Efficient and Versatile Synthesis of Novel 2α-Substituted 1α,25-Dihydroxyvitamin D_3 Analogues and Their Docking to Vitamin D Receptors

Yoshitomo Suhara,[†] Ken-ichi Nihei,[†] Masaaki Kurihara,[‡] Atsushi Kittaka,[†] Kentaro Yamaguchi,[§] Toshie Fujishima,[†] Katsuhiro Konno,[†] Naoki Miyata,[‡] and Hiroaki Takayama*,[†]

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-0195, Japan, National Institute of Health Sciences, Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan, and Chemical Analytical Center, Chiba University, Inage-ku, Chiba 263-8522, Japan

hi-takay@pharm.teikyo-u.ac.jp

Received April 11, 2001

Novel 2α-substituted 1α,25-dihydroxyvitamin D_3 analogues with 2α-alkyl and 2α-hydroxyalkyl groups were systematically synthesized from D-xylose. Their conformation on binding to the ligand binding domain (LBD) of the vitamin D receptor was analyzed. It has been found that the 2α-hydroxypropyl group best fits the cavity of the LBD, and the binding activity is three times higher than that for the natural hormone.

Introduction

1α,25-Dihydroxyvitamin D_3 (1α,25$(OH)_2D_3$) is the active form of vitamin D in the hormonal system regulating calcium homeostasis as well as cell differentiation, cell proliferation, and immunology and acts by binding to a specific receptor in the target organs, bone, intestine, and kidney.[1,2] Given the biological responses to this class of compounds, 1α,25$(OH)_2D_3$ might be a potential drug for the treatment of tumors, especially leukemias, breast and prostate cancers, or immunological disorders.[1,2] However, 1α,25$(OH)_2D_3$ can induce hypercalceia.[1] Therefore, the search for a noncalcemic therapeutic agent, and for convenient methods of synthesizing finely modified compounds, has been greatly stimulated by medical needs. Most approaches to date have involved modification of the side chain of the CD-ring moiety, while nonsteroidal vitamin D mimetics have been synthesized quite recently.[3]

To produce biologically active analogues, we have applied the A-ring modification of **1** using efficient synthetic procedures and investigated conformation−activity relationships. Recently, we reported the synthesis of A-ring diastereomers of 2-methyl-1,25-dihydroxyvitamin D_3 and found that the 2α-methyl isomer (**2**) was more potent than the native hormone in terms of vitamin D receptor (VDR) binding affinity, elevation of rat serum Ca concentration, and induction of HL-60 cell differentiation.[4] In addition, the combination of this 2α-methyl substitution with 20-epimerization, i.e., a double modification, produced a much more potent analogue.[5] Consequently, we decided to elucidate the A-ring conformation−activity relationship and the significance of the 2α-substitution. This time, we focused on the 2α-substitution of 1α,25$(OH)_2D_3$ and synthesized several analogues into which was introduced a 2α-alkyl or a 2α-hydroxyalkyl group into the A-ring. The resulting analogues showed significant biological activities: in particular, introduction of the 2α-(3-hydroxypropyl) group caused a 3-fold increase in binding activity to VDR and a ca. 500-fold increase in the potency of calcium-mobilizing activity.[6] Furthermore, we recently reported the synthesis and VDR binding affinity of 2α-(ω-hydroxyalkoxy)-1α,25-$(OH)_2D_3$,[7] in which the A-ring epimer of ED-71 was included.[8] Most of the biological actions of 1α,25$(OH)_2D_3$ are considered to be mediated by the VDR, which belongs to the nuclear receptor superfamily acting as a ligand-

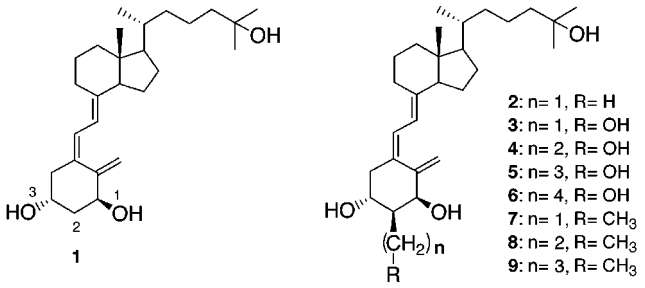


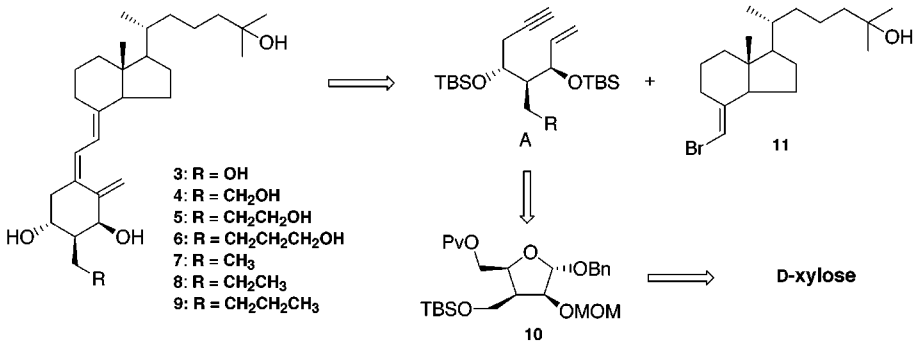
Figure 1. Structures of 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2D_3$, **1**) and its 2α-substituted analogues **2**−**9**.

[†] Teikyo University.
[‡] National Institute of Health Sciences.
[§] Chiba University.

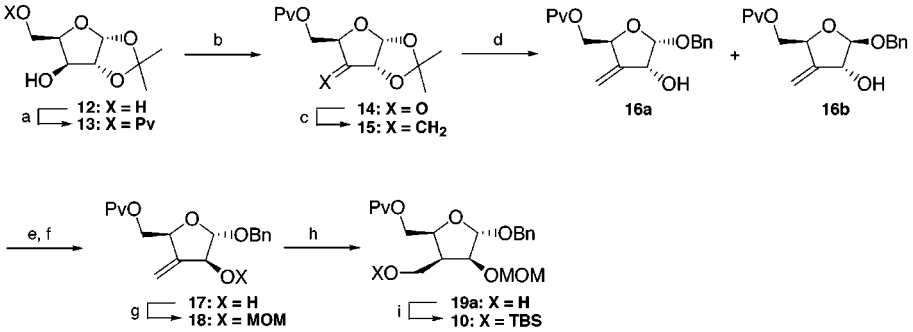
(1) (a) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: New York, 1997. (b) Ettinger, R. A.; DeLuca, H. F. *Adv. Drug Res.* **1996**, *28*, 269.
(2) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200.
(3) Boehm, M. F.; Fitzgerald, P.; Zou, A.; Elgort, M. G.; Bischoff, E. D.; Mere, L.; Mais, D. E.; Bissonnette, R. P.; Heyman, R. A.; Nadzan, A. M.; Reichman, M.; Allegretto, E. A. *Chem. Biol.* **1999**, *6*, 265.
(4) (a) Konno, K.; Maki, S.; Fujishima, T.; Liu, Z.-P.; Miura, D.; Chokki, M.; Takayama, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 151. (b) Konno, K.; Fujishima, T.; Maki, S.; Liu, Z.-P.; Miura, D.; Chokki, M.; Ishizuka, S.; Yamaguchi, K.; Kan, Y.; Kurihara, M.; Miyata, N.; Smith, C.; DeLuca, F. H.; Takayama, H. *J. Med. Chem.* **2000**, *43*, 4247.
(5) Fujishima, T.; Liu, Z.-P.; Miura, D.; Chokki, M.; Ishizuka, S.; Konno, K.; Takayama, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2145.
(6) Suhara, Y.; Nihei, K.; Tanigawa, H.; Fujishima, T.; Konno, K.; Nakagawa, K.; Okano, T.; Takayama, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1129.
(7) Kittaka, A.; Suhara, Y.; Takayanagi, H.; Fujishima, T.; Kurihara, M.; Takayama, H. *Org. Lett.* **2000**, *2*, 2619.

10.1021/jo010375i CCC: $20.00 © 2001 American Chemical Society
Published on Web 11/27/2001

Scheme 1



Scheme 2[a]



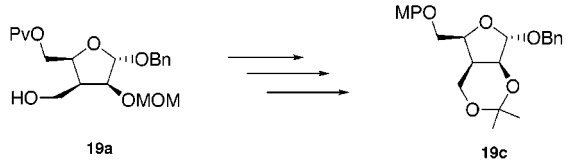
[a] Key: (a) PvCl, pyridine, 86%. (b) PCC, MS 4 Å, CH_2Cl_2, 98%. (c) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 85%. (d) 4.0 M HCl/dioxane, BnOH, toluene, $\alpha = 58\%$, $\beta = 32\%$. (e) *p*-nitrobenzoic acid, Ph_3P, DEAD, THF. (f) 1.0 M NaOH, H_2O/MeOH, 84% (two steps). (g) MOMCl, DIPEA, TBAI, CH_2Cl_2, 88%. (h) 9-BBN, THF, then 3.0 M NaOH, 30% H_2O_2, 85%. (i) TBSCl, imidazole, DMF, 99%.

dependent transcription factor with coactivators.[9] Therefore, investigation of the state of binding between the analogues and the VDR ligand binding domain is important to elucidate the mechanism of the biological action. In addition, the result would provide valuable information for the development of a new drug. We report here the efficient synthesis of 2α-substituted analogues as well as the analysis of their binding to the VDR by molecular mechanic calculations.

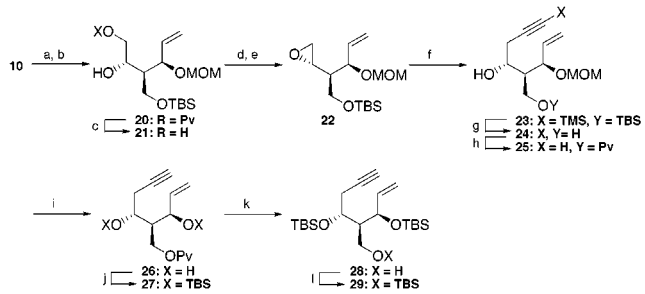
Results and Discussion

For the synthesis of analogues, the convergent method has several advantages over the classical steroidal approach.[10] Moreover, Trost's convergent synthesis using palladium-catalyzed coupling of the A-ring enyne synthon with a bromoolefin of the CD-ring portion is the most successful method for making vitamin D analogues.[11] We applied this procedure to the synthesis of 2α-substituted-1α,25(OH)$_2$D$_3$ derivatives on account of the easy modification of the A-ring portion. The retrosynthetic route for the 2α-substituted analogues **3**−**9** is shown in Scheme 1. The A-ring enyne synthon (**A**) with preintroduced 2α-substituents was prepared from D-xylose through the intermediate **10**. The carbohydrate is often used as a starting material on account of advantages for the chiral template. After introduction of the hydroxymethyl group at the C-3 position of the D-xylose derivative, the furanose

Scheme 3



Scheme 4[a]



[a] Key: (a) H_2, 20% $Pd(OH)_2$ on carbon, EtOH. (b) $Ph_3P^+CH_3Br^-$, LiHMDS, THF, 79% (two steps). (c) DIBAL-H, CH_2Cl_2, 84%. (d) TmCl, DMAP, CH_2Cl_2. (e) LiHMDS, THF, 86% (two steps). (f) TMSCCH, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, 80%. (g) TBAF, THF, 99%. (h) PvCl, pyridine/CH_2Cl_2, 85%. (i) PPTS, *t*-BuOH, 74%. (j) TBSOTf, lutidine, CH_2Cl_2, 99%. (k) DIBAL-H, CH_2Cl_2, 96%. (l) TBSCl, imidazole, DMF 88%.

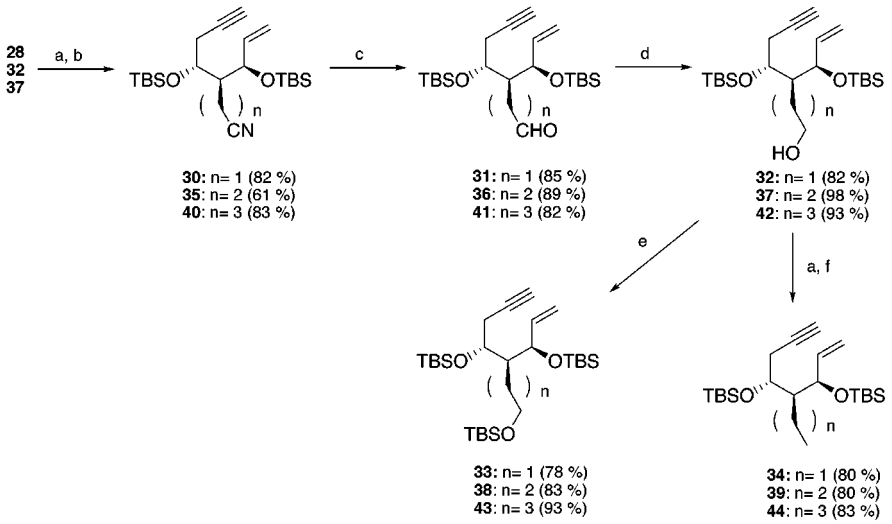
(8) (a) Ono, Y.; Watanabe, H.; Shiraishi, A.; Takeda, S.; Higuchi, Y.; Sato, K.; Tsugawa, N.; Okano, T.; Kobayashi, T.; Kubodera, N. *Chem. Pharm. Bull.* **1997**, *45*, 1626. (b) Tsugawa, N.; Nakagawa, K.; Kurobe, M.; Ono, Y.; Kubodera, N.; Ozono, K.; Okano, T. *Biol. Pharm. Bull.* **2000**, *23*, 66. (c) Okano, T.; Tsugawa, N.; Matsuda, S.; Takeuchi, A.; Kobayashi, T.; Takita, Y.; Nishii, Y. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 1444.

(9) (a) Umemoto, K.; Murakami, K. K.; Thompson, C. C.; Evans, R. M. *Cell* **1991**, *65*, 1255. (b) DeLuca, H. F.; Zierold, C. *Nutr. Rev.* **1998**, *56*, 54. (c) Takeyama, K.; Masuhiro, Y.; Fuse, H.; Endoh, H.; Murayama, A.; Kitanaka, S.; Suzawa, M.; Yanagisawa, J.; Kato, S. *Mol. Cell. Biol.* **1999**, *19*, 1049. (d) Yanagisawa, J.; Yanagi, Y.; Masuhiro, Y.; Suzawa, M.; Watanabe, M.; Kashiwagi, K.; Toriyabe, T.; Kawabata, M.; Miyazono, K.; Kato, S. *Science* **1999**, *283*, 1317.

(10) (a) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383. (b) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.

(11) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836.

Scheme 5[a]



[a] Key: (a) TmCl, DMAP, CH_2Cl_2. (b) NaCN, DMSO. (c) DIBAL-H, CH_2Cl_2. (d) $NaBH_4$, MeOH. (e) TBSCl, imidazole, DMF. (f) LAH, Et_2O.

ring was opened by a Wittig reaction to make the enyne structure. Elongation of the 2α-substituent of the A-ring synthon was carried out in a conventional manner by single-carbon elongation. On the other hand, the natural CD-ring portion (**11**) was prepared from vitamin D_3 by a reported method.[11] Finally, the 2α-substituted 1α,25-$(OH)_2D_3$ analogues were synthesized using palladium-catalyzed coupling of the A-ring enyne synthon with the CD-ring portion.[11]

The pathway to synthesize the A-ring enyne is described in Schemes 2−5. The synthesis of the A-ring portion was started with a commercially available D-xylose derivative (**12**) as shown in Scheme 2. D-Xylose is readily available and useful for stereoselective synthesis corresponding to the A-ring stereochemistry. In the case of 2-methyl analogues, all possible A-ring diastereomers were synthesized; however, we decided to synthesize the 1α,2α,3β-isomer stereoselectively. In this way, D-xylose was the most convenient for the synthesis of the desired 2α-substituted analogues. First, the C-5 primary alcohol of **12** was selectively protected with a pivaloyl group in 86% yield. Then, the C-3 secondary hydroxyl group of **13** was converted to ketone **14** with PCC oxidation in 98% yield. The conventional Wittig reaction afforded an exomethylene compound **13** in a high yield. In this step, we tried several bases, for example, NaH-DMSO, NaO*t*-Am, KO*t*Bu, and others, because the chemical yield of **15** depends on the base. We found NaHMDS or KHMDS to be the best choice for this reaction. To remove the 1,2-isopropylidene group while simultaneously forming benzyl glycoside, compound **15** was treated with 4.0 M HCl in dioxane/BnOH to afford alcohols **16a** and **16b**. The desired α-isomer **16a** was separated by silica gel column chromatography in 58% yield along with the β-isomer **16b**. For the synthesis of the same configuration corresponding to the 1α-hydroxyl group of the native hormone 1α,25$(OH)_2D_3$, the C-2 hydroxyl group of **16a** was inverted via the Mitsunobu reaction to give the 2β-secondary alcohol **17** in 84% yield. Under these reaction conditions, however, the β-isomer **16b** was not converted to the desired 2β-hydroxyl compound at all. Presumably, *p*-nitrobenzoate from **16b** was so strained that elimination of the substituent occurred under basic conditions

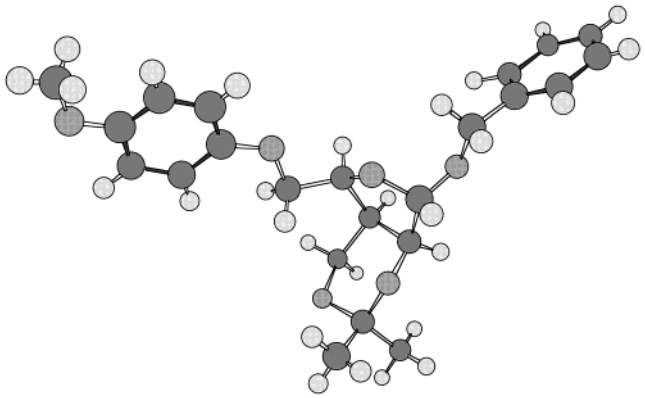
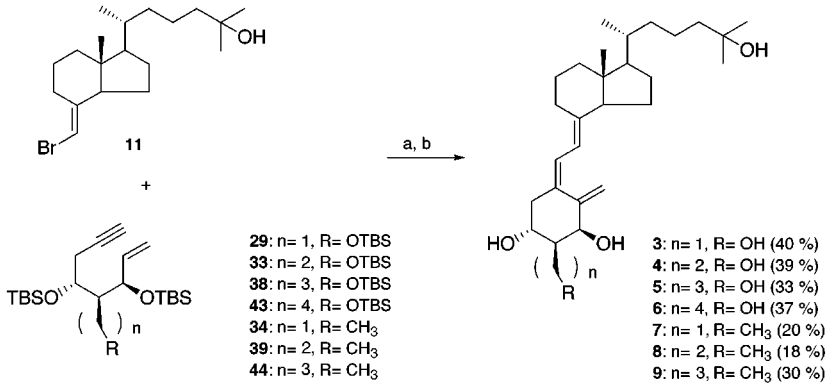


Figure 2. X-ray crystallographic analysis of compound **19c**.

for the hydrolysis. After protection of the hydroxyl group of **17** with the methoxymethyl (MOM) group, the exomethylene moiety was stereoselectively converted to the 3β-hydroxymethyl compound **19a** in a high yield by hydroboration with 9-BBN. Our first trial using the hydroboran−THF complex gave a poor stereoselectivity (3β-isomer **19a**:3α-isomer **19b** = 1:1) in this step; therefore, a bulky organoboran such as 9-BBN was essential. To determine the 3β-stereochemistry of **19a**, the ^{1}H NMR data of the isomer was not enough. Because the coupling constants $J_{2,3}$ and $J_{3,4}$ were not so different between the 3α-isomer (**19a**) and the 3β-isomer (**19b**), we tried to crystallize a derivative from compound **19a** for X-ray crystal analysis. After several examinations, we found that methoxyphenyl ether **19c**, which was derived from **19a** with replacement of the protective groups, could be clearly crystallized from a hexane solution (Scheme 3). Then, we confirmed unambiguously the stereochemistry of **19a** as having the 3β-hydroxymethyl group on the basis of X-ray crystal analysis of **19c** as shown in Figure 2.[12] Protection of the primary hydroxyl group of **19a** with a *tert*-butyldimethylsilyl (TBS) group afforded the TBS ether **10** in 99% yield. Thus, modifications of the C-2 and

(12) Crystal data of **19c** are as follows: space group $P2_1$ (monoclinic), $Z = 2$, $a = 8.7115(9)$ Å, $b = 22.447(1)$ Å, $c = 5.508(2)$ Å, $\beta = 90.03(1)°$, $V = 1077.1(3)$ Å^3, $D_c = 1.235$ g/cm^3.

Scheme 6[a]



[a] Key: (a) $(dba)_3Pd_2{\cdot}CHCl_3$, TPP, TEA/toluene. (b) CSA, MeOH.

C-3 hydroxyl groups of D-xylose, corresponding to the C-1 hydroxyl group and the C-2 alkyl or the C-2 hydroxyalkyl group of vitamin D analogues, respectively, were accomplished.

As shown in Scheme 4, the desired key A-ring synthon, enyne **29**, was obtained from the D-xylose derivative **10**. Hydrogenolysis of benzyl glycoside **10** with a palladium catalyst, followed by ring opening by means of the Wittig reaction, afforded **20** in good yield. In this reaction, LiHMDS gave a better yield than the other bases NaHMDS, KHMDS, KO*t*Bu, and *n*-BuLi. The olefin **21** was converted to epoxide **22** by sequential treatments with DIBAL-H, 2,4,6-trimethylbenzenesulfonyl chloride (TmCl), and LiHMDS in a high yield. The acetylene unit was introduced by the reaction of **22** with (trimethylsilyl)-acetylene/*n*-BuLi-$BF_3{\cdot}OEt_2$ in THF to give the alcohol **23** in 80% yield. Although some groups recently reported the introduction of an acetylene unit into epoxides using only lithium acetylide in THF, our desired compound could not be obtained without a Lewis acid.[13] In the next step, we changed the MOM protecting group of the hydroxyl group to TBS. The target vitamin D analogues cannot be exposed to a strong acid for deprotection on account of the triene system. The primary hydroxyl group should be distinguished from two secondary hydroxyls for the subsequent modification to synthesize a 2α-elongated alkyl or hydroxyalkyl group. Removal of both silyl protecting groups (TMS and TBS) by tetrabutylammonium fluoride (TBAF) to afford **24** in 99% yield and subsequent manipulation of the protecting groups by selective pivaloylation, removal of the MOM group, and silylation afforded the fully protected **27** in a good yield. Finally, further manipulation through **28** gave the desired A-ring synthon **29** in a high yield.

Elongation of the hydroxymethyl group of **28** was carried out in a conventional manner as shown in Scheme 5. Sulfonylation and cyanide substitution gave **30** in 82% yield, and reduction of **30** with DIBAL-H followed by further reduction of aldehyde **31** with $NaBH_4$ furnished the single-carbon-elongated alcohol **32** in a good overall yield. The hydroxyl group was protected to give the second A-ring synthon **33**. The alcohol **32** was further converted to the ethyl derivative **34** through the corresponding tosylate. In the same manner, the double- and triple-carbon-elongated synthons **38**, **39**, **43**, and **44** were prepared from **32** and **37**, respectively. This stepwise synthesis has some advantages; for example, deuterium or tritium can be introduced into the molecule for investigating the mechanism of intermolecular interaction between vitamin D_3 analogues and VDR. As a result, we demonstrated the importance of the ω-hydroxyls of the 2α-substituents for the affinity to VDR.

Table 1. Relative Binding Affinity of the 2α-Alkyl and 2α-Hydroxyalkyl Series for Bovine Thymus 1α,25$(OH)_2D_3$ Receptor (VDR)

compounds	binding affinity to VDR[a]
1α,25$(OH)_2D_3$	100
3: hydroxymethyl	20
4: hydroxyethyl	70
5: hydroxypropyl	300
6: hydroxybutyl	120
7: ethyl	40
8: propyl	20
9: butyl	8

[a] Potency of 1α,25$(OH)_2D_3$ is normalized to 100.

Finally, palladium-catalyzed coupling of the A-ring synthons **29**, **33**, **38**, **43**, **34**, **39**, and **44** with the CD-ring portion **11**, followed by deprotection with camphorsulfonic acid (CSA) in MeOH gave the target 2α-alkyl and 2α-hydroxyalkyl analogues **3**−**9** as shown in Scheme 6.[6] Since the deprotection of the 1α-hydroxyl group was relatively difficult in the case of 2α-alkyl derivatives, the total yield was not satisfactory. Thus, we have synthesized five novel 2α-substituted 1α,25-dihydroxyvitamin D_3 analogues.

The results of biological evaluations of **3**−**9** have already been reported in comparison with those of 1α,-25-dihydroxyvitamin D_3 (**1**) and 2α-methyl-1α,25-dihydroxyvitamin D_3 (**2**).[6] In addition, we newly investigated the VDR binding affinity of 2α-hydroxybutyl-1α,25-dihydroxyvitamin D_3 (**6**) and 2α-butyl-1α,25-dihydroxyvitamin D_3 (**9**) as shown in Table 1.[14]

In this study, we found that 2α-hydroxypropyl analogue (**5**) exhibited the most potent VDR binding affinity in this series. Because of this result, we investigated the three-dimensional structure of 2α-hydroxypropyl analogue **5** docking at the VDR ligand binding domain. Recently, Moras et al. reported the crystal structure of the natural ligand−VDR complex.[15] Then, we evaluated

(13) Moriety, R. M.; Kim, J.; Brumer, H., III. *Tetrahedron Lett.* **1995**, *36*, 51−54.

(14) Imae, Y.; Manaka, A.; Yoshida, N.; Ishimi, Y.; Shinki, T.; Abe, E.; Suda, T.; Konno, K.; Takayama, H.; Yamada, S. *Biochim. Biophys. Acta* **1994**, *1213*, 302−308.

(15) Rochel, N.; Wultz, J. M.; Mitschler, A.; Klaholz, B.; Moras, D. *Mol. Cell* **2000**, *5*, 173.

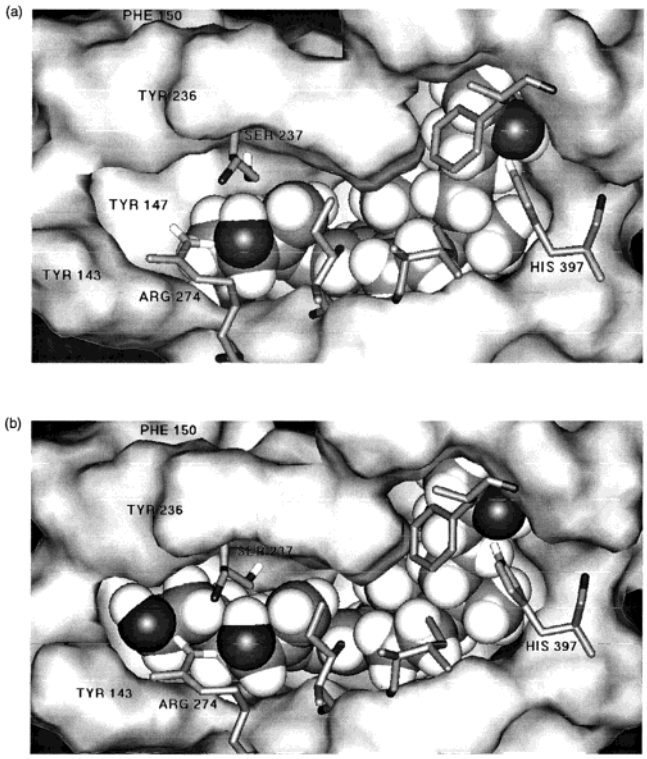


Figure 3. (a) Crystal structure of VDR bound to 1α,25(OH)$_2$D$_3$ **1** by D. Moras et al.[15] (b) Computer modeling of **5** in the VDR ligand binding domain.

the binding of **5** to VDR using Moras' X-ray results, and the preliminary modeling is shown below (Figure 3).[16] The space around the A-ring moiety seems to be mostly filled by the newly introduced 2α-hydroxypropyl group in the binding cavity. The 1α-hydroxyl group retains hydrogen bonds to Ser-237 and Arg-274 as originally formed in the VDR complex with ligand **1**.[15] It is important to note that an additional hydrogen bond to stabilize the complex was observed between the C-2α terminal hydroxyl group of **5** and Arg-274. In addition, the alkyl chain of the hydroxypropyl group of **5** would contribute to the hydrophobic interaction with the cavity surrounded by Phe-150, Tyr-143, Tyr-147, and Tyr-236. These findings would be the main reasons for the high binding affinity to VDR.

Conclusion

In summary, we have developed an efficient and systematic route for synthesizing new biologically active 2α-substituted analogues of 1α,25(OH)$_2$D$_3$ (**3**−**9**) from D-xylose. This method has the advantage that it should be applicable to a variety of 2α-substituted vitamin D analogues. The activity profiles of the synthesized analogues are highly structure sensitive, with even a single-carbon chain difference greatly altering the bioactivities. Consequently, we believe that these analogues will be important for studies on the action mechanism of vitamin D$_3$ and also as lead compounds for developing therapeutic agents. Further studies are needed to elucidate fully the activity profiles and modes of action of these analogues.

(16) Calculated by molecular dynamics and molecular mechanics energy minimization using MacroModel version 6.5 (Schrodinger, Inc.) on a SGI O2 Workstation.

Experimental Section

General. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz using $CDCl_3$ as a solvent unless otherwise specified. Chemical shifts are given in parts per million (δ) using tetramethylsilane (TMS) as the internal standard. High-resolution mass values were obtained with a high-resolution mass spectrometer at the Faculty of Pharmaceutical Sciences, Teikyo University. FT-IR spectra were recorded using NaCl plates. Ultraviolet spectra were recorded using ethanol as a solvent. Optical rotations were measured at 25 ± 2 °C. Column chromatography was carried out on silica gel 60 (70−230 mesh), and preparative TLC was run on silica gel 60F$_{254}$. Unless otherwise noted, all reagents were purchased from commercial suppliers and used as received.

1,2-*O*-Isopropylidene-5-*O*-pivaloyl-α-D-xylofuranoside (13). To a cold (0 °C) and stirred solution of 1,2-*O*-isopropylidene-α-D-xylofuranose (**12**, 15.0 g, 78.9 mmol) in pyridine (70 mL) was added dropwise over a period of 2 h trimethylacetyl chloride (9.9 g, 82.2 mmol). The resultant solution was stirred at 0 °C for 10 h. The reaction was quenched with MeOH (5 mL), and the mixture was concentrated in vacuo. The crude product was dissolved in Et$_2$O (500 mL) and washed successively with water (100 mL), saturated aqueous $CuSO_4$ solution (100 mL), water (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL). The aqueous layers were extracted with Et$_2$O (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (20% EtOAc in hexanes) gave 18.7 g (86%) of pivaloyl ester **13** as a colorless oil: $[\alpha]^{28}_D$ +16.61 (*c* 1.62, $CHCl_3$); IR (neat) 3480, 2980, 1732, 1375, 1285, 1217, 1165, 1113, 1075, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9 H), 1.32 (s, 3 H), 1.51 (s, 3 H), 3.74 (bs, 1 H), 4.10 (d, 1 H, J = 2.8 Hz), 4.17 (dd, 1 H, J = 5.6, 11.2 Hz), 4.25 (ddd, 1 H, J = 2.8, 5.6, 7.2 Hz), 4.50 (dd, 1 H, J = 7.2, 11.2 Hz), 4.56 (d, 1 H, J = 3.6 Hz), 5.93 (d, 1 H, J = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.8, 27.1, 38.9, 60.5, 74.2, 78.4, 84.9, 104.6, 111.8, 179.8; HREIMS calcd for $C_{12}H_{19}O_6$ ($M^+ - CH_3$) 259.1182, found 259.1182.

1,2-*O*-Isopropylidene-3-keto-5-*O*-pivaloyl-α-D-xylofuranoside (14). To a stirred solution of pivaloyl ester **13** (10.5 g, 38.3 mmol) in CH_2Cl_2 (800 mL) at room temperature were added freshly activated powdered molecular sieves (4 Å, 75 g) and pyridinium chlorochromate (36.5 g, 169.4 mmol). The resultant brown suspension was stirred for 3 h after which time TLC indicated the disappearance of the starting material. The reaction mixture was diluted with hexanes (800 mL) and filtrated through a pad of silica gel. Filtration and concentration followed by flash chromatography on silica gel (40% EtOAc in hexanes) gave 10.2 g (98%) of ketone **14** as a colorless oil: $[\alpha]^{23}_D$ +42.60 (*c* 1.31, $CHCl_3$); IR (neat) 2979, 1777, 1734, 1377, 1285, 1221, 1159, 1092, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 4.23 (dd, 1 H, J = 3.2, 11.6 Hz), 4.37 (dd, 1H, J = 1.2, 4.4 Hz), 4.39 (dd, 1 H, J = 3.2, 11.6 Hz), 4.57 (dt, 1 H, J = 1.2, 3.2 Hz), 6.10 (d, 1 H, J = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 27.6, 38.7, 63.2, 76.2, 77.2, 103.0, 114.3, 177.4, 207.6; HREIMS calcd for $C_{13}H_{20}O_6$ (M^+) 276.1260, found 276.1262.

3-Deoxy-1,2-*O*-isopropylidene-3-*C*-methylene-5-*O*-pivaloyl-α-D-*xylo*-pentofuranoside (15). Sodium bis(trimethylsilyl)amide (18.0 mL, 1.0 M solution in THF, 18.0 mmol) was slowly added at room temperature to a suspension of methyltriphenylphosphonium bromide (7.7 g, 21.6 mmol) in THF (100 mL). The resultant bright yellow solution was stirred at room temperature for 1.5 h. The solution was then cooled to −78 °C, and a THF (20 mL) solution of ketone **14** (4.3 g, 15.8 mmol) was slowly added. After being stirred for 30 min at −78 °C, the reaction mixture was allowed to warm to room temperature and stirred for another 1 h. The reaction was quenched at 0 °C with MeOH (10 mL), and the mixture was poured into Et$_2$O (200 mL) and washed with saturated aqueous NH_4Cl solution (3 × 100 mL) and brine (3 × 100 mL). The aqueous layers were extracted with Et$_2$O (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica

gel (10% EtOAc in hexanes) gave 3.6 g (85%) of olefin **15** as a colorless oil: $[\alpha]^{23}_D$ +115.79 (*c* 1.52, $CHCl_3$); IR (neat) 2997, 1732, 1374, 1282, 1235, 1159, 1071, 1015, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9 H), 1.39 (s, 3 H), 1.52 (s, 3 H), 4.19 (dd, 1 H, J = 4.8, 12.0 Hz), 4.23 (dd, 1H, J = 3.6, 12.0 Hz), 4.91 (dd, 1 H, J = 1.2, 4.0 Hz), 4.94 (ddd, 1 H, J = 2.4, 3.6, 4.8 Hz), 5.22 (t, 1 H, J = 1.2 Hz), 5.48 (dd, 1 H, J = 1.2, 2.4 Hz), 5.87 (d, 1 H, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 30.6, 41.9, 68.3, 80.8, 84.8, 107.8, 115.6, 115.8, 149.1, 181.3; HREIMS calcd for $C_{13}H_{19}O_5$ ($M^+ - CH_3$) 255.1235, found 255.1232.

Benzyl 3-Deoxy-3-*C*-methylene-5-*O*-pivaloyl-α-D-*xylo*-pentofuranoside (16a) and Benzyl 3-Deoxy-3-*C*-methylene-5-*O*-pivaloyl-*β*-D-*xylo*-pentofuranoside (16b). A cold (0 °C) and stirred mixture of olefin **15** (3.2 g, 11.9 mmol) and benzyl alcohol (8.0 g, 74.1 mmol) in toluene (22 mL) was treated with 4.0 M solution of HCl in dioxane (10 mL, 40.0 mmol). The reaction mixture was warmed to room temperature, and stirring was continued for 16 h. The mixture was poured into Et_2O (200 mL), and the reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$ solution (100 mL). The mixture was then washed with water (3 × 50 mL) and brine (3 × 50 mL). The aqueous layers were extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (20% EtOAc in hexanes) gave 2.20 g (58%) of alcohol **16a** and 1.22 g (32%) of alcohol **16b** each as a colorless oil. **16a**: $[\alpha]^{28}_D$ +169.58 (*c* 1.42, $CHCl_3$); IR (neat) 3486, 2975, 1732, 1285, 1159, 1090, 1017, 907, 739, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9 H), 2.29 (d, 1H, J = 11.6 Hz), 4.18 (dd, 1 H, J = 4.8, 12.0 Hz), 4.22 (dd, 1H, J = 3.6, 12.0 Hz), 4.53 (ddt, 1 H, J = 2.4, 4.4, 11.6 Hz), 4.60 (d, 1 H, J = 12.0 Hz), 4.73 (ddt, 1 H, J = 2.4, 3.6, 4.8 Hz), 4.81 (d, 1 H, J = 12.0 Hz), 5.15 (d, 1 H, J = 4.4 Hz), 5.18 (t, 1 H, J = 2.4 Hz), 5.39 (t, 1 H, J = 2.4 Hz), 7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 38.8, 65.8, 69.2, 73.5, 76.7, 100.0, 108.5, 127.9, 128.0, 128.5, 137.4, 147.6, 178.2; HREIMS calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1620. **16b**: $[\alpha]^{23}_D$ −34.80 (*c* 1.23, $CHCl_3$); IR (neat) 3447, 2975, 1730, 1285, 1159, 1105, 1057, 992, 916, 739, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9 H), 2.61 (bs, 1H), 4.14 (dd, 1 H, J = 6.8, 11.2 Hz), 4.19 (dd, 1H, J = 4.8, 11.2 Hz), 4.42 (t, 1 H, J = 1.2 Hz), 4.49 (d, 1 H, J = 11.6 Hz), 4.76 (d, 1 H, J = 11.6 Hz), 4.89 (ddt, 1 H, J = 1.2, 4.8, 6.2 Hz), 5.03 (s, 1 H), 5.26 (t, 1 H, J = 1.2 Hz), 5.49 (t, 1 H, J = 1.2 Hz), 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 38.8, 67.7, 69.1, 77.6, 78.1, 106.9, 112.4, 127.0, 127.9, 128.2, 128.3, 128.5, 137.1, 148.7, 178.3; HREIMS calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1621.

Benzyl 3-Deoxy-3-*C*-methylene-5-*O*-pivaloyl-α-D-*lyxo*-pentofuranoside (17). A mixture of alcohol **16a** (2.0 g, 6.25 mmol), *p*-nitrobenzoic acid (2.1 g, 12.6 mmol), and triphenylphosphine (3.3 g, 12.6 mmol) in THF (40 mL) was cooled to 0 °C and treated with a 40% solution of azodicarboxylic acid diethyl ester in toluene (5.8 g, 13.9 mmol). After being stirred for 15 min at 0 °C, the resultant solution was allowed to warm to room temperature and stirred for another 3 h. The reaction was quenched with MeOH (10 mL) at 0 °C, and the mixture was poured into Et_2O (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 × 50 mL) and brine (3 × 50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (10% EtOAc in hexanes) gave crude *p*-nitrobenzoate as a white solid, which was used in the next step without further purification.

To a cold (0 °C) and stirred solution of crude *p*-nitrobenzoate in MeOH (100 mL) was added dropwise 1.0 M aqueous NaOH solution (1.0 mL, 1.00 mmol), and the resultant solution was stirred for 1 h. After 1.0 M aqueous HCl solution (1.5 mL, 1.5 mmol) was added, the reaction mixture was concentrated in vacuo. The crude product was dissolved in Et_2O (200 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 × 50 mL) and brine (3 × 50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layer was dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (20% EtOAc in hexanes) gave 1.67 g (84%) of alcohol **17** as a colorless oil: $[\alpha]^{23}_D$ +97.30 (*c* 1.15, $CHCl_3$); IR (neat) 3467, 2975, 1730, 1285, 1161, 1102, 1053, 995, 914, 739, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9 H), 2.09 (d, 1H, J = 7.6 Hz), 4.25 (dd, 1 H, J = 4.8, 12.4 Hz), 4.33 (dd, 1H, J = 3.2, 12.4 Hz), 4.37 (d, 1H, J = 7.6 Hz), 4.55 (d, 1 H, J = 11.6 Hz), 4.74 (d, 1 H, J = 11.6 Hz), 4.75 (ddd, 1 H, J = 1.6, 3.2, 4.8 Hz), 5.10 (s, 1 H), 5.26 (s, 1 H), 5.54 (t, 1 H, J = 1.6 Hz), 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 38.8, 65.7, 68.9, 76.8, 76.9, 106.3, 112.6, 127.7, 127.8, 128.0, 128.4, 137.4, 148.0, 178.2; HREIMS calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1628.

Benzyl 3-Deoxy-3-*C*-methylene-2-*O*-methoxymethyl-5-*O*-pivaloyl-α-D-*lyxo*-pentofuranoside (18). To a cold (0 °C) and stirred solution of alcohol **17** (1.0 g, 3.13 mmol) in CH_2Cl_2 (25 mL) were added dropwise diisopropylethylamine (1.24 g, 9.61 mmol) and chloromethyl methyl ether (1.29 g, 16.0 mmol). Solid tetrabutylammonium iodide (360 mg, 975 μmol) was added to the reaction mixture, and the solution was allowed to warm to room temperature and stirred in the dark for 14 h. The mixture was poured into Et_2O (150 mL) and washed with saturated aqueous NH_4Cl solution (3 × 25 mL) and brine (3 × 25 mL). The aqueous layers were extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (10% EtOAc in hexanes) gave 1.01 g (88%) of MOM ether **18** as a colorless oil: $[\alpha]^{25}_D$ +90.17 (*c* 1.15, $CHCl_3$); IR (neat) 2957, 1732, 1285, 1152, 1103, 1033, 920, 754, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 3.35 (s, 3 H), 4.18 (dd, 1 H, J = 6.4, 11.2 Hz), 4.22 (dd, 1H, J = 5.2, 11.2 Hz), 4.37 (s, 1H), 4.55 (d, 1 H, J = 12.0 Hz), 4.60 (d, 1 H, J = 6.8 Hz), 4.69 (ddd, 1 H, J = 1.6, 5.2, 6.4 Hz), 4.75 (d, 1 H, J = 12.0 Hz), 4.76 (d, 1 H, J = 6.8 Hz), 5.21 (s, 1 H), 5.36 (s, 1 H), 5.46 (d, 1 H, J = 1.6 Hz), 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 38.8, 55.5, 66.5, 68.8, 78.0, 80.2, 94.1, 105.2, 114.0, 127.7, 127.9, 128.4, 137.5, 145.1, 178.3; HREIMS calcd for $C_{13}H_{21}O_6$ (M^+ − Bn) 273.1338, found 273.1336.

Benzyl 5-*O*-Pivaloyl-2-*O*-methoxymethyl-3-deoxy-3-*C*-hydroxymethyl-α-D-*lyxo*-pentofuranose (19a). To a cold (0 °C) and stirred solution of MOM ether **18** (2.0 g, 5.49 mmol) in THF (20 mL) was slowly added a 0.5 M solution of 9-borabicyclo[3.3.1]nonane in THF (20 mL, 10.0 mmol). The resultant solution was warmed to 50 °C, and stirring was continued for 3 h. The reaction mixture was cooled to 0 °C and treated sequentially with a 3.0 M aqueous NaOH solution (6.4 mL, 19.2 mmol) and a 30% aqueous H_2O_2 solution (12.8 mL). The resultant mixture was vigorously stirred at room temperature for 2 h, poured into EtOAc (200 mL), and washed with water (3 × 50 mL), 5% aqueous Na_2SO_3 solution (3 × 50 mL), and brine (3 × 50 mL). The aqueous layers were extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography on silica gel (30% EtOAc in hexanes) gave 1.78 g (85%) of alcohol **19a** as a colorless oil: $[\alpha]^{23}_D$ +61.33 (*c* 1.95, $CHCl_3$); IR (neat) 3503, 2959, 1730, 1285, 1154, 1113, 1051, 739, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.34 (t, 1H, J = 5.6 Hz), 2.89 (tt, 1H, J = 5.6, 8.4 Hz), 3.37 (s, 3H), 3.86 (dt, 1H, J = 5.6, 11.2 Hz), 3.88 (ddd, 1H, J = 5.6, 8.4, 11.2 Hz), 4.19 (dd, 1H, J = 7.2, 11.6 Hz), 4.20 (d, 1H, J = 5.6 Hz), 4.23 (dd, 1H, J = 5.6, 11.6 Hz), 4.38 (ddd, 1H, J = 5.6, 7.2, 8.4 Hz), 4.50 (d, 1H, J = 12.0 Hz), 4.66 (s, 2H), 4.73 (d, 1H, J = 12.0 Hz), 5.15 (s, 1H), and 7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 38.7, 45.0, 55.8, 57.6, 64.9, 68.9, 77.1, 82.4, 97.0, 105.1, 127.6, 127.8, 128.4, 137.7, 178.2; HREIMS calcd for $C_{19}H_{27}O_6$ (M^+ − OCH_3) 351.1807, found 351.1810.

Benzyl 5-*O*-Pivaloyl-2-*O*-methoxymethyl-3-deoxy-3-*C*-(*tert*-butyldimethylsilyloxymethyl)-α-D-*lyxo*-pentofuranose (10). A solution of alcohol **19a** (2.97 g, 7.77 mmol) in DMF (30 mL) was treated with imidazole (1.06 g, 15.6 mmol) and *tert*-butyldimethylsilyl chloride (1.76 g, 11.7 mmol) at room temperature. The resultant solution was stirred for 3 h, poured into Et_2O (200 mL), and washed with water (3 × 25 mL) and brine (3 × 25 mL). The aqueous layers were extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash

chromatography on silica gel (10% EtOAc in hexanes) gave 3.82 g (99%) of silyl ether **10** as a colorless oil: $[\alpha]^{28}_D$ +66.61 (*c* 1.15, $CHCl_3$); IR (neat) 2955, 1732, 1283, 1256, 1154, 1096, 1034, 837, 777, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.18 (s, 9H), 2.80 (ddt, 1H, J = 4.8, 6.8, 8.8 Hz), 3.28 (s, 3H), 3.70 (dd, 1H, J = 6.8, 10.0 Hz), 3.76 (dd, 1H, J = 8.8, 10.0 Hz), 4.07 (d, 1H, J = 4.8 Hz), 4.09 (dd, 1H, J = 7.4, 12.0 Hz), 4.13 (dd, 1H, J = 4.8, 12.0 Hz), 4.42 (ddd, 1H, J = 4.8, 7.4, 8.8 Hz), 4.46 (d, 1H, J = 12.0 Hz), 4.58 (d, 1H, J = 6.8 Hz), 4.61 (d, 1H, J = 6.8 Hz), 4.69 (d, 1H, J = 12.0 Hz), 5.10 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.1, 25.8, 27.2, 38.7, 45.4, 55.6, 57.4, 65.3, 69.0, 77.1, 81.1, 96.8, 105.3, 127.6, 127.8, 128.3, 137.9, 178.3; HREIMS calcd for $C_{25}H_{41}O_6Si$ ($M^+ - OCH_3$) 465.2673, found 465.2666.

(2*R*,3*R*,4*R*)-1-Pivalic Acid 3-(*tert*-Butyldimethylsilanyloxymethyl)-2-hydroxy-4-methoxymethoxyhex-5-enyl Ester (20). A solution of silyl ether **10** (3.98 g, 8.02 mmol) in EtOH (40 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (400 mg) for 12 h. Filtration through Celite and concentration in vacuo gave the desired crude hemiacetal as a colorless oil, which was used in the next step without further purification.

Lithium bis(trimethylsilyl)amide (29 mL, 1.0 M solution in THF, 29.0 mmol) was added dropwise at 0 °C to a suspension of methyltriphenylphosphonium bromide (10.9 g, 30.5 mmol) in THF (50 mL). The resultant bright yellow solution was stirred at room temperature for 40 min and then cooled to 0 °C. After a solution of crude hemiacetal in THF (20 mL) was added dropwise, the reaction mixture was stirred for 40 min at 0 °C. The reaction was quenched at 0 °C with MeOH (5 mL), poured into Et_2O (300 mL), and washed with saturated aqueous NH_4Cl solution (3 × 50 mL) and brine (3 × 50 mL). The aqueous layers were extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (15% EtOAc in hexanes) gave 2.57 g (79%) of olefin **20** as a colorless oil: $[\alpha]^{30}_D$ −48.96 (*c* 1.15, $CHCl_3$); IR (neat) 3505, 2957, 1732, 1285, 1256, 1157, 1090, 1032, 924, 839, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.21 (s, 9H), 2.74 (ddt, 1H, J = 3.6, 4.4, 7.2 Hz), 3.40 (s, 3H), 3.54 (d, 1H, J = 5.6 Hz), 3.82 (dd, 1H, J = 4.4, 10.4 Hz), 3.90 (dd, 1H, J = 4.4, 10.4 Hz), 4.14 (dd, 1H, J = 4.8, 10.8 Hz), 4.26 (dd, 1H, J = 5.6, 10.8 Hz), 4.28 (ddt, 1H, J = 3.6, 4.8, 5.6 Hz), 4.40 (t, 1H, J = 8.0 Hz), 4.58 (d, 1H, J = 6.4 Hz), 4.72 (d, 1H, J = 6.4 Hz), 5.30 (dd, 1H, J = 1.2, 16.8 Hz), 5.33 (dd, 1H, J = 1.2, 10.4 Hz), 5.70 (ddd, 1H, J = 8.0, 10.4, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.7, −5.6, 18.0, 25.8, 27.2, 38.8, 46.2, 55.9, 60.5, 66.7, 68.9, 76.1, 94.2, 119.1, 136.4, 178.4; HREIMS calcd for $C_{14}H_{29}O_4Si$ ($M^+ - OCH_3$) 373.2411, found 373.2421.

(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxymethoxyhex-5-ene-1,2-diol (21). To a cold (−78 °C) and stirred solution of olefin **20** (3.20 g, 7.92 mmol) in CH_2Cl_2 (50 mL) was added dropwise over a period of 30 min diisobutylaluminum hydride (19.8 mL, 1.0 M solution in toluene, 19.8 mmol). After 10 min, the reaction mixture was treated sequentially with MeOH (1 mL) and saturated aqueous NH_4Cl solution (1 mL), and the resultant suspension was diluted with Et_2O (250 mL) and filtered through a pad of Celite. The filtrate was washed with saturated aqueous NH_4Cl solution (3 × 25 mL) and brine (3 × 25 mL). The aqueous layers were extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (40% EtOAc in hexanes) gave 2.12 g (84%) of diol **21** as a colorless oil: $[\alpha]^{25}_D$ −60.26 (*c* 1.15, $CHCl_3$); IR (neat) 3443, 2932, 1256, 1156, 1084, 1034, 926, 839, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.77 (ddt, 1H, J = 3.6, 4.8, 8.0 Hz), 2.67 (dd, 1H, J = 4.4, 8.0 Hz), 3.40 (s, 3H), 3.52 (d, 1H, J = 6.4 Hz), 3.67 (ddd, 1H, J = 4.8, 8.0, 11.2 Hz), 3.73 (ddd, 1H, J = 4.4, 6.4, 11.2 Hz), 3.83 (d, 1H, J = 4.8 Hz), 4.14 (ddt, 1H, J = 3.6, 4.8, 6.4 Hz), 4.30 (t, 1H, J = 8.0 Hz), 4.57 (d, 1H, J = 6.8 Hz), 4.71 (d, 1H, J = 6.8 Hz), 5.29 (d, 1H, J = 16.8 Hz), 5.32 (d, 1H, J = 10.0 Hz), 5.69 (ddd, 1H, J = 8.0, 10.0, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, 18.1, 25.8, 47.1, 55.9, 61.0, 65.5, 71.1, 76.5, 94.1, 119.3, 136.2; HREIMS calcd for $C_{14}H_{29}O_4Si$ ($M^+ - OCH_3$) 289.1835, found 289.1838.

(3*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilanyloxymethyl)-3-(methoxymethoxy)-5,6-epoxyhex-1-ene (22). To a solution of diol **21** (3.20 g, 11.6 mmol) in CH_2Cl_2 (40 mL) was added 4-(dimethylamino)pyridine (2.84 g, 23.4 mmol). To the cold (0 °C) and vigorously stirred solution was slowly added 2-mesitylenesulfonyl chloride (3.80 g, 17.4 mmol). After being stirred for 4 h at 0 °C, the reaction mixture was poured into Et_2O (200 mL) and washed with water (3 × 25 mL) and brine (3 × 25 mL). The aqueous layers were extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration gave the desired crude sulfonate as a colorless oil, which was used in the next step without further purification.

The crude sulfonate was dissolve in THF (50 mL), and the solution was cooled to −78 °C and treated with a 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (2.5 mL, 2.50 mmol). After being stirred for 20 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred for another 20 min. The mixture was poured into Et_2O (200 mL) and washed with saturated aqueous NH_4Cl solution (3 × 25 mL) and brine (3 × 25 mL). The aqueous layers were extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (10% EtOAc in hexanes) gave 3.01 g (86%) of epoxide **22** as a colorless oil: $[\alpha]^{20}_D$ −68.78 (*c* 1.15, $CHCl_3$); IR (neat) 2930, 1259, 1154, 1103, 1034, 918, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.26 (dddd, 1H, J = 3.2, 4.0, 5.2, 7.2 Hz), 2.62 (dd, 1H, J = 2.8, 5.2 Hz), 2.87 (t, 1H, J = 5.2 Hz), 3.04 (ddd, 1H, J = 2.8, 3.2, 5.2 Hz), 3.35 (s, 3H), 3.70 (dd, 1H, J = 4.0, 10.0 Hz), 3.82 (dd, 1H, J = 5.2, 10.0 Hz), 4.31 (t, 1H, J = 7.2 Hz), 4.51 (d, 1H, J = 6.4 Hz), 4.68 (d, 1H, J = 6.4 Hz), 5.24 (d, 1H, J = 10.0 Hz), 5.25 (d, 1H, J = 17.2 Hz), 5.70 (ddd, 1H, J = 7.2, 10.0, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, −5.5, 18.2, 25.9, 48.1, 49.8, 51.0, 55.6, 60.6, 75.8, 94.1, 118.4, 136.6; HREIMS calcd for $C_{14}H_{27}O_3Si$ ($M^+ - OCH_3$) 271.1729, found 271.1732.

(4*R*,5*S*,6*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-6-(methoxymethoxy)-1-(trimethylsilanyl)-oct-7-en-1-yn-4-ol (23). To a cold (0 °C) and stirred solution of ethynyltrimethylsilane (3.88 g, 39.6 mmol) in THF (100 mL) was slowly added a 1.54 M solution of *n*-butyllithium in hexanes (22.7 mL, 36.0 mmol). After being stirred for 15 min at 0 °C, the reaction mixture was cooled at −78 °C and treated with a solution of epoxide **22** (3.01 g, 9.97 mmol) in THF (20 mL). Boron trifluoride diethyl ether complex (1.70 g 12.0 mmol) was added to the reaction mixture, and the solution was allowed to warm to room temperature and stirred for 40 min. The mixture was poured into Et_2O (300 mL) and washed with saturated aqueous NH_4Cl solution (3 × 50 mL) and brine (3 × 50 mL). The aqueous layers were extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (10% EtOAc in hexanes) gave 3.20 g (80%) of enyne **23** as a colorless oil: $[\alpha]^{20}_D$ −62.26 (*c* 1.15, $CHCl_3$); IR (neat) 3513, 2957, 1251, 1156, 1098, 1030, 926, 841, 777, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.11 (s, 9H), 0.87 (s, 9H), 1.93 (ddt, 1H, J = 4.0, 5.6, 8.0 Hz), 2.46 (dd, 1H, J = 8.0, 16.8 Hz), 2.63 (dd, 1H, J = 6.0, 16.8 Hz), 3.38 (s, 3H), 3.60 (d, 1H, J = 6.0 Hz), 3.81 (dd, 1H, J = 4.0, 10.8 Hz), 3.92 (dd, 1H, J = 5.6, 10.8 Hz), 4.21 (ddt, 1H, J = 4.0, 6.0, 8.0 Hz), 4.44 (t, 1H, J = 8.0 Hz), 4.58 (d, 1H, J = 6.4 Hz), 4.70 (d, 1H, J = 6.4 Hz), 5.28 (d, 1H, J = 17.2 Hz), 5.29 (d, 1H, J = 10.8 Hz), 5.71 (ddd, 1H, J = 8.0, 10.8, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.7, −5.6, 15.8, 16.9, 25.7, 26.6, 46.6, 55.8, 60.1, 69.4, 76.1, 77.1, 86.5, 94.2, 118.6, 136.6; HREIMS calcd for $C_{19}H_{37}O_3Si_2$ ($M^+ - OCH_3$) 369.2282, found 369.2276.

(2*S*,3*S*)-2-[(*R*)-1-(Methoxymethoxy)allyl]hex-5-yn-1,3-diol (24). A cold (0 °C) and stirred solution of enyne **23** (3.20 g, 8.0 mmol) in THF (45 mL) was treated with a 1.0 M solution of tetrabutylammonium fluoride in THF (17.6 mL, 17.6 mmol). The resultant solution was then warmed to room temperature,

and stirring was continued for 1 h. The reaction mixture was poured into EtOAc (200 mL) and washed with saturated aqueous NH_4Cl solution (3 × 25 mL) and brine (3 × 25 mL). The aqueous layers were extracted with EtOAc (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (40% EtOAc in hexanes) gave 1.69 g (99%) of diol **24** as a colorless oil: $[\alpha]^{21}_D$ −96.70 (*c* 1.15, $CHCl_3$); IR (neat) 3420, 3299, 2857, 1154, 1096, 1030, 924, 637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (ddt, 1H, J = 3.2, 7.2, 4.8 Hz), 2.05 (t, 1H, J = 2.8 Hz), 2.50 (ddd, 1H, J = 2.8, 6.8, 16.8 Hz), 2.60 (1H, bs), 2.62 (ddd, 1H, J = 2.8, 6.8, 16.8 Hz), 3.32 (d, 1H, J = 4.4 Hz), 3.42 (s, 3H), 3.83 (dd, 1H, J = 4.8, 11.2 Hz), 4.00 (dd, 1H, J = 4.8, 11.2 Hz), 4.30 (ddt, 1H, J = 3.2, 4.4, 6.8 Hz), 4.44 (tt, 1H, J = 1.2, 7.2 Hz), 4.61 (d, 1H, J = 6.8 Hz), 4.70 (d, 1H, J = 6.8 Hz), 5.33 (dt, 1H, J = 1.2, 10.4 Hz), 5.35 (dt, 1H, J = 1.2, 17.2 Hz), 5.78 (ddd, 1H, J = 7.2, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 47.2, 56.0, 59.9, 69.5, 70.6, 77.0, 80.8, 94.6, 118.9, 136.1; HREIMS calcd for $C_9H_{13}O_3$ ($M^+ - CH_2OCH_3$) 169.0865, found 169.0875.

1-Pivalic Acid (2*S*,3*S*)-3-Hydroxy-2-[(*R*)-1-(methoxymethoxy)allyl]hex-5-ynyl Ester (25). The diol **24** (1.62 g, 7.57 mmol) was dissolved in pyridine (1.7 mL) and CH_2Cl_2 (6.8 mL). To the cold (0 °C) and stirred solution was added dropwise over a period of 30 min trimethylacetyl chloride (1.08 g, 8.96 mmol). After being stirred for 1 h at 0 °C, the reaction mixture was allowed to warm to 20 °C and stirred for another 4 h. The mixture was poured into Et_2O (100 mL) and washed with saturated aqueous NH_4Cl solution (3 × 20 mL) and brine (3 × 20 mL). The aqueous layers were extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (20% EtOAc in hexanes) gave 1.92 g (85%) of alcohol **25** as a colorless oil: $[\alpha]^{20}_D$ −87.39 (*c* 1.15, $CHCl_3$); IR (neat) 3521, 3291, 2975, 1728, 1287, 1156, 1098, 1030, 924, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.03 (t, 1H, J = 2.4 Hz), 2.14 (ddt, 1H, J = 2.4, 4.8, 5.6 Hz), 2.46 (ddd, 1H, J = 2.4, 7.6, 16.8 Hz), 2.58 (ddd, 1H, J = 2.4, 6.4, 16.8 Hz), 3.10 (d, 1H, J = 2.4 Hz), 3.39 (s, 3H), 4.26 (ddt, 1H, J = 2.4, 6.4, 7.6 Hz), 4.29 (dd, 1H, J = 5.6, 11.6 Hz), 4.33 (dd, 1H, J = 5.6, 11.6 Hz), 4.40 (ddt, 1H, J = 1.2, 4.8, 6.8 Hz), 4.57 (d, 1H, J = 7.2 Hz), 4.70 (d, 1H, J = 7.2 Hz), 5.31 (dt, 1H, J = 1.2, 17.6 Hz), 5.34 (d, 1H, J = 1.2, 10.4 Hz), 5.71 (ddd, 1H, J = 6.8, 10.4, 17.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 27.2, 38.7, 45.2, 56.1, 61.2, 69.5, 70.4, 77.4, 80.9, 94.3, 118.8, 135.6, 178.4; HREIMS calcd for $C_{15}H_{23}O_4$ ($M^+ - OCH_3$) 267.1596, found 267.1599.

1-Pivalic Acid (2*S*,3*S*)-3-Hydroxy-2-[(*R*)-1-(hydroxy)allyl]hex-5-ynyl Ester (26). The alcohol **25** (2.10 g, 7.05 mmol) was dissolved in *tert*-BuOH (60 mL). Pyridinium *p*-toluenesulfonate (17.6 g, 70.0 mmol) was added, and the resultant solution was heated at reflux for 12 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was dissolved in Et_2O (200 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 × 20 mL) and brine (3 × 20 mL). The aqueous layers were extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (30% EtOAc in hexanes) gave 1.33 g (74%) of diol **26** as a colorless oil: $[\alpha]^{21}_D$ +15.13 (*c* 1.15, $CHCl_3$); IR (neat) 3438, 3306, 2977, 1730, 1287, 1163, 1040, 928, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.05 (t, 1H, J = 2.4 Hz), 2.06 (dddd, 1H, J = 2.4, 4.4, 5.6, 6.8 Hz), 2.43 (ddd, 1H, J = 2.4, 7.2, 16.8 Hz), 2.57 (ddd, 1H, J = 2.4, 7.2, 16.8 Hz), 2.73 (d, 1H, J = 4.4 Hz), 3.07 (d, 1H, J = 2.4 Hz), 4.24 (tt, 1H, J = 2.4, 7.2 Hz), 4.31 (dd, 1H, J = 5.6, 11.6 Hz), 4.43 (dd, 1H, J = 6.8, 11.6 Hz), 4.45 (ddt, 1H, J = 1.2, 4.4, 5.6 Hz), 5.28 (dt, 1H, J = 1.2, 10.4 Hz), 5.40 (dt, 1H, J = 1.2, 16.8 Hz), 5.92 (ddd, 1H, J = 5.6, 10.4, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 27.2, 38.8, 45.2, 61.4, 68.9, 70.8, 72.8, 80.7, 116.1, 138.6, 178.9; HREIMS calcd for $C_{10}H_{13}O_4$ ($M^+ - t$Bu) 197.0814, found 197.0806.

1-Pivalic Acid (2*S*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(*R*)-1-(*tert*-butyl-dimethylsilanyloxy)allyl]hex-5-ynyl Ester (27). A cold (0 °C) and stirred solution of diol **26** (1.31 g, 5.16 mmol) in CH_2Cl_2 (25 mL) was treated with 2,6-lutidine (2.21 g, 20.6 mmol) and *tert*-butyldimethylsilyl triflate (4.09 g, 15.5 mmol). The resultant solution was stirred at 0 °C for 2 h, poured into Et_2O (150 mL), and washed with saturated aqueous NH_4Cl solution (3 × 20 mL) and brine (3 × 20 mL). The aqueous layers were extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (2.5% EtOAc in hexanes) gave 2.47 g (99%) of silyl ether **27** as a colorless oil: $[\alpha]^{21}_D$ −3.22 (*c* 1.15, $CHCl_3$); IR (neat) 3316, 2957, 1732, 1285, 1256, 1159, 1089, 924, 837, 776, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.20 (s, 9H), 1.98 (t, 1H, J = 2.4 Hz), 2.19 (dq, 1H, J = 4.0, 6.0 Hz), 2.45 (ddd, 1H, J = 2.4, 4.8, 16.4 Hz), 2.54 (ddd, 1H, J = 2.4, 7.2, 16.4 Hz), 3.99 (dd, 1H, J = 6.0, 12.0 Hz), 4.16 (ddd, 1H, J = 4.0, 4.8, 7.2 Hz), 4.17 (dd, 1H, J = 6.0, 7.6 Hz), 4.25 (dd, 1H, J = 6.0, 12.0 Hz), 5.09 (d, 1H, J = 10.0 Hz), 5.16 (d, 1H, J = 17.2 Hz), 5.84 (ddd, 1H, J = 7.6, 10.0, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, −4.1, −3.6, 18.0, 18.2, 25.8, 25.9, 26.5, 27.2, 38.7, 48.5, 61.8, 69.1, 70.5, 74.1, 81.2, 115.7, 139.9, 178.3; HREIMS calcd for $C_{22}H_{41}O_4Si_2$ ($M^+ - t$Bu) 425.2543, found 425.2543.

(2*S*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]hex-5-yn-1-ol (28). To a cold (−78 °C) and stirred solution of silyl ether **27** (2.47 g, 5.12 mmol) in CH_2Cl_2 (20 mL) was added dropwise over a period of 30 min diisobutylaluminum hydride (7.7 mL, 1.0 M solution in toluene, 7.70 mmol). After being stirred for 10 min at −78 °C, the reaction mixture was treated sequentially with MeOH (1 mL) and saturated aqueous NH_4Cl solution (1 mL), and the resultant suspension was diluted with Et_2O (200 mL) and filtered through a pad of Celite. The filtrate was washed with saturated aqueous NH_4Cl solution (3 × 20 mL) and brine (3 × 20 mL). The aqueous layers were extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (10% EtOAc in hexanes) gave 1.96 g (96%) of alcohol **28** as a colorless oil: $[\alpha]^{20}_D$ +0.96 (*c* 1.15, $CHCl_3$); IR (neat) 3472, 3314, 2932, 1256, 1074, 926, 837, 777, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.90 (s, 18H), 2.01 (t, 1H, J = 2.8 Hz), 2.09 (dq, 1H, J = 4.8, 7.2 Hz), 2.46 (ddd, 1H, J = 2.8, 4.8, 16.8 Hz), 2.51 (ddd, 1H, J = 2.8, 6.8, 16.8 Hz), 3.07 (dd, 1H, J = 4.8, 7.2 Hz), 3.72 (ddd, 1H, J = 4.8, 7.2, 12.4 Hz), 3.82 (dt, 1H, J = 7.2, 12.4 Hz), 4.08 (dt, 1H, J = 4.8, 6.8 Hz), 4.33 (tt, 1H, J = 2.0, 7.2 Hz), 5.20 (dt, 1H, J = 2.0, 10.4 Hz), 5.28 (dt, 1H, J = 2.0, 17.2 Hz), 5.84 (ddd, 1H, J = 7.2, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.7, −4.4, −3.8, 17.9, 18.1, 25.8, 25.9, 26.8, 50.2, 61.0, 70.7, 70.9, 74.3, 80.5, 116.7, 138.7; HREIMS calcd for $C_{17}H_{33}O_3Si_2$ ($M^+ - t$Bu) 341.1968, found 341.1964.

(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilanyloxy)-4-(*tert*-butyldimethylsilanyloxymethyl)-oct-1-en-7-yne (29). A solution of alcohol **28** (40.0 mg, 101 μmol) in DMF (2.0 mL) was treated with imidazole (13.6 mg, 200 μmol) and *tert*-butyldimethylsilyl chloride (22.6 mg, 150 μmol) at room temperature. The resultant solution was stirred for 3 h, poured into Et_2O (20 mL), and washed with water (3 × 5 mL) and brine (3 × 5 mL). The aqueous layers were extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (2.0% toluene in hexanes) gave 46.0 mg (88%) of silyl ether **29** as a colorless oil: $[\alpha]^{23}_D$ +5.13 (*c* 1.15, $CHCl_3$); IR (neat) 3316, 2932, 1256, 1090, 922, 837, 776, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.04 (s, 3H), 0.06 (s, 6H), 0.10 (s, 3H), 0.89 (s, 9H), 0.90 (s, 18H), 1.93 (t, 1H, J = 2.8 Hz), 2.00 (ddt, 1H, J = 5.2, 5.6, 6.4 Hz), 2.44 (ddd, 1H, J = 2.8, 5.6, 16.8 Hz), 2.57 (ddd, 1H, J = 2.8, 5.6, 16.8 Hz), 3.56 (dd, 1H, J = 6.4, 10.0 Hz), 3.81 (dd, 1H, J = 6.4, 10.0 Hz), 4.09 (dt, 1H, J = 5.2, 5.6 Hz), 4.30 (ddt, 1H, J = 1.2, 5.6, 6.8 Hz), 5.03 (dt, 1H, J = 1.2, 9.6 Hz), 5.11 (dt, 1H, J = 1.2, 17.2 Hz), 5.92 (ddd, 1H, J = 6.8, 9.6, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −4.8, −4.6, −4.2, −4.0, 18.1,

18.2, 25.9, 26.0, 26.3, 51.5, 60.1, 69.2, 69.7, 73.1, 82.4, 114.4, 141.1; HREIMS calcd for $C_{27}H_{56}O_3Si_3$ (M^+) 512.3537, found 512.3533.

(3*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-3-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]hept-6-ynnitrile (30). To a solution of alcohol **28** (314 mg, 789 μmol) in CH_2Cl_2 (5.0 mL) was added 4-(dimethylamino)pyridine (372 mg, 3.04 mmol). To the cold (0 °C) and vigorously stirred solution was slowly added 2-mesitylenesulfonyl chloride (582 mg, 2.66 mmol). After being stirred for 12 h at 0 °C, the reaction mixture was poured into Et_2O (100 mL) and washed with water (3 × 15 mL) and brine (3 × 15 mL). The aqueous layers were extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration gave the desired crude sulfonate ester as a colorless oil, which was used in the next step without further purification.

The crude sulfonate ester was dissolved in DMSO (5.0 mL). Sodium cyanide (78.0 mg, 1.59 mmol) was added to the solution, and the resultant solution was heated at 70 °C for 2 h. The reaction mixture was cooled to room temperature, poured into Et_2O (100 mL) and washed with water (3 × 15 mL) and brine (3 × 15 mL). The aqueous layers were extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (5% EtOAc in hexanes) gave 263 mg (82%) of nitrile **30** as a colorless oil: $[\alpha]^{20}_D$ −3.83 (*c* 1.15, $CHCl_3$); IR (neat) 3314, 2932, 2247, 1256, 1090, 936, 836, 777, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.12 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 2.03 (t, 1H, J = 2.8 Hz), 2.29 (tt, 1H, J = 6.0, 6.8 Hz), 2.36 (dd, 1H, J = 6.0, 16.4 Hz), 2.46 (ddd, 1H, J = 2.8, 4.4, 16.8 Hz), 2.48 (dd, 1H, J = 6.0, 16.4 Hz), 2.52 (ddd, 1H, J = 2.8, 6.8, 16.8 Hz), 4.04 (dt, 1H, J = 4.4, 6.8 Hz), 4.20 (ddt, 1H, J = 1.2, 6.4, 6.8 Hz), 5.24 (dt, 1H, J = 1.2, 10.4 Hz), 5.31 (dt, 1H, J = 1.2, 16.8 Hz), 5.82 (ddd, 1H, J = 6.4, 10.4, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, −4.2, −3.9, 13.5, 18.1, 18.2, 25.8, 25.9, 26.5, 46.1, 69.0, 71.3, 74.0, 79.9, 117.8, 120.1, 137.6; HREIMS calcd for $C_{22}H_{41}O_2NSi_2$ (M^+) 407.2676, found 407.2659.

(3*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-3-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]hept-6-ynal (31). To a cold (−78 °C) and stirred solution of nitrile **30** (184 mg, 452 μmol) in CH_2Cl_2 (2.0 mL) was added dropwise over a period of 10 min diisobutylaluminum hydride (530 μL, 1.0 M solution in toluene, 530 μmol). After being stirred for 1 h at −78 °C, the reaction mixture was treated sequentially with MeOH (1 mL) and saturated aqueous NH_4Cl solution (1 mL), and the resultant suspension was diluted with Et_2O (100 mL) and filtered through a pad of Celite. The filtrate was washed with saturated aqueous NH_4Cl solution (3 × 10 mL) and brine (3 × 10 mL). The aqueous layers were extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (5% EtOAc in hexanes) gave 157 mg (85%) of aldehyde **31** as a colorless oil: $[\alpha]^{20}_D$ +6.70 (*c* 1.15, $CHCl_3$); IR (neat) 3314, 2932, 2716, 1728, 1256, 1080, 930, 837, 777, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 2.04 (t, 1H, J = 2.8 Hz), 2.37 (ddd, 1H, J = 2.8, 6.0, 16.8 Hz), 2.40 (ddd, 1H, J = 2.8, 6.4, 17.2 Hz), 2.42 (ddd, 1H, J = 1.6, 7.2, 17.2 Hz), 2.44 (ddd, 1H, J = 2.8, 6.0, 16.8 Hz), 2.68 (ddt, 1H, J = 5.2, 6.4, 7.2 Hz), 3.84 (dt, 1H, J = 5.2, 6.0 Hz), 4.23 (ddt, 1H, J = 1.6, 6.4, 6.8 Hz), 5.18 (dt, 1H, J = 1.6, 10.0 Hz), 5.21 (dt, 1H, J = 1.6, 16.0 Hz), 5.73 (ddd, 1H, J = 6.8, 10.0, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.6, −4.3, −4.0, 18.0, 18.2, 25.8, 25.9, 26.4, 40.5, 45.4, 70.0, 71.1, 74.3, 80.3, 117.2, 138.1, 202.6; HREIMS calcd for $C_{22}H_{42}O_3Si_2$ (M^+) 410.2673, found 410.2667.

(3*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-3-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]hept-6-yn-1-ol (32). A cold (0 °C) and stirred solution of aldehyde **31** (157 mg, 383 μmol) in MeOH (2.0 mL) was treated with sodium tetrahydroborate (28.0 mg, 741 μmol). After being stirred for 30 min at 0 °C, the reaction mixture was diluted with Et_2O (100 mL) and washed with saturated aqueous NH_4Cl (3 × 10 mL) and brine (3 × 10 mL). The aqueous layers were extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (10% EtOAc in hexanes) gave 129 mg (82%) of alcohol **32** as a colorless oil: $[\alpha]^{21}_D$ +12.17 (*c* 1.15, $CHCl_3$); IR (neat) 3420, 3314, 2932, 1256, 1073, 926, 837, 776, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.10 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.67 (m, 2H), 2.01 (t, 1H, J = 2.4 Hz), 2.04 (ddt, 1H, J = 5.6, 7.2, 4.8 Hz), 2.41 (ddd, 1H, J = 2.4, 5.6, 17.2 Hz), 2.45 (ddd, 1H, J = 2.4, 5.6, 17.2 Hz), 2.93 (bs, 1H), 3.65 (m, 2H), 3.85 (q, 1H, J = 5.6 Hz), 4.27 (ddt, 1H, J = 1.2, 4.8, 6.8 Hz), 5.18 (dt, 1H, J = 1.2, 10.8 Hz), 5.21 (dt, 1H, J = 1.2, 17.6 Hz), 5.86 (ddd, 1H, J = 6.8, 10.8, 17.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, −4.3, −4.1, 18.0, 18.2, 25.8, 26.1, 28.8, 48.2, 62.5, 70.6, 71.6, 75.4, 81.0, 116.6, 138.4; HREIMS calcd for $C_{22}H_{44}O_3Si_2$ (M^+) 412.2829, found 412.2834.

(3*R*,4*S*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]oct-1-en-7-yne (33). Alcohol **32** (60.0 mg, 146 μmol) was converted to silyl ether **33** (59.0 mg, 78%) according to the same procedure described above for obtaining compound **29** from **28**. Data for **33**: colorless oil; $[\alpha]^{25}_D$ +7.83 (*c* 1.15, $CHCl_3$); IR (neat) 3316, 2930, 1256, 1082, 924, 835, 776, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 27H), 1.55 (m, 2H), 1.84 (ddt, 1H, J = 3.6, 5.2, 6.4 Hz), 1.95 (t, 1H, J = 2.8 Hz), 2.36 (ddd, 1H, J = 2.8, 6.4, 16.8 Hz), 2.41 (ddd, 1H, J = 2.8, 6.4, 16.8 Hz), 3.57 (dt, 1H, J = 6.4, 10.0 Hz), 3.69 (dd, 1H, J = 6.4, 10.0 Hz), 4.01 (dt, 1H, J = 3.6, 6.4 Hz), 4.13 (t, 1H, J = 6.4 Hz), 5.11 (d, 1H, J = 10.4 Hz), 5.17 (d, 1H, J = 17.2 Hz), 5.82 (ddd, 1H, J = 6.4, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −4.6, −4.5, −4.1, −3.7, 18.1, 18.2, 18.4, 25.9, 26.0, 29.1, 46.1, 62.9, 70.0, 71.5, 75.7, 82.0, 121.5, 139.9; HREIMS calcd for $C_{24}H_{49}O_3Si_3$ (M^+ − *t*Bu) 469.2990, found 469.3021.

(3*R*,4*S*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-4-ethyloct-1-en-7-yne (34). To a solution of alcohol **32** (100 mg, 243 μmol) in CH_2Cl_2 (2.0 mL) was added 4-(dimethylamino)-pyridine (74.0 mg, 606 μmol). To the cold (0 °C) and vigorously stirred solution was slowly added 2-mesitylenesulfonyl chloride (106 mg, 485 μmol). After being stirred for 12 h at 0 °C, the reaction mixture was poured into Et_2O (100 mL) and washed with water (3 × 10 mL) and brine (3 × 10 mL). The aqueous layers were extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration gave the desired crude sulfonate as a colorless oil, which was used in the next step without further purification.

To a cold (0 °C) and stirred solution of crude sulfonate in Et_2O (2.0 mL) was slowly added lithium aluminum hydride (46.0 mg, 1.20 μmol). After being stirred for 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for another 3 h. The mixture was treated with EtOAc (1 mL) at 0 °C and saturated aqueous NH_4Cl solution (1 mL), and the resultant suspension was diluted with Et_2O (100 mL) and filtered through a pad of Celite. The filtrate was washed with saturated aqueous NH_4Cl solution (3 × 10 mL) and brine (3 × 10 mL). The aqueous layers were extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography on silica gel (1% EtOAc in hexanes) gave 77.0 mg (80%) of enyne **34** as a colorless oil: $[\alpha]^{21}_D$ +16.87 (*c* 1.15, $CHCl_3$); IR (neat) 3316, 2957, 1254, 1073, 924, 837, 776, 629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 18H), 0.94 (t, 3H, J = 7.6 Hz), 1.36 (m, 2H), 1.68 (ddt, 1H, J = 3.6, 5.2, 6.0 Hz), 1.95 (t, 1H, J = 2.8 Hz), 2.39 (ddd, 1H, J = 2.8, 6.4, 16.8 Hz), 2.42 (ddd, 1H, J = 2.8, 6.4, 16.8 Hz), 4.01 (dt, 1H, J = 3.6, 6.4 Hz), 4.14 (ddt, 1H, J = 1.2, 5.2, 7.2 Hz), 5.08 (dt, 1H, J = 1.2, 10.4 Hz), 5.14 (dt, 1H, J = 1.2, 16.8 Hz), 5.86 (ddd, 1H, J = 7.2, 10.4, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.4, −4.2, −3.7, 14.0, 18.1, 19.0, 25.9, 26.1, 51.3, 69.8, 71.5, 75.7, 82.3, 115.2, 140.6; HREIMS calcd for $C_{18}H_{35}O_2Si_2$ (M^+ − tBu) 339.2175, found 339.2194.

(4*S*,5*R*)-5-(*tert*-Butyldimethylsilanyloxy)-4-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]oct-7-ynnitrile (35). Alcohol **32** (129 mg, 313 μmol) was converted to nitrile **35** (80.0 mg, 61%) according to the procedure described above for converting **30** from **28**. Data for **35**: colorless oil; $[\alpha]^{20}_D$ +1.39 (*c* 1.15, $CHCl_3$); IR (neat) 3314, 2932, 2247, 1256, 1078, 928, 837, 777, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 6H), 0.10 (s, 3H), 0.90 (s, 18H), 1.73 (m, 2H), 1.96 (q, 1H, *J* = 6.4 Hz), 2.03 (t, 1H, *J* = 2.4 Hz), 2.38 (ddd, 1H, *J* = 2.4, 6.0, 16.8 Hz), 2.43 (ddd, 1H, *J* = 2.4, 4.8, 16.8 Hz), 2.50 (dt, 2H, *J* = 4.0, 8.4 Hz), 3.88 (dt, 1H, *J* = 4.8, 6.0 Hz), 4.18 (tt, 1H, *J* = 1.2, 6.4 Hz), 5.19 (dt, 1H, *J* = 1.2, 10.4 Hz), 5.25 (dt, 1H, *J* = 1.2, 17.2 Hz), 5.80 (ddd, 1H, *J* = 6.4, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.6, −4.3, −4.2, 17.0, 18.0, 18.2, 22.4, 25.9, 26.0, 26.7, 48.3, 71.0, 71.1, 75.2, 80.5, 116.6, 120.4, 138.2; HREIMS calcd for $C_{23}H_{43}O_2NSi_2$ (M^+) 421.2814, found 421.2794.

(4*S*,5*R*)-5-(*tert*-Butyldimethylsilanyloxy)-4-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]oct-7-ynal (36). Nitrile **35** (80.0 mg, 190 μmol) was converted to aldehyde **36** (71.0 mg, 89%) according to the procedure described above for obtaining **31** from **30**. Data for **36**: colorless oil; $[\alpha]^{20}_D$ +3.22 (*c* 1.15, $CHCl_3$); IR (neat) 3314, 2932, 2712, 1728, 1256, 1078, 926, 837, 777, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.69 (m, 2H), 1.87 (ddt, 1H, *J* = 5.2, 5.6, 6.0 Hz), 1.99 (t, 1H, *J* = 2.8 Hz), 2.40 (ddd, 1H, *J* = 2.8, 6.0, 17.2 Hz), 2.43 (ddd, 1H, *J* = 2.8, 6.0, 17.2 Hz), 2.57 (ddd, 1H, *J* = 2.0, 2.8, 6.0 Hz), 2.59 (ddd, 1H, *J* = 2.0, 3.2, 6.0 Hz), 3.94 (dt, 1H, *J* = 4.4, 6.0 Hz), 4.17 (ddt, 1H, *J* = 1.6, 5.6, 6.8 Hz), 5.14 (dt, 1H, *J* = 1.6, 10.4 Hz), 5.21 (dt, 1H, *J* = 1.6, 17.2 Hz), 5.83 (ddd, 1H, *J* = 6.8, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, −4.2, −3.9, 18.2, 18.3, 25.9, 26.4, 30.9, 43.8, 48.4, 70.5, 71.4, 75.6, 81.2, 116.1, 139.2, 203.0; HREIMS calcd for $C_{23}H_{44}O_3Si_2$ (M^+) 424.2829, found 424.2829.

(4*S*,5*R*)-5-(*tert*-Butyldimethylsilanyloxy)-4-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]oct-7-yn-1-ol (37). Aldehyde **36** (71.0 mg, 167 μmol) was converted to alcohol **37** (70.0 mg, 98%) according to the procedure described above for obtaining **32** from **31**. Data for **37**: colorless oil; $[\alpha]^{21}_D$ +10.26 (*c* 1.15, $CHCl_3$); IR (neat) 3340, 3314, 2932, 1254, 1067, 924, 837, 776, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.39 (m, 2H), 1.57 (bs, 1H), 1.66 (q, 2H, *J* = 6.4 Hz), 1.85 (ddt, 1H, *J* = 4.8, 5.2, 5.6 Hz), 1.98 (t, 1H, *J* = 2.8 Hz), 2.39 (ddd, 1H, *J* = 2.8, 6.4, 16.8 Hz), 2.43 (ddd, 1H, *J* = 2.8, 6.4, 16.8 Hz), 3.61 (t, 2H, *J* = 6.4 Hz), 3.97 (dt, 1H, *J* = 4.8, 6.4 Hz), 4.16 (ddt, 1H, *J* = 1.2, 5.6, 7.2 Hz), 5.12 (dt, 1H, *J* = 1.2, 9.6 Hz), 5.17 (dt, 1H, *J* = 1.2, 16.8 Hz), 5.84 (ddd, 1H, *J* = 7.2, 9.6, 16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, −4.3, −4.1, 18.0, 18.2, 21.5, 25.8, 25.9, 26.1, 32.3, 48.6, 63.0, 70.2, 71.5, 75.7, 81.2, 115.7, 139.0; HREIMS calcd for $C_{23}H_{46}O_3Si_2$ (M^+) 426.2985, found 426.2977.

(3*R*,4*S*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-4-[3-(*tert*-butyldimethylsilanyloxy)propyl]oct-1-en-7-yne (38). Alcohol **37** (60.0 mg, 141 μmol) was converted to silyl ether **38** (63.0 mg, 83%) according to the procedure described above for obtaining **33** from **32**. Data for **38**: colorless oil; $[\alpha]^{25}_D$ +8.70 (*c* 1.15, $CHCl_3$); IR (neat) 3316, 2932, 1256, 1102, 924, 837, 776, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 27H), 1.32 (m, 2H), 1.56 (m, 2H), 1.75 (ddt, 1H, *J* = 4.0, 6.4, 6.8 Hz), 1.95 (t, 1H, *J* = 2.8 Hz), 2.38 (ddd, 1H, *J* = 2.8, 6.4, 16.8 Hz), 2.42 (ddd, 1H, *J* = 2.8, 6.4, 16.8 Hz), 3.56 (t, 2H, *J* = 6.8 Hz), 4.03 (dt, 1H, *J* = 4.0, 6.0 Hz), 4.12 (dd, 1H, *J* = 6.4, 7.6 Hz), 5.08 (d, 1H, *J* = 10.0 Hz), 5.14 (d, 1H, *J* = 17.2 Hz), 5.84 (ddd, 1H, *J* = 7.6, 10.0, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, −4.6, −4.4, −4.1, −3.6, 18.1, 18.2, 22.1, 25.9, 26.0, 26.1, 32.6, 49.2, 63.6, 69.9, 71.5, 75.9, 82.1, 115.5, 140.4; HREIMS calcd for $C_{25}H_{51}O_3Si_3$ (M^+) 483.3146, found 483.3141.

(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilanyloxy)-4-propyl-oct-1-en-7-yne (39). Alcohol **37** (70.0 mg, 164 μmol) was converted to enyne **39** (54.0 mg, 80%) according to the procedure described above for obtaining **34** from **32**. Data for **39**: colorless oil; $[\alpha]^{22}_D$ +19.39 (*c* 1.15, $CHCl_3$); IR (neat) 3316, 2957, 1254, 1075, 926, 837, 776, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.09 (s, 3H), 0.87 (t, 3H, *J* = 7.2 Hz), 0.89 (s, 18H), 1.27 (m, 2H), 1.36 (m, 2H), 1.76 (ddt, 1H, *J* = 4.0, 5.2, 6.0 Hz), 1.95 (t, 1H, *J* = 2.8 Hz), 2.39 (ddd, 1H, *J* = 2.8, 6.4, 17.6 Hz), 2.41 (ddd, 1H, *J* = 2.8, 6.4, 17.6 Hz), 3.99 (dt, 1H, *J* = 4.0, 6.4 Hz), 4.12 (ddt, 1H, *J* = 6.0, 8.0, 1.2 Hz), 5.07 (dt, 1H, *J* = 1.2, 10.4 Hz), 5.13 (dt, 1H, *J* = 1.2, 17.2 Hz), 5.85 (ddd, 1H, *J* = 8.0, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, −4.2, −3.7, 14.4, 18.0, 18.1, 22.3, 25.8, 25.9, 26.0, 28.2, 49.2, 69.7, 71.6, 75.7, 82.3, 115.2, 140.5; HREIMS calcd for $C_{19}H_{37}O_2Si_2$ (M^+) 353.2330, found 353.2332.

(5*S*,6*R*)-6-(*tert*-Butyldimethylsilanyloxy)-5-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]non-8-ynnitrile (40). Alcohol **37** (470 mg, 1.10 mmol) was converted to nitrile **40** (400 mg, 83%) according to the procedure described above for obtaining **30** from **28**. Data for **40**: colorless oil; $[\alpha]^{20}_D$ +2.21 (*c* 1.27, $CHCl_3$); IR (neat) 3314, 2930, 2361, 1255, 1078, 928, 837, 777, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.72 (s, 3H), 0.09 (s, 3H), 0.89 (s, 18H), 1.43 (m, 2H), 1.73 (m, 3H), 1.99 (t, 1H, *J* = 2.6 Hz), 2.28 (t, 2H, *J* = 7.3 Hz), 2.39 (ddd, 2H, *J* = 2.8, 6.4, 6.4 Hz), 3.88 (dt, 1H, *J* = 2.8, 6.7 Hz), 4.18 (dd, 1H, *J* = 5.8, 7.7 Hz), 5.14 (dt, 1H, *J* = 1.2, 10.4 Hz), 5.19 (dt, 1H, *J* = 1.2, 17.1 Hz), 5.80 (ddd, 1H, *J* = 7.0, 10.4, 17.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, −4.2, −3.8, 17.5, 18.1, 18.2, 25.1, 25.3, 25.86, 25.9, 26.4, 48.5, 70.6, 71.1, 75.5, 81.1, 116.2, 119.8, 139.2; HREIMS calcd for $C_{20}H_{36}O_2NSi_2$ ($M^+ - t$Bu) 378.2285, found 378.2298.

(5*S*,6*R*)-6-(*tert*-Butyldimethylsilanyloxy)-5-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]non-9-ynal (41). Nitrile **40** (400 mg, 920 μmol) was converted to aldehyde **41** (320 mg, 82%) according to the procedure described above for obtaining **31** from **30**. Data for **41**: colorless oil; $[\alpha]^{20}_D$ +6.30 (*c* 1.78, $CHCl_3$); IR (neat) 3314, 2930, 2712, 2361, 1730, 1253, 1072, 924, 837, 775, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.830 (s, 9H), 0.833 (s, 9H), 1.3 (m, 2H), 1.69 (m, 2H), 1.82 (m, 1H), 1.96 (t, 1H, *J* = 2.4 Hz), 2.40 (ddd, 1H, *J* = 2.8, 6.0, 17.2 Hz), 2.43 (ddd, 1H, *J* = 2.8, 6.0, 17.2 Hz), 2.37 (m, 3H), 3.96 (m, 1H), 4.12 (dd, 1H, *J* = 5.8, 7.0 Hz), 5.10 (dt, 1H, *J* = 1.6, 10.4 Hz), 5.17 (dt, 1H, *J* = 1.6, 16.5 Hz), 5.83 (ddd, 1H, *J* = 7.3, 10.4, 16.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.4, −4.2, −3.7, 18.09, 18.17, 25.4, 25.9, 26.3, 44.4, 49.0, 70.3, 71.2, 75.6, 81.5, 115.8, 139.8, 202.8; HREIMS calcd for $C_{20}H_{37}O_3Si_2$ ($M^+ - t$Bu) 381.2281, found 381.2278.

(5*S*,6*R*)-6-(*tert*-Butyldimethylsilanyloxy)-5-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)allyl]non-8-yn-1-ol (42). Aldehyde **41** (320 mg, 731 μmol) was reduced to alcohol **42** (300 mg, 93%) according to the procedure described above for obtaining **32** from **31**. Data for **42**: colorless oil; $[\alpha]^{21}_D$ +8.56 (*c* 0.63, $CHCl_3$); IR (neat) 3314, 2932, 2361, 1253, 1070, 924, 837, 775, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.37 (m, 2H), 1.54 (m, 2H), 1.78 (m, 1H), 1.97 (t, 1H, *J* = 2.6 Hz), 2.39 (m, 2H), 3.61 (t, 2H, *J* = 6.4 Hz), 3.97 (dt, 1H, *J* = 6.2, 10.0 Hz), 4.13 (t, 1H, *J* = 6.8 Hz), 5.09 (dt, 1H, *J* = 1.2, 10.4 Hz), 5.16 (dt, 1H, *J* = 1.2, 17.1 Hz), 5.84 (ddd, 1H, *J* = 7.3, 10.4, 17.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.4, −4.2, −3.7, 18.1, 18.2, 25.4, 25.7, 25.9, 26.0, 26.2, 33.3, 49.3, 63.0, 70.0, 71.5, 75.7, 82.0, 115.5, 140.3; HREIMS calcd for $C_{24}H_{48}O_3Si_2$ (M^+) 440.3142, found 440.3148.

(3*R*,4*S*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-4-[4-(*tert*-butyldimethylsilanyloxy)butyl]oct-1-en-7-yne (43). Alcohol **42** (90.0 mg, 205 μmol) was converted to silyl ether **43** (105 mg, 93%) according to the procedure described above for obtaining **33** from **32**. Data for **43**: colorless oil; $[\alpha]^{25}_D$ +7.58 (*c* 1.29, $CHCl_3$); IR (neat) 3316, 2930, 2359, 1253, 1100, 924, 837, 775, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.06 (s, 3H), 0.09 (s, 3H), 0.844 (s, 9H), 0.848 (s, 9H), 0.850 (s, 9H), 1.32 (m, 2H), 1.48 (m, 2H), 1.75 (m, 1H), 1.95 (t, 1H, *J* = 2.5 Hz), 2.39 (dd, 2H, *J* = 2.5, 6.4 Hz), 2.42 (t, 1H, *J* = 6.4 Hz), 3.58 (t, 2H, *J* = 6.4 Hz), 4.03 (dt, 1H, *J* = 6.4, 10.0 Hz), 4.13 (dd, 1H, *J* = 5.5, 7.3 Hz), 5.08 (dt, 1H, *J* = 1.2, 10.0 Hz), 5.14 (dt, 1H, *J* = 1.2, 17.2 Hz), 5.80 (ddd, 1H, *J* = 7.6, 10.0, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)

δ −5.2, −4.6, −4.4, −4.2, −3.7, 18.1, 18.2, 18.4, 25.5, 25.89, 25.95, 26.00, 26.10, 33.5, 49.5, 63.3, 69.9, 71.5, 75.7, 82.2, 115.3, 140.5; HREIMS calcd for $C_{30}H_{62}O_3Si_3$ (M^+) 554.4007, found 554.4021

(3*R*,4*S*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-4-butylnon-1-en-7-yne (44). Alcohol **43** (90.0 mg, 205 μmol) was reduced to enyne **44** (72.0 mg, 83%) according to the procedure described above for obtaining **34** from **32**. Data for **44**: colorless oil; $[\alpha]^{22}_D$ +6.69 (*c* 0.78, $CHCl_3$); IR (neat) 3314, 2930, 2361, 1255, 1074, 924, 837, 777, 629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.09 (s, 3H), 0.87 (t, 3H, *J* = 7.2 Hz), 0.88 (s, 9H), 0.89 (s, 9H), 1.28 (m, 6H), 1.76 (m, 1H), 1.95 (t, 1H, *J* = 2.7 Hz), 2.39 (dd, 2H, *J* = 2.7, 6.1 Hz), 3.99 (dt, 1H, *J* = 4.0, 6.1 Hz), 4.15 (m, 1H), 5.08 (dt, 1H, *J* = 1.2, 10.4 Hz), 5.15 (dt, 1H, *J* = 1.2, 17.2 Hz), 5.83 (ddd, 1H, *J* = 8.0, 10.4, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.4, −4.2, −3.7, 14.0, 18.1, 18.2, 23.2, 25.89, 25.95, 26.04, 31.5, 49.5, 69.8, 71.7, 75.7, 82.4, 115.3, 140.5; HREIMS calcd for $C_{24}H_{48}O_2Si_2$ (M^+) 424.3013, found 424.3201.

(5*Z*,7*E*)-(1*S*,2*S*,3*R*,20*R*)-9,10-Seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol (3). The silyl ether **29** (20.0 mg, 39.1 μmol) and vinyl bromide **11** (20.0 mg, 58.0 μmol) were dissolved in TEA/toluene (3:1, 2.0 mL), and tris(dibenzylideneacetone)−dipalladium(0)−chloroform adduct (4.0 mg, 3.86 μmol) and triphenylphosphine (10.0 mg, 38.1 μmol) were added. After being stirred for 15 min at room temperature, the resultant yellow solution was heated at reflux for 2 h. The reaction mixture was filtered through a pad of silica gel. Concentration followed by preparative thin-layer chromatography on silica gel (20% EtOAc in hexanes) gave the crude protected vitamin as a white solid, which was used in the next step without further purification.

To a cold (0 °C) and stirred solution of the crude protected vitamin in MeOH (2.0 mL) was added (+)-10-camphorsulfonic acid (10.0 mg, 43.0 μmol). After being stirred for 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for another 12 h. The resultant solution was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 × 1 mL) and brine (3 × 1 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layer was dried over Na_2SO_4. Filtration and concentration followed by preparative thin-layer chromatography on silica gel (20% MeOH in CH_2Cl_2) gave 7.0 mg (40%) of 2α-(hydroxymethyl)-1α,25-dihydroxyvitamin D_3 **3** as a white solid; $[\alpha]^{20}_D$ +12.95 (*c* 0.0085, $CHCl_3$); UV (EtOH) λ_{max} 269 nm, λ_{min} 226 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, *J* = 6.8 Hz), 2.31 (m, 2H), 2.67 (dd, 1H, *J* = 4.4, 12.8 Hz), 2.73 (bs, 1H), 2.84 (m, 1H), 4.01 (m, 2H), 4.24 (m, 1H), 4.47 (bs, 1H), 5.02 (d, 1H, *J* = 2.0 Hz), 5.30 (d, 1H, *J* = 2.0 Hz), 5.98 (d, 1H, *J* = 10.8 Hz), 6.45 (d, 1H, *J* = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 18.8, 20.8, 22.2, 23.5, 27.7, 29.1, 29.2, 29.4, 36.1, 36.4, 40.5, 44.4, 45.0, 45.9, 50.4, 56.3, 56.5, 63.9, 68.0, 71.1, 115.0, 116.8, 125.4, 132.0, 143.8, 145.9; HREIMS calcd for $C_{28}H_{44}O_3$ ($M^+ - H_2O$) 428.3290, found 428.3287.

(5*Z*,7*E*)-(1*S*,2*S*,3*R*,20*R*)-9,10-Seco-5,7,10(19)-cholestatriene-2-(2-hydroxyethyl)-1,3,25-triol (4). Silyl ether **33** (25.0 mg, 47.5 μmol) was converted to 2α-(hydroxyethyl)-1α,-25-dihydroxyvitamin D_3 **4** (8.5 mg, 39%) according to the procedure described above for **3**. Data for **4**: white solid; $[\alpha]^{20}_D$ +13.85 (*c* 0.00722, $CHCl_3$); UV (EtOH) λ_{max} 268 nm, λ_{min} 228 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, *J* = 6.4 Hz), 2.26 (dd, 1H, *J* = 8.0, 12.8 Hz), 2.53 (bs, 1H), 2.66 (dd, 1H, *J* = 4.0, 13.2 Hz), 2.83 (m, 1H), 3.79 (m, 2H), 3.94 (m, 1H), 4.37 (d, 1H, *J* = 2.0 Hz), 5.02 (d, 1H, *J* = 1.2 Hz), 5.30 (bs, 1H), 6.01 (d, 1H, *J* = 10.8 Hz), 6.40 (d, 1H, *J* = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.8, 20.8, 22.2, 23.5, 27.6, 29.07, 29.14, 29.3, 31.8, 36.1, 36.4, 40.5, 43.9, 44.4, 45.9, 48.6, 56.3, 56.5, 61.6, 70.5, 71.0, 74.9, 113.7, 116.9, 124.8, 132.5, 143.4, 146.4; HREIMS calcd for $C_{29}H_{48}O_4$ (M^+) 460.3553, found 460.3557.

(5*Z*,7*E*)-(1*S*,2*S*,3*R*,20*R*)-9,10-Seco-5,7,10(19)-cholestatriene-2-(3-hydroxypropyl)-1,3,25-triol (5). Silyl ether **38** (25.0 mg, 46.3 μmol) was converted to 2α-(hydroxypropyl)-1α,-25-dihydroxyvitamin D_3 **5** (7.2 mg, 33%) according to the procedure described above for **3**. Data for **5**: white solid; $[\alpha]^{20}_D$ +161.29 (*c* 0.00186, $CHCl_3$); UV (EtOH) λ_{max} 268 nm, λ_{min} 227 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, *J* = 6.4 Hz), 2.25 (dd, 1H, *J* = 8.4, 13.2 Hz), 2.66 (dd, 1H, *J* = 4.0, 13.2 Hz), 2.83 (m, 1H), 3.70 (t, 2H, *J* = 5.6 Hz), 3.90 (dt, 1H, *J* = 4.0, 8.0 Hz), 4.38 (d, 1H, *J* = 3.6 Hz), 5.00 (d, 1H, *J* = 1.6 Hz), 5.28 (d, 1H, *J* = 1.6 Hz), 6.00 (d, 1H, *J* = 11.2 Hz), 6.40 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.9, 21.0, 22.4, 23.0, 23.7, 27.8, 29.2, 29.3, 29.5, 30.3, 36.2, 36.5, 40.6, 44.4, 44.5, 46.0, 49.1, 56.4, 56.6, 62.9, 70.4, 71.1, 73.6, 113.5, 116.8, 124.7, 132.5, 143.2, 146.4; HREIMS calcd for $C_{30}H_{50}O_4$ (M^+) 474.3709, found 474.3709.

(5*Z*,7*E*)-(1*S*,2*S*,3*R*,20*R*)-9,10-Seco-5,7,10(19)-cholestatriene-2-(4-hydroxybutyl)-1,3,25-triol (6). Silyl ether **43** (25.0 mg, 45.1 μmol) was converted to 2α-(hydroxybutyl)-1α,-25-dihydroxyvitamin D_3 **6** (8.2 mg, 37%) according to the procedure described above for **3**. Data for **6**: white solid; $[\alpha]^{20}_D$ +86.15 (*c* 0.0650, $CHCl_3$); UV (EtOH) λ_{max} 268 nm, λ_{min} 227 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.93 (d, 3H, *J* = 6.6 Hz), 2.24 (dd, 1H, *J* = 8.4, 13.2 Hz), 2.66 (dd, 1H, *J* = 4.4, 13.2 Hz), 2.83 (m, 1H), 3.71 (m, 4H), 3.89 (ddd, 1H, *J* = 4.4, 7.8, 13.2 Hz), 4.38 (t, 1H, *J* = 3.1 Hz), 4.99 (d, 1H, *J* = 1.6 Hz), 5.26 (d, 1H, *J* = 1.6 Hz), 6.00 (d, 1H, *J* = 11.5 Hz), 6.40 (d, 1H, *J* = 11.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.8, 20.8, 22.2, 23.4, 23.5, 26.2, 27.7, 29.1, 29.2, 29.4, 32.8, 36.1, 36.4, 40.5, 44.4, 45.9, 49.5, 56.3, 56.5, 62.8, 70.4, 71.1, 73.5, 113.6, 116.9, 124.8, 132.6, 143.4, 146.6; HREIMS calcd for $C_{31}H_{52}O_4$ (M^+) 488.3866, found 488.3867.

(5*Z*,7*E*)-(1*S*,2*S*,3*R*,20*R*)-9,10-Seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol (7). Enyne **34** (30.0 mg, 75.8 μmol) was converted to 2α-ethyl-1α,25-dihydroxyvitamin D_3 **7** (6.8 mg, 20%) according to the procedure described above for **3**. Data for **7**: white solid; $[\alpha]^{20}_D$ +80.79 (*c* 0.108, $CHCl_3$); UV (EtOH) λ_{max} 269 nm, λ_{min} 227 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, *J* = 6.0 Hz), 0.95 (t, 3H, *J* = 7.2 Hz), 2.24 (dd, 1H, *J* = 8.8, 12.8 Hz), 2.66 (dd, 1H, *J* = 4.0, 13.2 Hz), 2.83 (m, 1H), 3.89 (m, 1H), 4.37 (bs, 1H), 4.99 (d, 1H, *J* = 1.6 Hz), 5.27 (bs, 1H), 6.00 (d, 1H, *J* = 11.2 Hz), 6.40 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 12.0, 18.8, 19.3, 20.8, 22.2, 23.5, 27.6, 29.07, 29.14, 29.3, 36.1, 36.4, 40.5, 44.4, 45.9, 51.1, 56.3, 56.5, 70.1, 71.0, 73.0, 113.4, 116.9, 124.7, 132.8, 143.3, 146.7; HREIMS calcd for $C_{29}H_{48}O_3$ (M^+) 444.3603, found 460.3604.

(5*Z*,7*E*)-(1*S*,2*S*,3*R*,20*R*)-9,10-Seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol (8). Enyne **39** (30.0 mg, 73.2 μmol) was converted to 2α-propyl-1α,25-dihydroxyvitamin D_3 **8** (6.2 mg, 18%) according to the procedure described above for **3**. Data for **8**: white solid; $[\alpha]^{20}_D$ −202.91 (*c* 0.06653, $CHCl_3$); UV (EtOH) λ_{max} 269 nm, λ_{min} 227 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, *J* = 6.4 Hz), 1.01 (t, 3H, *J* = 6.8 Hz), 2.24 (dd, 1H, *J* = 8.8, 12.4 Hz), 2.66 (dd, 1H, *J* = 4.0, 13.2 Hz), 2.83 (m, 1H), 3.89 (m, 1H), 4.39 (bs, 1H), 4.99 (d, 1H, *J* = 1.6 Hz), 5.27 (bs, 1H), 6.00 (d, 1H, *J* = 11.2 Hz), 6.40 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 14.4, 18.8, 20.4, 20.8, 22.3, 23.6, 27.7, 28.7, 29.1, 29.2, 29.4, 36.1, 36.4, 40.5, 44.3, 44.4, 45.9, 49.3, 56.4, 56.6, 70.4, 71.1, 73.4, 113.3, 116.9, 124.8, 132.8, 143.3, 146.8; HREIMS calcd for $C_{30}H_{50}O_3$ (M^+) 458.3760, found 458.3755.

(5*Z*,7*E*)-(1*S*,2*S*,3*R*,20*R*)-9,10-Seco-5,7,10(19)-cholestatriene-2-butyl-1,3,25-triol (9). Enyne **44** (25.0 mg, 59.0 μmol) was converted to 2α-butyl-1α,25-dihydroxyvitamin D_3 **9** (8.40 mg, 30%) according to the procedure described above for **3**. Data for **9**: white solid; $[\alpha]^{20}_D$ +40.70 (*c* 0.36118, $CHCl_3$); UV (EtOH) λ_{max} 269 nm, λ_{min} 227 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 2.24 (dd, 1H, *J* = 8.8, 13.2 Hz), 2.66 (dd, 1H, *J* = 4.4, 13.8 Hz), 2.82 (m, 1H), 3.72 (m, 2H), 3.89 (ddd, 1H, *J* = 4.4, 8.2, 13.2 Hz), 4.38 (t, 1H, *J* = 3.8 Hz), 4.99 (d, 1H, *J* = 2.2 Hz), 5.26 (d, 1H, *J* = 1.1 Hz), 6.00 (d, 1H, *J* = 11.0 Hz), 6.40 (d, 1H, *J* = 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 14.4, 18.8, 20.4, 20.8, 22.2, 23.1, 23.5, 26.1, 27.7, 29.1, 29.2, 29.4, 29.5, 36.1, 36.4, 40.5, 44.4, 45.9, 49.5, 56.4, 56.6, 70.4, 71.1, 73.4, 113.3, 116.9, 124.8, 132.8, 143.3, 146.8; HREIMS calcd for $C_{31}H_{52}O_3$ (M^+) 472.3916, found 472.3902.

Acknowledgment. We are grateful to Ms. Junko Shimode, Ms. Jinko Nonobe, and Ms. Maroka Kitsukawa (Teikyo University) for the spectroscopic measurements. This study was supported in part by Grants-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan.

Supporting Information Available: ^{1}H NMR spectra for all new compounds, synthetic route of compound **19c** from **19a**, and elemental analysis data for **19c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010375I