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Syntheses of Two Diastereoisomers of Panaxytriol, a Potent Antitumor Agent Isolated from *Panax Ginseng*

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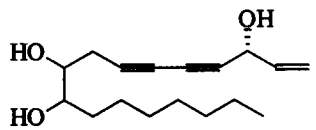
Abstract: (3*R*, 9*R*, 10*R*) and (3*R*, 9*S*, 10*S*) diastereoisomers (2 and 3) of panaxytriol (1) were synthesized, and the absolute configuration of panaxytriol was confirmed as (3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol.

For thousands of years the roots of *panax ginseng* C. A. Meyer have been used as an analeptic, stomachic and erythropoietic agent in China, Japan and Korea. The biologically active constituents of *panax ginseng* have been pursued extensively, and recently many reports have demonstrated that *panax ginseng* C. A. Meyer contains several types of polyacetylenic alcohols, which suppressed *in vitro* growth of cultured tumor cells.[1] Panaxytriol (1) was first isolated in 1983 as a characteristic polyacetylenic constituent[2] of *panax ginseng*. It exhibited inhibitory acitivity on growth of MK-1 cells by clonogenic assay with a 50% inhibition value of 8.5ng/ml.[3] Panaxytriol also suppressed the growth of B16 melanoma transplanted into mice[4] and showed a stimulative effect on the antitumor acitivity of mitomycin C in cultured tumor cells.[5] The structure of panaxytriol was elucidated as heptadec-1-ene-4,6-diyne-3,9,10-triol.[1d] The absolute configuration of C-3 was confirmed to be *R* by the Mosher method, and in which C-9 and C-10 were defined as 9*R* and 10*R* by the CD analysis.[6] However, Fujimoto *et al.* reported that panaxytriol had 9*S* and 10*S* configurations by synthesis of a diastereomeric mixture at C-3 of **1**.[7] In order to elucidate the absolute configurations of panaxytriol, the only possible solution to this problem seemed to involve the total syntheses of two possible diastereoisomers. Therefore, we synthesized the possible (3*R*, 9*R*, 10*R*) and (3*R*, 9*S*, 10*S*) diastereoisomers (2 and 3) of panaxytriol, and confirmed the absolute stereostructure of nature panaxytriol to be (3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol. In previous work, we have already reported the synthesis of (3*R*, 9*R*, 10*R*)-panaxytriol (2) as a brief communication.[8] Herein we describe the synthesis of (3*R*, 9*R*, 10*R*) and (3*R*, 9*S*, 10*S*)-panaxytriol (2 and 3) in detail.



panaxytriol **1**

Polyacetylene compounds are usually obtained through coupling of two acetylenic fragments.[9] Among the coupling methods available, the Cadiot-Chodkiewicz reaction, where a copper salt catalyzes the crossing-coupling of a bromoacetylene with a terminal acetylene, is one of the most general.[10] The retrosynthetic analysis of panaxytriol showed the reaction needed two fragments, one being terminal acetylene (4), the other being bromoacetylene (5) (Scheme 1).

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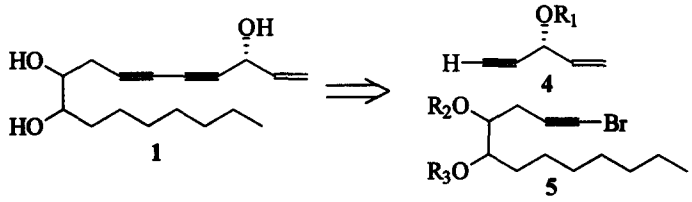
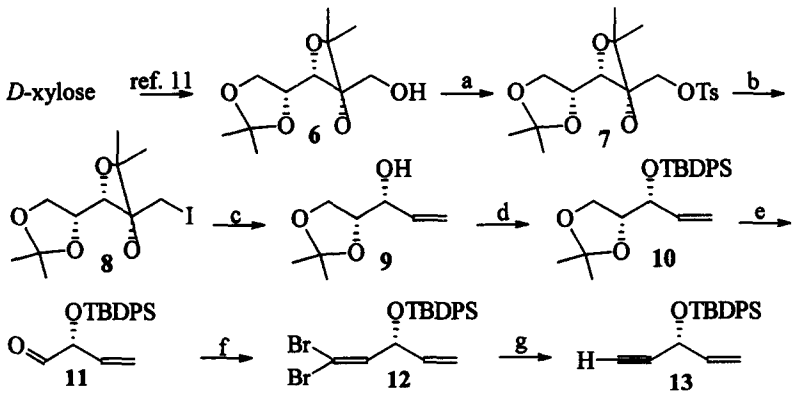


Scheme 1

Firstly, the (3*R*) configuration acetylene (**13**) was constructed by the method shown in Scheme 2. Accordingly, *D*-xylose was transformed to 2,3;4,5-diisopropylene *D*-xylitol (**6**) according to the known procedure.[11] Compound **6** was converted into iodide (**8**) via its tosylate (**7**), and iodide (**8**) on interaction with activated Zn in reflux ethanol underwent a facile elimination[12] to afford the allyl alcohol (**9**) in good yield. *tert*- Butyldiphenyl chlorosilane (TBDPS) was chosen to protect the hydroxy group in **9** obtaining the silyl ether (**10**). When **10** was treated with periodic acid[13] in AcOEt the aldehyde (**11**) was obtained, which was subjected to Wittig reaction by the Corey-Fuchs method[14] to afford dibromide (**12**) in high yield (82% over two steps).

We now anticipated that the reaction of the dibromide (**12**) with 2 equiv. *n*-BuLi would afford the desired acetylene (**13**) in high yield.[14] However, **13** was only obtained in a modest yield (45-51%). Pale *et al.*[15] reported that dibromoalkene treatment with NaHMDS could give very cleanly and quantitatively bromoacetylene. These workers subsequently exchanged the bromo group with *n*-BuLi, and the correponding acetylene was trapped in high yield. We used LDA to examine the possibility of effectively changing **12** into **13**. Addition of 1.5 eq. of LDA to **12** in THF at -78°C, followed by 2.2 eq. of *n*-BuLi (1 equiv is used to neutralize the diisopropylamine) afforded the desired acetylene (**13**) in 91% yield.

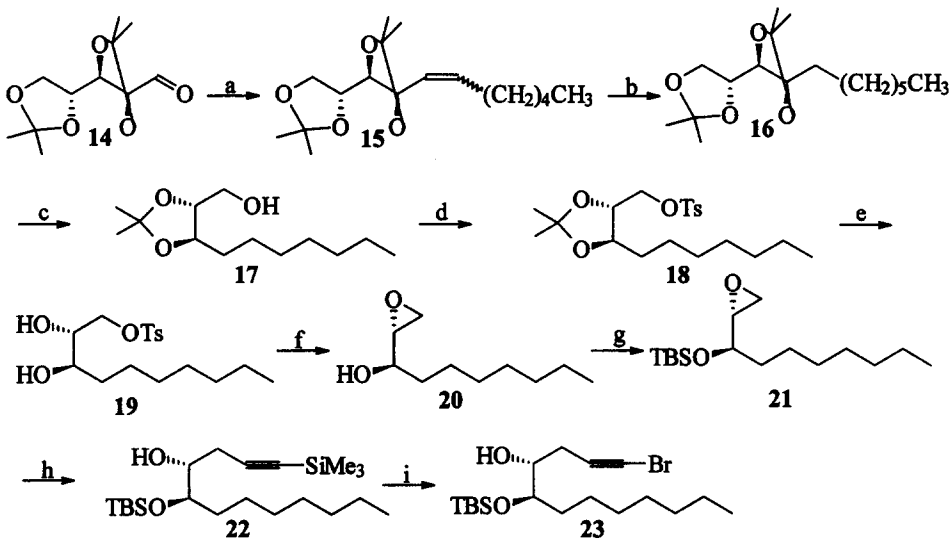


Scheme 2

Reagents and conditions: a) *p*-TsCl, py, rt; b) NaI, acetone, reflux, 24h; c) Zn, EtOH, reflux, 81% over three steps; d) TBDPSCl, imidazole, CH_2Cl_2, rt, 96%; e) H_5IO_6, AcOEt, rt; f) CBr_4, Zn, PPh_3, CH_2Cl_2, 0°C, 82% over two steps; g) i. 1.5 eq LDA, THF, -78°C; ii. 2.2 eq n-BuLi, -78°C, 91%.

Synthesis (3*R*, 9*R*, 10*R*) compound **2**, the bromoacetylene (**23**) was obtained by using *D*-arabinose as a chiral template as depicted in Scheme 3. Diisopropylene *D*-arabinose (**14**) was prepared according to the

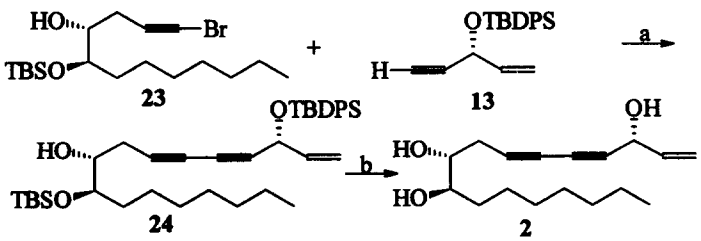
known procedure from *D*-gluconolactone.[16] The aldehyde was then subjected to a Wittig reaction to provide alkene (**15**), and subsequently catalytic hydrogenation yielded saturated compound **16**. Selective cleavage of the terminal acetal,[13] and reduction of the resulting aldehyde with $NaBH_4$ gave the primary alcohol (**17**), which on successive treatment with *p*-TsCl in pyridine, acidic methanol, and excess K_2CO_3 in methanol led to the epoxy alcohol (**20**). The secondary hydroxy group of **20** was protected as a *tert*-butyldimethylsilyl (TBS) ether to yield **21**, which was subjected to the coupling reaction with trimethylsilyl acetylene lithium in the presence of boron trifluoride etherate to afford silylacetylene (**22**). By treatment with NBS and $AgNO_3$, **22** was converted into bromoacetylene (**23**) in high yield.[17]



Scheme 3

Reagents and conditions: a) $C_6H_{13}PPh_3Br$, *n*-BuLi, THF, -78 to 0°C, 87%; b) 10% Pd/C, 95% EtOH, 97%; c) i. H_5IO_6, AcOEt, rt; ii. $NaBH_4$, EtOH, 71%; d) *p*-TsCl, Pyridine; e) TsOH, MeOH; f) K_2CO_3, MeOH, 81% over three steps; g) TBDMSCl, pyridine, $AgNO_3$, THF, 92%; h) Trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}Et_2O$, -78°C, 93%; i) NBS, $AgNO_3$, acetone, 87%.

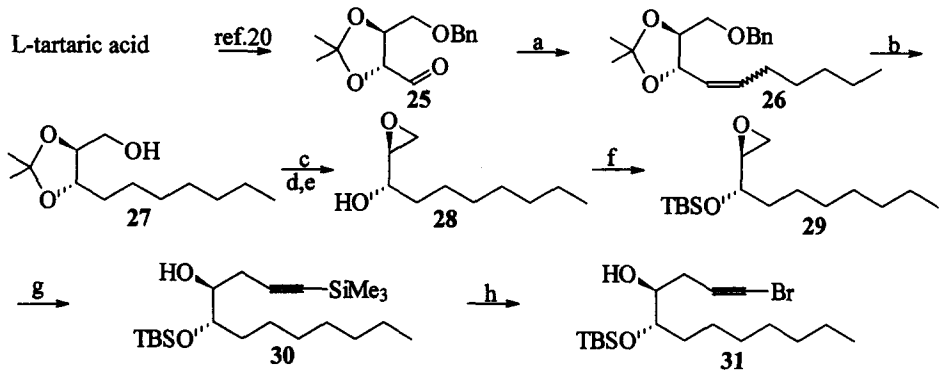
Bromoacetylene (**23**) was then coupled with acetylene (**13**) using the Cadiot-Chodkiewicz procedure[10,18] at 0°C to obtain the coupling product **24**. Subsequently, deprotection of the silyl groups with tetrabutylammonium fluoride afforded (3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol (**2**) in 83% yield (Scheme 4).



Scheme 4

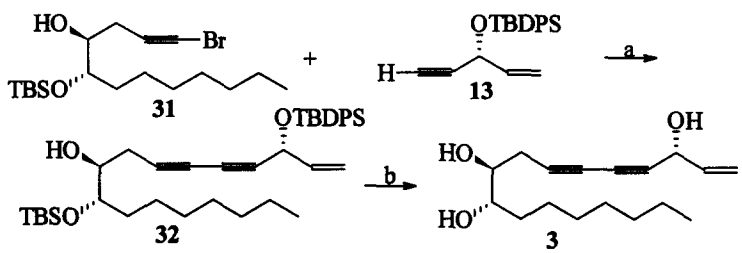
Reagents and conditions: a) CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, 0°C, 75%; b) Bu_4NF, THF, 83%.

Synthesis (3*R*, 9*S*, 10*S*) compound **3**, the absolute configurations of C9 and C10 was established using *L*-tartaric acid as a chiral template (Scheme **5**). Aldehyde (**25**) was prepared from *L*-tartaric acid according to a known method,[20] and subsequent Wittig reaction and catalytic hydrogenation afforded the primary alcohol (**27**). Using the same procedure as in the synthesis of **23**, bromoacetylene (**31**) was prepared (Scheme **5**), and coupled with acetylene **13**, followed by removal of the silyl groups to afford (3*R*, 9*S*, 10*S*)-heptadec-1-ene-4,6-diyne-3,9,10-triol (**3**) (Scheme **6**).



Scheme **5**

Reagents and conditions: a) $C_6H_{13}PPh_3Br$, *n*-BuLi, THF, 0 to -78°C, 75%; b) 10% Pd/C, EtOH, 85%; c-h) the same as (d-i) in Scheme **3**. Yield: c) 96%; d-e) 90% over two steps; f) 93%; g) 94%; h) 86%.



Scheme **6**

Reagents and conditions: the same as in Scheme **4**. Yield: a) 71%; b) 79%.

The ^{1}H-NMR and ^{13}C-NMR spectra of compounds **2** and **3** were very similar, which agreed with the reported data of natural panaxytriol (**1**), because the interplay between chiral centers C3 and C9-C10 is very weak for the long distance between them. The optical rotation of **2** was nearly identical to that reported for the natural sample: **2**, $[\alpha]_D$ –21.2 (c, 0.55, $CHCl_3$), –18.9 (c, 0.60, MeOH), and the natural, $[\alpha]_D$ –25.4 (c, 1.54, $CHCl_3$),[6b] –19.0 (c, 1.0, MeOH).[6a] Meanwhile, the $[\alpha]_D$ value of **3**, –49.2 (c, 0.90, $CHCl_3$), was significantly different to that of the natural product. Consequently, the absolute stereostructure of panaxytriol (**1**) was confirmed to be (3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol. This approach gives an access to the other similar polyacetylene alcohols isolated from *panax ginseng* C. A. Meyer, and this work is now in progress in our group.

Experimental

All melting points (Mp) are uncorrected. Optical rotations were measured with a Perkin-Elmer 241MS Autopol polarimeter. IR spectra were taken with a Perkin-Elmer 598B or Nicolt Magan 750 infrared spectrometer. NMR were recorded with a Gemini-300 spectrometer. MS spectra were obtained on MAT 711, MAT-95, MAT-8430 and HT5989 instruments. Flash column chromatography was performed on silica gel H (200-300 mesh).

(2*R*, 3*R*)-3-Hydroxy-1,2-methylethylidenedioxy-4-pentene (9). To an ice-cooled solution of *D*-xylitol (**6**) (5.70 g, 24.5 mmol) in pyridine (50 mL) was added *p*-TsCl (5.70 g, 30 mmol). After being stirred in an ice-bath for 1 hr and then at room temperature for 10 hr, the mixture was poured into an ice-cooled 10% HCl solution, and extracted with ether. The extract was washed with water, dried ($MgSO_4$) and concentrated to give the crude tosylate (**7**) as a white solid, m.p. 64-66 °C; ^{1}H NMR ($CDCl_3$) δ_H 1.32 (3 H, s), 1.34 (3 H, s), 1.36 (3 H, s), 1.37 (3 H, s), 2.44 (3 H, s), 3.81 (1 H, dd, *J* 6.9, 8.4 Hz), 3.91 (1 H, m), 4.01 (1 H, dd, *J* 6.7, 8.4 Hz), 4.13 (4 H, m), 7.34 (2 H, d, *J* 8.0 Hz), 7.79 (2 H, d, *J* 8.0 Hz) ppm; EIMS (m/z) 371 (M^+-CH_3), 313, 285, 253, 227, 155, 139, 101, 91.

The crude tosylate (**7**) was then dissolved in acetone (150 mL), and NaI (21 g, 0.14 mol) was added to the solution. After being stirred under reflux for 24 hr, the solvent was removed, and the residue was dissolved in water, extracted with ether. The extract was washed with water, aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$ and concentrated to give the crude iodide (**8**) as a colorless oil, which was directly used in next step without further purification. EIMS (m/z) 327 (M^+-CH_3), 269, 241, 207, 183, 157, 101.

The crude iodide was dissolved in 95% EtOH (250 mL) and Zn dust (20 g) was added to the solution. The mixture was stirred under reflux for 2 hr, cooled to room temperature and filtered. The filtrate was concentrated, the residue was dissolved in CH_2Cl_2, washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (petroleum ether:AcOEt = 6:1) to give compound **9** (3.14 g, 81% over three steps) as a colorless oil, $[\alpha]_D$ +9.26 (*c* 0.70, $CHCl_3$); IR (film) 3450, 3115, 2920, 2860, 1643, 1456, 1373, 1215, 1066, 931, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 1.36 (3 H, s), 1.45 (3 H, s), 1.91 (1 H, br), 3.80 (1 H, m), 4.06 (3 H, m), 5.21 (1 H, d, *J* 10.5 Hz), 5.38 (1 H, d, *J* 17.2 Hz), 5.81 (1 H, ddd, *J* 6.0, 10.5, 17.2 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ_C 25.3, 26.7, 65.9, 74.1, 78.6, 109.9, 117.8, 136.2.

(2*R*, 3*R*)-3-*tert*-Butyldiphenylsilyloxy-1,2-methylethylidenedioxy-4-pentene (10). To a solution of compound **9** (3.0 g, 19 mmol) and imidazole (3.86 g, 56.8 mmol) in CH_2Cl_2 (80 mL) was added *tert*-butyldiphenyl chlorosilane (6.24 g, 22.7 mmol). After being stirred at room temperature for 12 hr, the mixture was diluted with ether (150 mL), washed with brine, dried ($MgSO_4$) and concentrated to give the crude product **10**, which was chromatographed over silica gel (petroleum ether:AcOEt = 100:1) to afford pure **10** (7.15 g, 96%) as a colorless oil, $[\alpha]_D$ +36.8 (*c* 1.70, $CHCl_3$); IR (film) 3030, 2920, 2860, 1589,

1473, 1427, 1369, 1213, 1112, 1066, 929, 821 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.08 (9 H, s), 1.23 (3 H, s), 1.32 (3 H, s), 3.83 (1 H, dd, *J* 6.3, 8.4 Hz), 3.92 (1 H, dd, *J* 6.6, 8.4 Hz), 4.05 (1 H, dd, *J* 6.3, 12.0 Hz), 4.29 (1 H, dt, *J* 1.2, 5.7 Hz), 5.10 (1 H, dt, *J* 1.5, 10.6 Hz), 5.15 (1 H, dt, *J* 1.5, 17.1 Hz), 5.83 (1 H, ddd, *J* 6.1, 10.6, 17.1 Hz), 7.39, 7.67 (10 H, Ar-H) ppm; EIMS (m/z) 381 (M^+-CH_3), 339, 321, 281, 227, 203, 183, 135, 105.

(3*R*)-1,1-Dibromo-3-*tert*-butyldiphenylsilyloxy-1,4-pentdiene (12). To a solution of compound **10** (1.31 g, 3.31 mmol) in AcOEt (30 mL) was added periodic acid (1.15 g, 5.05 mmol). The mixture was stirred at room temperature for 3 hr and filtered. The filtrate was diluted with ether (30 mL) and washed with aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$ and brine, then dried ($MgSO_4$) and concentrated gave the aldehyde (**11**) as a colorless oil, which was used directly in next reaction.

Under nitrogen atomosphere, PPh_3 (3.5 g, 13.4 mmol) was added to a CH_2Cl_2 solution (20 mL) of CBr_4 (2.2 g, 6.63 mmol) and Zn dust (220 mg, 3.36 mmol) at 0°C, and the mixture was stirred for one hour at the same temperature. Then a CH_2Cl_2 solution of the above aldehyde (**11**) was added to the reaction solution. Stirring was continued for 2 hr, and the reaction mixture was poured into petroleum ether (250 mL), and left standing overnight. The precipitate was filtered off and the filtrate was concentrated. Silica gel column chromatography of the residue (petroleum ether) gave the dibromide (**12**) (1.30 g, 82%) as a colorless oil, $[\alpha]_D$ +54.6 (*c* 1.35, $CHCl_3$); IR (film) 3040, 1572, 1473, 1369, 1213, 1111, 821 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.09 (9 H, s), 4.77 (1 H, m), 5.22 (1 H, m), 5.29 (1 H, m), 5.78 (1 H, m), 6.36 (1 H, d, *J* 7.9 Hz), 7.40, 7.65 (10 H, Ar-H) ppm; EIMS (m/z) 421 (M^+-$C(CH_3)_3$), 343, 317, 261, 117. HREIMS (m/z) M^+-$C(CH_3)_3$, calc. for $C_{17}H_{15}{}^{79}Br_2OSi$ 420.9259; found 420.9259.

(3*R*)-*tert*-Butyldiphenylsilyloxy-pent-1-en-4-yne (13). Under nitrogen atomosphere, a solution of LDA (6 mmol, prepared from *i*-Pr_2NH and *n*-BuLi (3.8 mL, 6 mmol, 1.6 M in hexane)) in THF (30 mL) was added to a THF solution (20 mL) of dibromide (**12**) (1.92 g, 4 mmol) at -78 °C. The mixture was stirred for 30 min, then warmed to 0 °C and stirred for 20 min. Then the reaction mixture was cooled to -78 °C again, then a solution of *n*-BuLi (5.5 mL, 8.8 mmol, 1.6 M in hexane) was added dropwise to the reaction solution, which was stirred for an additional 2 hr. The mixture was warmed to 0 °C, and the reaction was quenched by adding aqueous NH_4Cl. The aqueous solution was extracted with ether, and organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, acetylene (**13**) (1.17 g, 91%) was obtained by silica gel column chromatography (petroleum ether:AcOEt = 200:1) as a colorless oil, $[\alpha]_D$ +45.9 (*c* 1.30, $CHCl_3$); IR (film) 3305, 2119, 1747, 1473, 1427, 1113, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.01 (9 H, s), 2.45 (1 H, d, *J* 2.2 Hz), 4.84 (1 H, ddd, *J* 1.3, 2.2, 5.3 Hz), 5.14 (1 H, dt, *J* 1.3, 10.2 Hz), 5.34 (1 H, dt, *J* 1.3, 17.0 Hz), 5.92 (1 H, ddd, *J* 5.3, 10.1, 17.0 Hz), 7.41, 7.72 (10 H, Ar-H) ppm; EIMS (m/z) 320 (M^+), 263 (M^+-$C(CH_3)_3$), 207, 285, 147; HREIMS (m/z) M^+, calc. for $C_{21}H_{24}OSi$ 320.1596; found 320.1564.

Preparation of compound 15. A solution of *n*-BuLi (13.6 mL, 21.7 mmol, 1.6 M in hexane) was added dropwise to a stirred suspension of *n*-$C_6H_{13}P^+Ph_3Br^-$ (9.61 g, 22.6 mmol) in THF (125 mL) under

nitrogen at -78 °C. The mixture was stirred for 30 min, and diisopropylene *D*-arabinose (**14**) (4.0 g, 17.4 mmol) in THF (10 mL) was added. After being stirred at -78 °C for one hour, the reaction mixture was slowly warmed to room temperature and stirred for 6 hr. The reaction was quenched by adding water, and the aqueous solution was extracted with ether. The organic layer was washed with brine and dried ($MgSO_4$). Compound **15** (4.51 g, 87%) was obtained by silica gel chromatography (petroleum ether: AcOEt = 40:1) as a colorless oil, IR (film) 2920, 2860, 1662, 1456, 1381, 1371, 1240, 1215, 1065, 879 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.27 (6 H, m), 1.32 (3 H, s), 1.38 (3 H, s), 1.40 (3 H, s), 1.41 (3 H, s), 2.14 (2 H, m), 3.71 (1 H, t, *J* 6.4 Hz), 3.92 (1 H, dd, *J* 5.4, 8.0 Hz), 4.07 (1 H, m), 4.13 (1 H, m), 4.68 (1 H, t, *J* 8.4 Hz), 5.39 (1 H, ddt, *J* 1.4, 8.6, 10.6Hz), 5.65 (1 H, dt, *J* 7.4, 10.6 Hz) ppm, EIMS (m/z) 298(M^+), 283(M^+-CH_3), 225, 196, 168, 139, 101. Anal. calc. for $C_{17}H_{30}O_4$ C, 68.42; H, 10.13. found C, 68.47; H, 10.27.

Preparation of compound 16. A solution of compound **15** (4.50 g, 15.1 mmol) in 95% EtOH (80 mL) was hydrogenated over 10% Pd/C (450 mg) for 6 hr at room temperature. Filtration and evaporation of the solvent provided an oil, which was purified by silica gel chromatography (petroleum ether: AcOEt = 40:1) to give **16** (4.45 g, 97%) as a colorless oil, $[\alpha]_D$ +15.95 (*c* 1.20, $CHCl_3$); IR (film) 2920, 2860, 1456, 1371, 1215, 1066, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.20-1.70 (12 H, m), 1.34 (3 H, s), 1.35 (3 H, s), 1.38 (3 H, s), 1.40 (3 H, s), 3.54 (1 H, t, *J* 7.5 Hz), 3.88 (1 H, m), 3.92 (1 H, m), 4.02 (1 H, m), 4.10 (1 H, dd, *J* 5.7, 7.8 Hz) ppm; EIMS (m/z) 300 (M^+), 25 (M^+-CH_3), 199, 101; Anal. calc. for $C_{17}H_{32}O_4$ C, 67.94; H, 10.74. found C, 67.90; H, 10.54.

(2*R*, 3*R*)-2,3-Methylethylidenedioxy-1-decanol (17). Compound **16** (2.0 g, 6.67 mmol) was dissolved in AcOEt (65 mL), and periodic acid (1.82 g, 8.0 mmol) was added to the solution. The mixture was stirred at room temperature for 3 hr and filtered. The filtrate was diluted with ether and washed with aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$ and brine. The solution was dried and concentrated to give the crude aldehyde.

The crude aldehyde was dissolved in EtOH (40 mL), and $NaBH_4$ (380 mg, 10 mmol) was added. After stirring for 3 hr at room temperature, the mixture was poured into cold 5% HOAc solution (aq.) and extracted with ether. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed (petroleum ether: AcOEt = 10:1 to 5:1) to gave **17** (1.09, 71% over two steps) as a colorless oil, $[\alpha]_D$ +24.3 (*c* 1.60, $CHCl_3$); IR (film) 3450, 2920, 2860, 1728, 1458, 1369, 1247, 1167, 1051, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.20-1.70 (12 H, m), 1.41 (3 H, s), 1.42 (3 H, s), 1.91 (1 H, br), 3.60 (1 H, dd, *J* 4.3, 11.7 Hz), 3.74 (1 H, m), 3.81 (1 H, dd, *J* 2.9, 11.7 Hz), 3.88 (1 H, m) ppm; EIMS (m/z) 230 (M^+), 215 (M^+-CH_3), 199, 187, 99, 81; HREIMS (m/z)a M^+, cacld. for $C_{13}H_{26}O_3$ 230.1882; found 230.1848.

(2*R*, 3*R*)-1,2-Epoxy-3-decanol (20). To an ice-cooled solution of **17** (854 mg, 3.71 mmol) in pyridine (20 mL) was added *p*-TsCl (850 mg, 4.46 mmol). After being stirred in an ice-bath for one hour and then at room temperature for 6 hr, the mixture was poured into 10% HCl solution and extracted with ether. The

extract was washed, dried and concentrated to give crude tosylate (**18**), $[\alpha]_D$ +23.2 (*c* 0.60, $CHCl_3$); IR (film) 2920, 2860, 1599, 1456, 1367, 1178, 1077, 983, 85 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.15-1.65 (12 H, m), 1.28 (3 H, s), 1.35 (3 H, s), 2.44 (3 H, s), 3.77 (2 H, m), 4.09 (2 H, ddd, *J* 4.3, 7.5, 15.6 Hz), 7.34 (2 H, d, *J* 8.0), 7.79 (2 H, d, *J* 8.0 Hz) ppm; EIMS (m/z) 369 (M^+-CH_3), 227, 212, 155, 91.

The crude tosylate was then dissolved in MeOH (25 mL), and *p*-TsOH (150 mg) was added to the solution. After stirring at room temperature overnight, K_2CO_3 (1.17 g, 8.5 mmol) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. The mixture was poured into ice-water, and extracted with ether. The extract was washed with brine and dried ($MgSO_4$). Concentration and chromatography (petroleum ether: AcOEt = 10:1) gave **20** (517 mg, 81% over three steps) as a colorless oil, $[\alpha]_D$ + 3.4 (*c* 1.0, $CHCl_3$); IR (film) 3412, 2920, 2860, 1466, 1253, 919, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.20-1.70 (12 H, m), 1.83 (1 H, br), 2.70 (1 H, dd, *J* 2.8, 4.9 Hz), 2.81 (1 H, dd, *J* 4.1, 4.9 Hz), 2.97 (1 H, ddd, *J* 2.8, 4.1, 5.1 Hz), 3.43 (1 H, m) ppm; EIMS (m/z) 173 (MH^+), 155 (MH^+-H_2O), 129, 111, 73, 69.

(2*R*, 3*R*)-3-tert-Butyldimethylsilyloxy-1,2-epoxydecane (21). To a solution of epoxy alcohol (**20**) (216 mg, 1.26 mmol) in THF (10 mL) were added $AgNO_3$ (260 mg, 53 mmol) and pyridine (0.44 mL, 5.46 mmol). After the mixture was stirred at room temperature for 20 min, *tert*-butyldimethylchlorosilane (283 mg, 1.88 mmol) was added. The reaction mixture was stirred for 24 hr, and then the white precipitate was filtered off, washed with ether (50 mL), and the combined filtrates were washed with water and brine, dried and concentrated to give the crude silyl ether, which was purified by silica gel column chromatography (petroleum ether:AcOEt = 100:1) to give silyl ether (**21**) (300 mg, 92%) as a colorless oil, IR (film) 2920, 2860, 1464, 1256, 101, 937, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.05 (3 H, s), 0.11 (3 H, s), 0.88 (3 H, *J* 6.8 Hz), 0.90 (9 H, s), 1.20-1.60 (12 H, m), 2.53 (1 H, dd, *J* 2.7, 4.9 Hz), 2.73 (1 H, dd, *J* 4.2, 4.9 Hz), 2.90 (1 H, ddd, *J* 2.7, 4.2, 6.8 Hz), 3.25 (1 H, m) ppm; EIMS (m/z) 286 (M^+), 271 (M^+-CH_3), 257, 243, 229, 199, 133, 101.

(4*R*, 5*R*)-5-*tert*-Butyldimethylsilyloxy-1-trimethylsilyl-1-dodadecyn-4-ol (22). Under nitrogen atmosphere, a solution of *n*-BuLi (1.25 mL, 2 mmol, 1.6 M in hexane) was added to a THF solution (5 mL) of trimethylsilylacetylene (197 mg, 2 mmol) at -78 °C. After the mixture was stirred for 30 min, boron trifluoride etherate (0.25 mL, 2 mmol) was added to the solution and stirring was continued for 30 min at -78°C. The reaction was quenched by adding aqueous NH_4Cl after warming to room temperature, and the aqueous solution was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$, and silylacetylene (**22**) (357 mg, 93%) was obtained by silica gel column chromatography (petroleum ether:ether = 40:1) as a colorless oil, $[\alpha]_D$ -21.7 (*c* 0.95, $CHCl_3$); IR (film) 3554, 2920, 2860, 2175, 1464, 1361, 1252, 1070, 970, 840, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.10 (3 H, s), 0.11 (3 H, s), 0.15 (9 H, s), 0.88 (3 H, t, *J* 6.8 Hz), 0.90 (9 H, s), 1.28 (12 H, m), 2.41 (2 H, m), 3.63 (1 H, ddd, *J* 2.0, 6.0, 8.1 Hz), 3.85 (1 H,

ddd, *J* 2.0, 4.5, 6.6 Hz) ppm; EIMS (m/z) 369 (M^+– CH_3), 327 (M^+–$(CH_3)_3$), 273, 257, 243, 229, 215, 147, 75; Anal. calc. for $C_{21}H_{44}O_2Si_2$ C, 65.56; H, 11.53. found C, 65.88; H, 11.65.

(4*R*, 5*R*)-1-Bromo-5-*tert*-butyldimethylsilyl-1-dodadecyn-4-ol (23). The silylacetylene (**22**) (289 mg, 0.75 mmol) was dissolved in acetone (5 mL). NBS (200 mg, 1.13 mmol) and $AgNO_3$ (25.5 mg, 0.15 mmol) were added to this solution. The reaction mixture was stirred at room temperature for 3 hr. The mixture was cooled to 0 °C, mixed with cold water and extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ether = 60:1) to give bromoacetylene (**23**) (256 mg, 87%) as a colorless oil, $[\alpha]_D$ -15.9 (*c* 0.41, $CHCl_3$); IR (film) 3460, 2920, 2860, 2195, 1471, 1254, 1072, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.09 (6 H, s), 0.88 (3 H, t, *J* 6.8 Hz), 0.89 (9 H, s), 1.27 (12 H, m), 2.39 (2 H, m), 3.65 (1 H, m), 3.75 (1 H, ddd, *J* 2.2, 4.6, 7.0 Hz) ppm; EIMS (m/z): 375 (M^+-CH_3), 333 (M^+-$(CH_3)_3$), 273, 257, 243, 229, 105, 75; Anal. calc. for $C_{18}H_{35}BrO_2Si$ C, 55.23; H, 9.01. found C, 55.28; H, 9.16.

(3*R*, 9*R*, 10*R*)-10-*tert*-Butyldimethylsilyloxy-3-*tert*-butyldiphenylsilyloxy-heptadec-1-ene-4,6-diyne-9-ol (24). The acetylene (**13**) (104 mg, 0.323 mmol) followed by the bromoacetylene (**23**) (115 mg, 0.294 mol) were added to a stirred solution of CuCl (1.5 mg), NH_2OH·HCl (6.1 mg) and 65% aqueous $EtNH_2$ (0.35 mL) in MeOH (1 mL) at 0°C. After 10 min at 0°C, water was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography (petroleum ether: ether = 35:1) to give (**24**) (135 mg, 75%) as a colorless oil, IR (film) 3550, 3466, 2920, 2860, 2256, 1589, 1471, 1427, 1256, 1113, 1068, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.10 (6 H, s), 0.88 (3 H, t, *J* 6.8 Hz), 0.90 (9 H, s), 1.08 (9 H, s), 1.27 (12 H, m), 2.46 (2 H, m), 3.66 (1 H, ddd, *J* 2.1, 5.9, 7.8 Hz), 3.74 (1 H, ddd, *J* 2.0, 4.8, 7.0 Hz), 4.82 (1 H, m), 5.11 (1 H, dt, *J* 1.3, 10.1 Hz), 5.27 (1 H, dt, *J* 1.3, 17.0 Hz), 5.85 (1 H, ddd, *J* 5.3, 10.1, 17.0 Hz), 7.39 (6 H, m), 7.70 (4 H, m) ppm; EIMS (m/z) 630 (M^+-CH_3), 573 (M^+-$(CH_3)_3$), 555, 517, 481, 431, 385, 359, 317, 357, 243, 199, 135; Anal. calc. for $C_{39}H_{58}O_3Si_2$ C, 74.23; H, 9.26. found C, 73.92; H, 9.47.

(3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol (2). Under nitrogen atmosphere, a solution of Bu_4NF (1.4 mmol, 1 M in THF) was added to a THF solution (3 mL) of (**24**) (200 mg, 0.349 mmol). After stirring at 0 °C for 4 hr, aqueous NH_4Cl was added and the reaction mixture was then extracted with AcOEt, the organic layer was washed with brine, dried and concentrated, and the residue was purified by silica gel chromatography (petroleum ether: ether = 3:1) to give **2** (52 mg, 83%) as a white wax, $[\alpha]_D$ -21.2 (*c* 0.55, $CHCl_3$), -18.9 (*c* 0.60, MeOH); IR (film): 3327, 2920, 2860, 2256, 1628, 1466, 1417, 1338, 1130, 1061,958, 937 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 0.89 (9 H, s), 1.25-1.38 (10 H, m), 1.51 (2 H, m), 1.96 (3 H, br), 2.59 (2 H, d, *J* 5.6 Hz), 3.60 (1 H, m), 3.65 (1 H, m), 4.92 (1 H, d, *J* 5.4 Hz), 5.25 (1 H, ddd, *J* 1.1, 2.2, 10.1 Hz), 5.47 (1 H, ddd, *J* 1.1, 2.3, 17.1 Hz), 5.95 (1 H, ddd, *J* 5.4, 10.1, 17.0 Hz); ^{13}C NMR

($CDCl_3$) δ_C 136.0, 117.2, 78.1, 74.7, 73.1, 72.1, 70.9, 66.5, 63.5, 33.5, 31.8, 29.5, 29.2, 25.6, 25.0, 22.6, 14.1; EIMS (m/z) 261 (MH^+-H_2O), 243, 159, 145, 102. Anal. calc. for $C_{17}H_{26}O_3$ C, 73.35; H, 9.41. found C, 73.17; H, 9.34.

(2*S*, 3*S*)-1-Phenylmethoxyl-2,3-Methylethylidenedioxy-4-decene (26). This reaction was carried out according to the procedure for **15**. Thus, **26** (3.21 g, 75%) was obtained as a colorless oil from aldehyde (**25**) (3.38 g, 13.44 mmol), $[\alpha]_D$ +4.2 (*c* 3.17, $CHCl_3$). IR (film): 3030, 2920, 2860, 1497, 1454, 1397, 1240, 1086, 1029, 862, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.26 (6 H, m), 1.43 (6 H, s), 2.08 (2 H, m), 3.57 (2 H, m), 3.86 (1 H, ddd, *J* 3.1, 5.4, 8.5 Hz), 4.59 (2 H, s), 4.63 (1 H, m), 5.38 (1 H, ddt, *J* 1.5, 9.0, 10.9 Hz), 5.67 (1 H, m), 7.34 (5 H, m) ppm; EIMS (m/z) 318 (M^+), 303 (M^+-CH_3), 260, 231, 187, 168, 97, 91. Anal. calc. for $C_{20}H_{30}O_3$ C, 75.43; H, 9.49. found C, 75.31; H, 9.59.

(2*S*, 3*S*)-2,3-Methylethylidenedioxy-1-decanol (27). A solution of **26** (2.8 g, 8.8 mmol) in 95% EtOH (60 mL) was hydrogenated over 10% Pd/C (560 mg) for 72 hr at room temperature. Filtering and evaporating of the solvent provided an oil, which was purified by silica gel chromatography (petroleum ether: AcOEt = 6:1) to give **27** (1.72 g, 85%) as a colorless oil, $[\alpha]_D$ -27.9 (*c* 1.90, $CHCl_3$); IR (film) 2448, 2920, 2860, 1458, 1379, 1248, 1219, 1167, 1051, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.20-1.60 (12 H, m), 1.41 (3 H, s), 1.42 (3 H, s), 1.80 (1 H, br), 3.59 (1 H, dd, *J* 4.3, 11.7 Hz), 3.72 (1 H, m), 3.80 (1 H, dd, *J* 3.0, 11.7 Hz), 3.87 (1 H, m) ppm; EIMS (m/z) 229 (M^+-H), 215 (M^+-CH_3), 199, 173, 155, 137, 95, 81. Anal. calc. for $C_{13}H_{26}O_3$ C, 67.77; H, 11.38 found C, 67.98; H, 11.44.

(2*S*, 3*S*)-1,2-Epoxy-3-decanol (28). This reaction was carried out according to the procedure for **20**. Thus, the epoxy alcohol (**28**) (1.93 g, 86% over three steps) was obtained as a colorless oil from alcohol (**27**) (3.0 g, 13.04 mmol), $[\alpha]_D$ +3.5 (*c* 1.0, $CHCl_3$). IR (film) 3423, 2920, 2860, 1647, 1379, 1254, 1086, 920, 897, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 1.20-1.60 (12 H, m), 1.88 (1 H, br), 2.71 (1 H, dd, *J* 2.8, 4.9 Hz), 2.81 (1 H, dd, *J* 4.1, 4.9 Hz), 2.97 (1 H, ddd, *J* 2.7, 4.1, 5.1 Hz), 3.42 (1 H, m) ppm; Anal. calc. for $C_{10}H_{20}O_2$ C, 69.22; H, 11.70 found C, 69.66; H, 11.75.

(2*R*, 3*R*)-3-*tert*-Butyldimethylsilyloxy-1,2-epoxydecane (29). This reaction was carried out according to the procedure for **21**. Thus, the silyl ether **29** (421 mg, 93%) was obtained as a colorless oil from **28** (300 mg, 1.75 mmol). IR (film) 2920, 2860, 1464, 1256, 1101, 937, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.05 (3 H, s), 0.10 (3 H, s), 0.87 (3 H, t, *J* 6.8 Hz), 0.90 (9 H, s), 1.20-1.60 (12 H, m), 2.54 (1 H, dd, *J* 2.8, 4.9 Hz), 2.77 (1 H, dd, *J* 4.2, 4.9 Hz), 2.91 (1 H, ddd, *J* 2.8, 4.1, 6.8 Hz), 3.24 (1 H, m). EIMS (m/z): 271 (M^+-CH_3), 243, 229, 199.

(4*S*, 5*S*)-5-*tert*-Butyldimethylsilyloxy-1-trimethylsilyl-1-dotadecyn-4-ol (30). This reaction was carried out according to the procedure for **22**. Thus, silylacetylene **30** (361 mg, 94%) was obtained as a colorless oil

from 29 (286 mg, 1.0 mmol), $[\alpha]_D$ +21.9 (*c* 1.0, $CHCl_3$); IR (film) 3554, 2920, 2860, 2175, 1471, 1252, 1070, 970, 840, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.09 (3 H, s), 0.10 (3 H, s), 0.15 (9 H, s), 0.88 (3 H, t, *J* 6.8 Hz), 0.90 (9 H, s), 1.20-1.60 (12 H, m), 2.42(2H, m), 3.63 (1 H, ddd, *J* 2.0, 5.9, 8.0 Hz), 3.85 (1 H, ddd, *J* 2.0, 4.4, 6.5 Hz) ppm; EIMS (m/z) 369 (M^+-CH_3), 327 (M^+-$(CH_3)_3$), 273, 257, 243, 229, 215, 147; Anal. calc. for $C_{21}H_{44}O_2Si_2$ C, 65.56; H, 11.53. found C, 65.64; H, 11.66.

(4*S*, 5*S*)-1-Bromo-5-*tert*-butyldimethylsilyl-1-dotadecyn-4-ol (31). This reaction was carried out according to the procedure for **23**. Thus, bromoacetylene **31** (263 mg, 86%) was obtained as a colourless oil from **30** (300 mg, 0.78 mmol). $[\alpha]_D$ +16.58 (c, 0.55, $CHCl_3$), IR (film) 3458, 2920, 2860, 2217, 1464, 1253, 1072, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.09 (6 H, s), 0.88 (3 H, t, *J* 6.8 Hz), 0.89 (9 H, s), 1.20-1.60 (12 H, m), 2.39 (2 H, m), 3.65 (1 H, ddd, *J* 2.3, 6.3, 7.5 Hz), 3.75 (1 H, ddd, *J* 2.3, 4.9, 7.4 Hz) ppm; EIMS (m/z) 375 (M^+-CH_3), 333 (M^+-$(CH_3)_3$), 319, 273, 257, 243, 229, 105, 75; Anal. calc. for $C_{18}H_{35}BrO_2Si$ C, 55.23; H, 9.01. found C, 55.59; H, 9.21.

(3*R*, 9*S*, 10*S*)-10-*tert*-Butyldimethylsilyloxy-3-*tert*-butyldiphenylsilyloxy-heptadec-1-ene-4 ,6-diyne-9-ol (32). This reaction was carried out according to the procedure for **24**. Thus, from **31** (200 mg, 0.51 mmol) was isolated compound **32** (223 mg, 71%) as a colorless oil, IR(film) 3552, 2920, 2860, 2256, 1589, 1471, 1427, 1256, 1113, 1068, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.10 (6 H, s), 0.88 (3 H, t, *J* 6.8 Hz), 0.90 (9 H, s), 1.08 (9 H, s), 1.27 (12 H, m), 2.47 (2 H, m), 3.66 (1 H, ddd, *J* 2.1, 6.1, 7.5 Hz), 3.75 (1 H, ddd, *J* 2.0, 4.8, 6.9 Hz), 4.83 (1 H, m), 5.10 (1 H, dt, *J* 1.3, 10.1 Hz), 5.27 (1 H, dt, *J* 1.3, 17.0 Hz), 5.85 (1 H, ddd, *J* 5.4, 10.1, 17.0 Hz), 7.40 (6 H, m), 7.70 (4 H, m) ppm; EIMS (m/z) 630 (M^+), 573 (M^+-$(CH_3)_3$), 555, 517, 481, 431, 385, 359, 317, 357, 199, 135; Anal. calc. for $C_{39}H_{58}O_3Si_2$ C, 74.23; H, 9.26. found C, 74.13; H, 9.43.

(3*R*, 9*S*, 10*S*)-Heptadec-1-ene-4,6-diyne-3,9,10-triol (3). This reaction was carried out according to the procedure for **2**. Thus, compound **3** (52 mg, 79%) was obtained as a white wax from **32** (210 mg, 0.366 mmol), $[\alpha]_D$ -49.2 (*c* 0.90, $CHCl_3$); IR (film) 3332, 2920, 2860, 2256, 1643, 1466, 1417, 1118, 1018, 985, 933 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.88 (3 H, t, *J* 6.8 Hz), 0.89 (9 H, s), 1.25-1.40 (10 H, m), 1.50 (2 H, m), 2.25 (3 H, br), 2.57 (2 H, d, *J* 5.6 Hz), 3.58 (1 H, m), 3.63 (1 H, m), 4.91 (1 H, d, *J* 5.2Hz), 5.24 (1 H, d, *J* 10.1 Hz), 5.45 (1 H, d, *J* 17.0 Hz), 5.93 (1 H, ddd, *J* 5.4, 10.1, 17.0 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ_C 136.1, 117.1, 78.2, 74.8, 73.1, 72.2, 70.9, 66.5, 63.5, 33.6, 31.8, 29.5, 29.2, 25.6, 25.0, 22.6, 14.0; EIMS (m/z) 261 (MH^+-H_2O), 243, 159, 145, 102; HREIMS (m/z) M^+-H_2O. calc. for $C_{17}H_{24}O_2$ 260.1776; found: 260.1773.

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