 mL), filtered through Celite, and washed with AcOEt and water. After layers were separated, the aqueous layer was extracted with AcOEt (20 mL), and organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (50:1 to 8:1 to 4:1)) gave ring opened product **29a** (337.0 mg, 75%) as a colorless oil.

$[\alpha]_D^{19}$ −14.5° (*c* 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.09 (6H, s), 0.90 (9H, s), 1.19 (9H, s), 1.49 (1H, ddd, *J* = 4.4, 9.6, 14.0 Hz), 1.69 (1H, ddd, *J* = 4.2, 8.2, 14.0 Hz), 1.88 (1H, br s), 2.54 (1H, m), 3.47 (1H, dd, *J* = 4.4, 11.1 Hz), 3.59 (1H, dd, *J* = 4.2, 11.1 Hz), 3.79 (1H, apparent dq, *J* = 8.2, 4.3 Hz), 3.94 (1H, dd, *J* = 6.4, 10.8 Hz), 4.01 (1H, dd, *J* = 6.8, 10.8 Hz), 5.08–5.16 (2H, m), 5.62 (1H, ddd, *J* = 8.5, 11.1, 16.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.4, −4.2, 18.1, 25.9, 27.2, 35.7, 38.8, 39.6, 66.9, 67.2, 70.7, 116.9, 138.5, 178.2. IR (neat, cm^{-1}) 3476, 2932, 1732, 1474, 1287, 1254, 1163, 837, 776. LRMS (EI(+)) *m*/*z* 313 ($[M-CH_2OH]^+$), 287 ($[M-t\text{-}Bu]^+$), 211, 185, 159, 117 (bp). HRMS (EI(+)) calcd for $C_{17}H_{33}O_3Si$ ($[M-CH_2OH]^+$) 313.2199, found 313.2193.

Compound **29b** could also be prepared according to essentially the same manner (61%) as a colorless oil.

3.6.11. (*S*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-hydroxypropyl]but-3-enyl pivalate (29b). $[\alpha]_D^{19}$ +26.0° (*c* 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.08 (6H, s), 0.90 (9H, s), 1.19 (9H, s), 1.49 (1H, ddd, *J* = 5.0, 9.3, 13.9 Hz), 1.69 (1H, ddd, *J* = 5.1, 8.5, 13.9 Hz), 1.90 (1H, br s), 2.41 (1H, m), 3.45 (1H, dd, *J* = 5.0, 11.3 Hz), 3.60 (1H, dd, *J* = 3.5, 11.3 Hz), 3.80 (1H, dddd, *J* = 3.5, 5.0, 5.0, 8.5 Hz), 3.94 (1H, dd, *J* = 5.6, 10.8 Hz), 4.01 (1H, dd, *J* = 7.2, 10.8 Hz), 5.05–5.14 (2H, m), 5.63 (1H, ddd, *J* = 8.8, 10.4, 16.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.5, −4.4, 18.1, 25.9, 27.2, 34.9, 38.8, 40.0, 65.5, 66.7, 70.5, 116.9, 138.4, 178.2. IR (neat, cm^{-1}) 3484, 2932, 1732, 1480, 1287, 1256, 1159, 837, 756. LRMS (EI(+)) *m*/*z* 313 ($[M-CH_2OH]^+$), 287 ($[M-t\text{-}Bu]^+$), 211, 185, 159, 117 (bp). HRMS (EI(+)) calcd for $C_{17}H_{33}O_3Si$ ($[M-CH_2OH]^+$) 313.2199, found 313.2200.

3.6.12. (*R*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(4-toluenesulfonyloxy)propyl]but-3-enyl pivalate. Under an Ar atmosphere, a solution of alcohol **29a** (70.2 mg, 0.203 mmol), Et_3N (85 μL, 0.610 mmol), DMAP (24.7 mg, 0.202 mmol), TsCl (56.9 mg, 0.298 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 13 h. The reaction was quenched by the addition of water (5 mL), and the mixture was extracted with AcOEt (5 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (15:1)) gave tosylate (88.9 mg, 88%) as a colorless oil.

$[\alpha]_D^{21}$ −13.6° (*c* 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.00 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 1.17 (9H, s), 1.38–1.47 (1H, m), 1.52 (1H, ddd, *J* = 3.6, 8.0, 13.6 Hz), 2.45 (3H, s), 2.48–2.59 (1H, m), 3.80–3.91 (3H, m), 3.87 (1H, dd, *J* = 6.4, 10.7 Hz), 3.97 (1H, dd, *J* = 6.2, 10.7 Hz), 5.03–5.14 (2H, m), 5.53 (1H, ddd, *J* = 8.4, 10.4, 17.2 Hz), 7.32–7.38 (2H, m), 7.78–7.81 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.6, −4.1, 18.0, 21.7, 25.8, 27.2, 35.7, 38.8, 39.3, 67.1, 67.9, 73.2, 117.5, 127.9, 129.8, 132.8, 137.9, 144.8, 178.1. IR (neat, cm^{-1}) 2930, 1727, 1480, 1352, 1285, 1175, 1130, 924, 835, 814, 777. LRMS (EI(+)) *m*/*z* 483 ($[M-CH_3]^+$), 441 ($[M-t\text{-}Bu]^+$), 329, 313 ($[M-CH_2OTs]^+$), 230 (bp), 211, 159. HRMS (EI(+)) calcd for $C_{24}H_{39}O_6SSi$ ($[M-CH_3]^+$) 483.2237, found 483.2238.

Tosylate from **29b** could be prepared as essentially the same manner (93%) as a colorless oil.

3.6.13. (*S*)-2-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(4-toluenesulfonyloxy)propyl]but-3-enyl pivalate. $[\alpha]_D^{20}$ +14.4° (*c* 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.00 (3H, s), 0.02 (3H, s), 0.83 (9H, s), 1.17 (9H, s), 1.46 (1H, ddd, *J* = 5.2, 8.8, 13.9 Hz), 1.62 (1H, ddd, *J* = 6.3, 6.3, 13.9 Hz), 2.34–2.50 (1H, m), 2.45 (3H, s), 3.82–3.96 (3H, m), 3.90 (1H, dd, *J* = 5.4, 10.7 Hz), 3.95 (1H, dd, *J* = 6.8, 10.7 Hz), 4.98–5.08 (2H, m), 5.58 (1H, ddd, *J* = 8.6, 10.2, 17.0 Hz), 7.31–7.38 (2H, m), 7.76–7.82 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −4.8, −4.5, 18.0, 21.7, 25.7, 27.2, 35.4, 38.8, 39.4, 66.3, 68.0, 72.7, 117.0, 127.9, 129.7, 132.8, 138.2, 144.7, 178.1. IR (neat, cm^{-1}) 2934, 1730, 1460, 1366, 1285, 1179, 988, 839, 810, 781. LRMS (EI(+)) *m*/*z* 483 ($[M-CH_3]^+$), 441 ($[M-t\text{-}Bu]^+$), 339, 329, 313 ($[M-CH_2OTs]^+$), 229 (bp), 211, 159. HRMS (EI(+)) calcd for $C_{24}H_{39}O_6SSi$ ($[M-CH_3]^+$) 483.2237, found 483.2250.

3.6.14. (*R*)-2-[(*S*)-2-Oxiranylmethyl]but-3-enyl pivalate (30a). To a solution of tosylate (88.9 mg, 0.178 mmol) in THF (0.75 mL) was added TBAF (1 M in THF, 445 μL, 445 μmol), and the solution was stirred at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL) and the mixture was extracted with AcOEt (2×2 mL). The combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (15:1 to 4:1)) gave epoxide **30a** (30.1 mg, 80%) as a colorless oil.

$[\alpha]_D^{21}$ −22.9° (*c* 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.19 (9H, s), 1.55–1.68 (2H, m), 2.48 (1H, dd, *J* = 2.8, 5.0 Hz), 2.68 (1H, m), 2.78 (1H, dd, *J* = 4.4, 5.0 Hz), 2.96 (1H, m), 4.03 (1H, dd, *J* = 6.6, 10.7 Hz), 4.07 (1H, dd, *J* = 6.4, 10.7 Hz), 5.11–5.21 (2H, m), 5.69 (1H, ddd, *J* = 8.6, 10.2, 17.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 27.2, 34.5, 38.8, 41.2, 47.6, 50.4, 66.6, 117.1, 137.7, 178.2. IR (neat, cm^{-1}) 2975, 1730, 1482, 1285, 1157, 1038, 994, 926. LRMS (EI(+)) *m*/*z* 212 (M^+), 182 ($[M-CH_2O]^+$), 57 (*t*-Bu, bp). HRMS (EI(+)) calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1412.

Compound **30b** could also be prepared essentially in the same manner (81%).

3.6.15. (*S*)-2-[(*S*)-2-Oxiranylmethyl]but-3-enyl pivalate (30b). $[\alpha]_D^{22}$ +5.6° (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.19 (9H, s), 1.63 (1H, ddd, *J* = 6.0, 6.0, 14.1 Hz), 1.69 (1H, ddd, *J* = 6.0, 7.8, 14.1 Hz), 2.47 (1H, dd, *J* = 2.7, 5.0 Hz), 2.63 (1H, m), 2.77 (1H, m), 2.97 (1H, ddt, *J* = 2.7, 3.9, 6.0 Hz), 4.03 (1H, dd, *J* = 5.8, 11.0 Hz), 4.09 (1H, dd, *J* = 6.6, 11.0 Hz), 5.10–5.19 (2H, m), 5.75 (1H, ddd, *J* = 8.0, 10.4, 17.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 27.2, 34.3, 38.8, 41.0, 47.1, 50.5, 66.3, 116.6, 138.0, 178.2. IR (neat, cm^{-1}) 2934, 1730, 1482, 1285, 1157, 1036, 995, 924. LRMS (EI(+)) *m*/*z* 212 (M^+), 182 ($[M-CH_2O]^+$), 57 (*t*-Bu, bp). HRMS (EI(+)) calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1422.

3.6.16. (2*R*,4*S*)-2-Vinylhept-6-yne-1,4-diol (31a). To a cooled (−78 °C) solution of the epoxide **30a** (126.9 mg, 0.598 mmol) in THF (1 mL) was added a solution of TMS lithium acetylide (0.5 M in hexane/THF, prepared from TMS–acelylene and *n*-BuLi, 3.6 mL, 1.8 mmol) and $BF_3{\cdot}OEt_2$ (114 μL, 0.90 mmol), and stirred at the same temperature for 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (5 mL), and the mixture was extracted with AcOEt (2× 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (2 mL) and cooled on ice-water bath. NaOMe (28% in MeOH, 345 μL, 1.79 mmol) was added and stirred at room temperature for 18 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (3 mL), and the mixture was extracted with AcOEt (4× 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (AcOEt) gave the diol (72.8 mg, 79%) as a colorless oil.

$[\alpha]_D^{19}$ −18.8° (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.58 (1H, ddd, *J* = 3.3, 8.5, 14.2 Hz), 1.64 (1H, ddd, *J* = 5.5, 9.2, 14.2 Hz), 2.07 (1H, t, *J* = 2.7 Hz), 2.16 (2H, br s), 2.36 (1H, ddd, *J* = 2.7, 6.6, 16.8 Hz), 2.43 (1H, ddd, *J* = 2.7, 5.4, 16.8 Hz), 2.53 (1H, m), 3.56 (2H, d, *J* = 6.0 Hz), 3.84 (1H, dddd, *J* = 3.3, 5.4, 6.6, 9.2 Hz), 5.15–5.22 (2H, m), 5.65 (1H, ddd, *J* = 8.5, 10.5, 16.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 28.2, 38.1, 44.1, 66.1, 68.1, 71.0, 80.7, 117.3, 139.0. IR (neat, cm^{-1}) 3349, 3303, 3083, 2932, 2120, 1642, 1422, 1065, 1030, 924. LRMS (EI(+)) *m*/*z* 154 (M^+), 135 ($[M-H_2O-H]^+$), 115 ($[M-C_3H_3]^+$), 97 (bp). HRMS (EI(+)) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0997.

Diol from **30b** could also be prepared as in the same manner (80%) as a colorless oil.

3.6.17. (2*S*,4*S*)-2-Vinylhept-6-yne-1,4-diol (31b). $[\alpha]_D^{20}$ −1.5° (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.67 (1H, ddd, *J* = 7.6, 7.6, 14.2 Hz), 1.74 (1H, ddd, *J* = 4.9, 6.4, 14.2 Hz), 2.02 (2H, br s), 2.07 (1H, t, *J* = 2.7 Hz), 2.36 (1H, ddd, *J* = 2.7, 6.6, 16.6 Hz), 2.45 (1H, ddd, *J* = 2.7, 4.9, 16.6 Hz), 2.47 (1H, m), 3.56 (1H, dd, *J* = 6.6, 10.7 Hz), 3.63 (1H, dd, *J* = 6.0, 10.7 Hz), 3.92 (1H, dddd, *J* = 4.9, 4.9, 6.6, 7.6 Hz), 5.15–5.21 (2H, m), 5.74 (1H, ddd, *J* = 8.3, 9.7, 17.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 27.3, 37.5, 43.3, 65.3, 67.9, 71.0, 80.6, 117.1, 139.2. IR (neat, cm^{-1}) 3357, 3299, 3081, 2934, 2120, 1642, 1422, 1038, 918. LRMS (EI(+)) *m*/*z* 154 (M^+), 135 ($[M-H_2O-H]^+$), 115 ($[M-C_3H_3]^+$), 97 (bp). HRMS (EI(+)) calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0998.

3.6.18. (3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)oct-1-en-7-yne (32a). Under an Ar atmosphere, to a cooled (−78 °C) solution of diol (8.9 mg, 57.7 μmol), 2,6-lutidine (36 μL, 0.309 mmol) in CH_2Cl_2 (250 μL) was added TBSOTf (36 μL, 0.157 mmol), and the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (500 μL), and the mixture was extracted with AcOEt (2 mL). The organic layer was washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt (50:1)) gave the bis-TBS ether **32a** (16.8 mg, 76%) as a colorless oil.

$[\alpha]_D^{21}$ −26.8° (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.02 (6H, s), 0.06 (3H, s), 0.07 (3H, s), 0.89 (18H, s), 1.61 (1H, ddd, *J* = 3.4, 10.3, 13.8 Hz), 1.70 (1H, ddd, *J* = 3.7, 8.7, 13.8 Hz), 1.97 (1H, t, *J* = 2.7 Hz), 2.30 (1H, ddd, *J* = 2.7, 7.0, 16.6 Hz), 2.46 (1H, ddd, *J* = 2.7, 5.0, 16.6 Hz), 2.38 (1H, m), 3.47 (1H, dd, *J* = 6.6, 9.7 Hz), 3.52 (1H, dd, *J* = 6.0, 9.7 Hz), 3.83 (1H, dddd, *J* = 3.4, 5.0, 7.0, 8.7 Hz), 5.01–5.10 (2H, m), 5.63 (1H, ddd, *J* = 8.4, 9.6, 18.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.2, −5.2, −4.4, −4.1, 18.1, 18.4, 25.8, 25.9, 26.0, 28.3, 38.2, 42.8, 67.2, 68.9, 70.0, 81.5, 116.0, 139.9. IR (neat, cm^{-1}) 3316, 3079, 2932, 1472, 1256, 1100, 837, 776. LRMS (EI(+)) *m*/*z* 382 (M^+), 367 ($[M-Me]^+$), 343 ($[M-C_3H_3]^+$), 325 ($[M-t\text{-}Bu]^+$), 257, 211, 193, 147, 73 (bp). HRMS (EI(+)) calcd for $C_{21}H_{42}O_2Si_2$ (M^+) 382.2723, found 382.2724.

Compound **32b** could also be prepared as in the same manner (85%) as a colorless oil.

3.6.19. (3*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldimethylsilyloxymethyl)oct-1-en-7-yne (32b). $[\alpha]_D^{22}$ +3.8° (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.03 (6H, s), 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 1.51 (1H, ddd, *J* = 5.7, 8.8, 13.7 Hz), 1.83 (1H, ddd, *J* = 5.6, 7.1, 13.7 Hz), 1.95 (1H, t, *J* = 2.7 Hz), 2.29 (1H, m), 2.30 (1H, ddd, *J* = 2.7, 5.7, 16.8 Hz), 2.37 (1H, ddd, *J* = 2.7, 5.7, 16.8 Hz), 3.51 (2H, d, *J* = 6.0 Hz), 3.86 (1H, dddd, *J* = 5.7, 5.7, 5.7, 7.1 Hz), 5.01–5.09 (2H, m), 5.69 (1H, ddd, *J* = 8.4, 10.4, 17.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ −5.3, −5.3, −4.5, −4.3, 18.2, 18.4, 25.8, 25.9, 26.0, 27.1, 38.1, 42.9, 66.5, 69.1, 69.9, 81.7, 115.5, 140.2. IR (neat, cm^{-1}) 3316, 3079, 2930, 2122, 1472, 1256, 1094, 810, 776. LRMS (EI(+)) *m*/*z* 382 (M^+), 367 ($[M-Me]^+$), 343 ($[M-C_3H_3]^+$), 325 ($[M-t\text{-}Bu]^+$), 257, 211, 193, 147, 73 (bp). HRMS (EI(+)) calcd for $C_{21}H_{42}O_2Si_2$ (M^+) 382.2723, found 382.2719.

3.6.20. 25-Hydroxy-1β-hydroxymethylvitamin D_3 (4a). Under an Ar atmosphere, a solution of A-ring enyne **32a** (14.8 mg, 38.7 μmol), CD-ring bromoolefin **6**[12] (58.0 mg, 0.163 mmol), $Pd(PPh_3)_4$ (5.0 mg, 4.3 μmol) in PhMe

(200 μL)–Et_3N (200 μL) was stirred at 80 °C for 2 h. After cooled to room temperature, the mixture was filtered through silica gel pad, washed with PhMe and AcOEt, and the filtrate was concentrated. The residue was dissolved in THF (250 μL) and cooled on ice-water bath. HF·py (50 μL) was added and the mixture was stirred at the same temperature for 1.5 h and then at room temperature for 30 min. The mixture was partitioned between AcOEt (1 mL) and saturated aqueous $NaHCO_3$ solution (1 mL), and the aqueous layer was extracted with AcOEt (2 mL). The combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography ($CHCl_3$/MeOH (40:1)) gave the product **4a** (6.5 mg, 39%) as a pale yellow powder.

$[\alpha]_D^{23}$ −22.3° (*c* 0.1, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$, ppm) δ 0.54 (3H, s), 0.94 (3H, d, J = 6.7 Hz), 1.02–1.10 (1H, m), 1.22 (6H, s), 1.15–1.76 (17H, m), 1.83–1.92 (2H, m), 1.96–2.03 (2H, m), 2.13 (1H, dddd, J = 0.8, 3.7, 4.8, 13.5 Hz), 2.33 (1H, dd, J = 6.3, 13.3 Hz), 2.48 (1H, apparent tt, J = 5.7, 5.7 Hz), 2.59 (1H, dd, J = 3.7, 13.3 Hz), 2.79–2.86 (1H, m), 3.72 (1H, dd, J = 5.7, 10.9 Hz), 3.78 (1H, dd, J = 5.7, 10.9 Hz), 4.02 (1H, tt, J = 3.7, 6.3 Hz), 4.99 (1H, d, J = 1.7 Hz), 5.12 (1H, m), 6.00 (1H, d, J = 11.3 Hz), 6.29 (1H, d, J = 11.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 12.0, 18.8, 20.8, 22.3, 23.6, 27.6, 29.1, 29.2, 29.4, 36.1, 36.4, 37.3, 40.5, 44.2, 44.4, 45.9, 45.9, 56.3, 56.6, 66.4, 68.0, 71.1, 113.1, 117.0, 123.1, 135.0, 143.0, 146.0. IR (film, cm^{-1}) 3364, 2942, 1642, 1377, 1034, 911, 760. LRMS (EI(+)) *m/z* 430 (M^+), 412 ($[M-H_2O]^+$), 400($[M-CH_2O]^+$), 394 ($[M-2\times H_2O]^+$), 381 ($[M-H_2O-CH_2OH]^+$), 363 ($[M-2\times H_2O-CH_2OH]^+$), 135, 59 (bp). HRMS (EI(+)) calcd for $C_{28}H_{46}O_3$ (M^+) 430.3447, found 430.3440.

1α-Hydroxymethylated derivative (**4b**) could also be prepared as in the same manner (65%) as a white powder.

$[\alpha]_D^{26}$ +83.1° (*c* 0.2, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$, ppm) δ 0.52 (3H, s), 0.93 (3H, d, J = 6.6 Hz), 1.02–1.09 (1H, m), 1.22 (6H, s), 1.19–1.60 (15H, m), 1.62–1.74 (2H, m), 1.80 (1H, ddd, J = 6.3, 9.0, 12.9 Hz), 1.83–1.90 (1H, m), 1.90–1.96 (1H, m), 1.96–2.03 (2H, m), 2.27 (1H, dd, J = 8.1, 12.9 Hz), 2.60 (1H, dd J = 3.9, 12.9 Hz), 2.63 (1H, m), 2.78–2.84 (1H, m), 3.56–3.64 (2H, m), 4.01 (1H, m), 5.00 (1H, d, J = 2.4 Hz), 5.16 (1H, m), 5.95 (1H, d, J = 11.4 Hz), 6.32 (1H, d, J = 11.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 11.9, 18.8, 20.8, 22.2, 23.6, 27.7, 29.1, 29.2, 29.3, 36.1, 36.4, 37.4, 40.5, 44.4, 45.9, 46.2, 56.3, 56.5, 64.2, 67.0, 71.1, 113.9, 117.0, 123.7, 134.2, 143.3, 145.4. IR (film, cm^{-1}) 3312, 2944, 1658, 1632, 1468, 1044, 905, 751. LRMS (EI(+)) *m/z* 430 (M^+), 412 ($[M-H_2O]^+$), 400 ($[M-CH_2O]^+$), 394 ($[M-2\times H_2O]^+$), 380 ($[M-H_2O-CH_2OH-H]^+$), 363 ($[M-2\times H_2O-CH_2OH]^+$), 135 (bp). HRMS (EI(+)) calcd for $C_{28}H_{46}O_3$ (M^+) 430.3447, found 430.3449.

4. Reporter assays using luciferase as a reporter

Human breast cancer cell line MCF7 cells were grown at 37 °C in DMEM supplemented with 10% FBS and 1% P/S in an atmosphere of 95% air and 5% CO_2. Cells were collected, suspended in the DMEM supplemented with 5% FBS (stripped with dextran-coated charcoal) and 1% P/S without phenol red, and plated in 24-well plate (2.5×10^4 cells/well). Cells were incubated in CO_2 incubator at 37 °C overnight. Ligand stock solutions were prepared at various concentrations in DMSO (10^{-7} to 10^{-3} M). DMSO itself was used as vesicle. Plasmids used in our assays were as follows; receptor plasmids (pM(GAL4-hVDR(DEF)) for wild type hVDR, and pM(GAL4-hVDR(R274L)(DEF)) for mutant hVDR, the latter prepared by site-directed mutagenesis using QuikChange II XL Site-Directed Mutagenesis Kits (Stratagene)), reporter plasmid (17M2-G-Luc) and internal standard plasmid (pRL-CMV). Plasmids were diluted in OPTI-MEM medium at concentrations of 50 ng/well for receptor plasmid, 0.2 μg/well for reporter plasmid, and 2.5 ng/well for internal plasmid. Transfections were carried out by using TransFast reagent (Promega) according to the manufacturer's instruction. After 3–6 h of transfection, ligand stock solutions were added at the final concentrations of 10^{-10} to 10^{-6} M, and cells were further incubated overnight. Luciferase assays were performed by using Dual-Luciferase Reporter Assay System Kit (Promega). All experiments were carried out at least three times and data were shown as average ± SD.

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