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Asymmetric total syntheses of panaxytriol and panaxydol, potent antitumor agents from *Panax ginseng*☆

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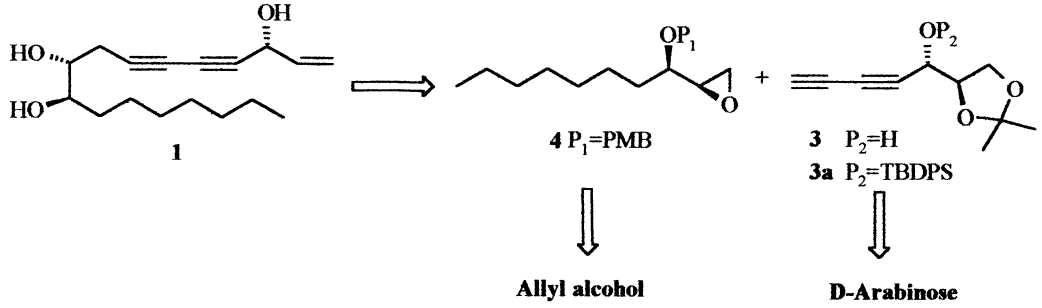
Abstract—A stereoselective syntheses of panaxytriol **1** and panaxydol **2** from D-arabinose using base induced double elimination of 4,5-*O*-isopropylidene propargyl chloride as a key step is described.

Red ginseng is the processed root of the most important oriental medicinal plant, *Panax ginseng* C. A. Meyer. It has been used as an analeptic, stomachic and erythopoietic agent[1] in Asian countries for thousand of years and is now available as a commercial medicinal drug in Japan.[2] Red ginseng contains several chiral polyacetylenic alcohols[3] including characteristic panaxytriol **1**[3b] and panaxydol **2**,[3a] which showed cytotoxic and antiplatelet activity,[4] respectively. Although these polyacetylenic alcohols have received great attention as a potent new class of antitumor agent, only a few syntheses have been reported.[5]

The structures of panaxytriol and panaxydol were evidenced as (3*R*,9*R*,10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol and (3*R*,9*R*,10*S*)-9,10-epoxy-heptadec-1-ene-4,6-diyn-3-ol, respectively.[5] Herein we describe the syntheses of both the natural products from the same intermediate in detail. The salient feature of our syntheses is the utilization of efficient and practical preparation of chiral diacetylenic alcohols via base mediated double elimination of 4,5-*O*-isopropylidene propargyl chloride, the methodology that was recently developed by us.[6]

Retrosynthetically, panaxytriol can be divided into two halves, an epoxide component **4** and a diacetylenic component **3a**, which could be coupled using the Yamaguchi method[7] as shown in Scheme 1.

Firstly, the diacetylenic intermediate **3a** was constructed. Accordingly D-arabinose was transformed to 2,3:4,5-diisopropylidene arabinose **5** following a known procedure.[8] Compound **5** was converted to dibromovinyl **6** in the presence of PPh_3, CBr_4 in DCM at 0°C.[9a] When dibromovinyl compound **6** was treated with 2.5 equiv. of LDA in THF at −78°C and quenched with $(HCHO)_n$ at 0°C[10] it produced propargyl alcohol **7** in 82% yield. This was converted to propargyl chloride **8** by refluxing with PPh_3 and CCl_4 in presence of sodium bicarbonate.[11] The addition of 3 equiv. of $LiNH_2$ in liq. NH_3 to this chloride **8** produced chiral diacetylenic alcohol **3** in 85% yield. The



Scheme 1.

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Keywords: asymmetric total synthesis; *Panax ginseng*; panaxytriol.

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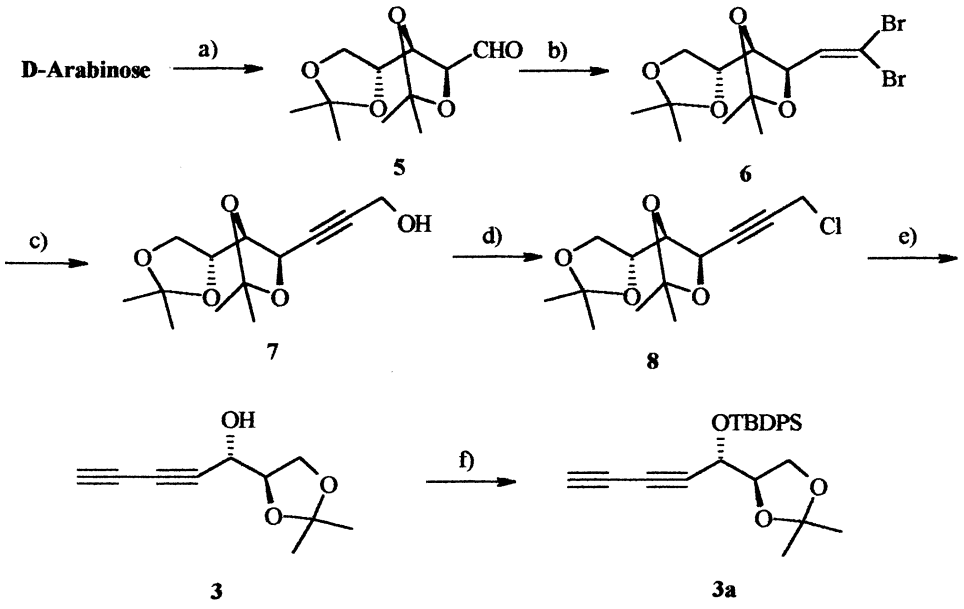
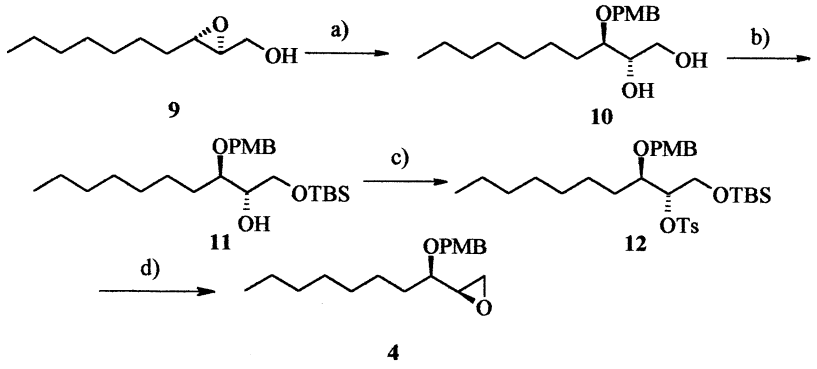


Scheme 2. *Reagents and conditions*: (a) See Ref. 8; (b) PPh_3, CBr_4, DCM, rt, 86%; (c) LDA, $(HCHO)_n$, −78°C-rt, 82%; (d) PPh_3, CCl_4, reflux, 96%; (e) $LiNH_2$, liq. NH_3, 85%; (f) TBDPSCl, imidazole, DCM, rt, 88%.



Scheme 3. *Reagents and conditions*: (a) $Ti(OiPr)_4$, PMBOH, toluene, reflux, 84%; (b) TBSCl, imidazole, DCM, rt, 88%; (c) TsCl, Et_3N, DCM, rt, 80%; (d) TBAF, THF, rt, 92%.

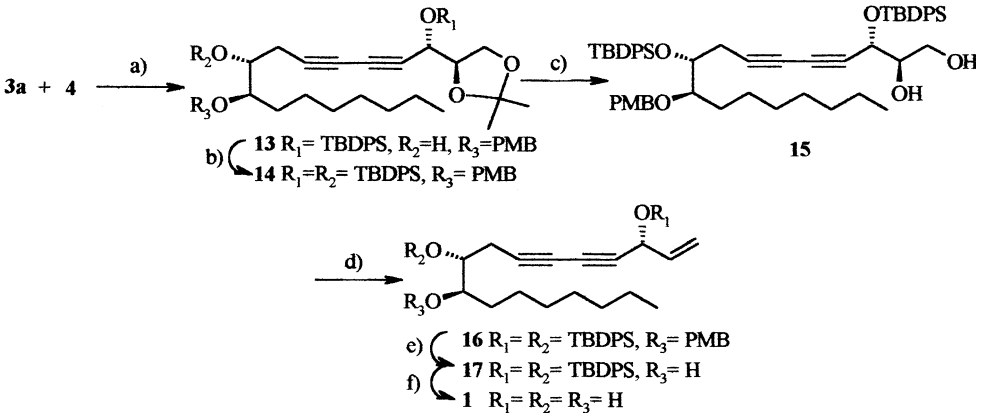
hydroxyl group was protected as a silyl ether using TBDPSCl and imidazole to give retron **3a** in 88% yield (Scheme 2).

In order to synthesize the epoxide **4** we have prepared epoxyalcohol **9** according to the known procedure.[12] This was subjected to $Ti(^iOPr)_4$ mediated regioselective opening[13] of the epoxide to afford 1,2 diol **10** in 84% yield as single regioisomer. After silylation and tosylation of the hydroxyl groups in **10**, treatment with TBAF effected deprotective elimination to yield **4** in 64% overall yield (Scheme 3).

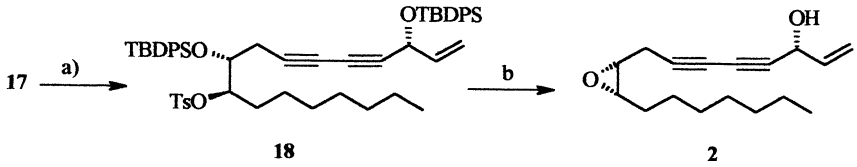
The stage was now set to carry out the coupling of diacetylenic alcohol **3a** and the epoxide **4** under Yamaguchi conditions[7] to afford regioselective ring opening product **13** in 75% yield as shown in the Scheme 4. The secondary hydroxyl group in **13** was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether to yield **14**, which was subjected to selective acetonide deprotection with $CuCl_2{\cdot}2H_2O$ in acetonitrile[14] to produce diol **15** in 94% yield. Finally, diol **15** was converted to olefin **16** with PPh_3, I_2, and imidazole in refluxing toluene[15] in 89% yield. Selective deprotection of the PMB group with DDQ in aq. DCM[16] afforded **17**. This was treated with TBAF affording panaxytriol **1**; (3*R*,9*R*,10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol in 91% yield.

Synthetic panaxytriol **1** showed a superimposable ^1H and ^{13}C NMR spectra with the reported data of the natural product.[5d,e] Moreover the optical rotation of synthetic **1** was close to the value reported for the natural sample: synthetic $\{[\alpha]_D^{25}=-22.1$ (c 1.5, $CHCl_3)\}$ and natural $\{[\alpha]_D=-25.4$ (c 1.54, $CHCl_3)\}$.

Tosylation of the alcohol **17**, followed by treatment with TBAF readily afford panaxydol **2**. This also showed ^1H and ^{13}C NMR spectra in agreement with the natural isomer and also showed $\{[\alpha]_D^{25}=-86.3$ (c 1.5, $CHCl_3)\}$ which was also close to the reported values $\{[\alpha]_D^{25}=-81.8$ (c 1.52, $CHCl_3)\}$ and $\{[\alpha]_D^{25}=-96.1$ (c 1.30, $CHCl_3)\}$ (Scheme 5).[5b]



Scheme 4. *Reagents and conditions*: (a) BuLi, $BF_3{\cdot}OEt_2$, −78°C, 75%; (b) TBDPSCl, imidazole, CH_2Cl_2, rt, 91%; (c) $CuCl_2{\cdot}2H_2O$, CH_3CN, rt, 94%; (d) PPh_3, I_2, imidazole, toluene, reflux, 89%; (e) DDQ, CH_2Cl_2, rt, 82%; (f) TBAF, THF, rt, 91%.



Scheme 5. *Reagents and conditions*: (a) TsCl, Et_3N, DCM, rt, 81%; (b) TBAF, THF, rt, 76%.

In conclusion, the synthesis of the title compounds demonstrates the practical utility of the methodology, the preparation of chiral diacetylenic alcohols, developed by us and will find widespread application in the synthesis of this type of compounds.

1. Experimental

1.1. General remarks

Melting points were recorded on a Buchi R-535 apparatus. Infrared (IR) spectra were recorded on a Perkin–Elmer-Infrared-683 spectrophotometer with NaCl optics. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on Varian GEMINI-200, Varian UNITY-400 and Varian INOVA-500 NMR spectrometer in deuteriochloroform unless otherwise stated. In the ^{1}H NMR spectra tetramethysilane (TMS) (δ 0 ppm) was used as an internal reference, where as for ^{13}C NMR spectra, $CDCl_3$ (δ 77.0 ppm) was used as an internal reference. Chemical shifts were reported in ppm downfield from TMS and were given on the δ-scale. The multiplicity, coupling constants (hertz), and number of protons were indicated in parentheses and were specified as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet for unresolved lines), br (broad) etc.^{13}C spectra were obtained with proton decoupling. Mass measurements were carried out on either on Fnnigan-MAT1020B or MicroMass VG70-70H mass spectrometer operating at 70 eV using direct inlet system and were given in the mass units (*m/z*). Unless otherwise stated, all nonaqueous reactions were performed under an atmosphere of nitrogen in flame-dried glass equipped with stir bar and a rubber septum. Standard inert atmosphere techniques were used in handling all air and moisture-sensitive reagents. Reactions were monitored by analytical thin layer chromatography (TLC) using 0.25 mm E.Merk precoated silicagel plate ($60F_{254}$). The spots were detected using UV light (254 nm), blowing I_2 or by dipping into anisaldehyde/sulfuric acid (A) or β-napthol/sulfuric acid (B) solution followed by charring on a hot plate. Product purification by flash column chromatography was performed using on silica gel (100–200 mesh). Solutions in organic solvents were dried over anhydrous sodium sulfate and solvents were stripped off with a Buchi rotary evaporator connected to water aspirator. Trace solvent was removed on a vacuum pump. All compounds were stored at −5°C in vials flushed with nitrogen. Compound names were given according to IUPAC nomenclature using ACD/Name software version 1.0β.

Pyridine and triethylamine (Et_3N) were dried over KOH. Solvents were dried and purified in the following fashion: toluene and benzene was distilled over P_2O_5; Et_2O and THF were distilled from sodium-benzophenone ketyl; dichloromethane (CH_2Cl_2) and dimethyl sulphoxide (DMSO) distilled from calcium hydride and methanol was distilled from magnesium methoxide.

1.1.1. 4-(2,2-Dibromovinyl)-5-[2,2-dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(4*R*,5*S*)-1,3-dioxolane (6). To a stirred solution of CBr_4 (4.30 g, 13.0 mmol) in dry DCM (80 mL) under nitrogen, was added dropwise at −20°C a solution of PPh_3 (5.12 g, 19.56 mmol) in dry DCM (50 mL). An intense yellow color developed which darkened after 30 min at this temperature. Then a solution of aldehyde **5** (1.5 g, 6.52 mmol) and Et_3N (0.90 mL, 6.5 mmol) in dry DCM (50 mL) was added at the same temperature. The mixture was allowed to warm to 0°C.

After stirring at 0°C for 30 min, the reaction mixture was warmed to room temperature and concentrated to 90 mL the mixture was poured into 450 mL of hexane. The mixture was filtered through a Celite pad and the solid was washed with cold ether. The filtrate was concentrated under reduced pressure, and the product was purified by flash column chromatography to yield 2.17 g of **6** in 86% yield. R_f=0.33 (10% EtOAc/hexane; A: greenish blue); $[\alpha]_D^{25}$=+1.18 (*c* 3.77, $CHCl_3$); IR (film) ν_{max} 2990, 2935, 2884, 1630, 1455, 1380, 1216, 1155, 1067, 879 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35, 1.41 (2s, 12H, 2×C(CH_3)$_2$), 3.75 (m, 2H, CH_2(O)), 4.10 (m, 2H, C*H*(O)C*H*(O)), 4.52 (m, 1H, Br_2CCHCH(O)), 6.45 (d, *J*=7.5 Hz, 1H, Br_2CCH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.27, 26.72, 26.98 (2C), 66.84, 76.06, 79.18, 80.26, 94.65, 109.65, 110.26, 135.59; Anal. Calcd for $C_{12}H_{18}Br_2O_4$: C 37.33, H 4.70. Found: C 37.30, H 4.85.

1.1.2. 3-[5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(4*R*,5*S*)-1,3-dioxolane-4-yl]-2-propyn-1ol (7). To a stirred solution of **6** (1.5 g, 3.89 mmol) in dry THF (15 mL) was added a freshly prepared solution of LDA (prepared from 4.49 mL of 2.6 M BuLi in hexane and 1.64 mL of DIPA) at −78°C. After 2 h, the reaction mixture was allowed to warm to 0°C. To this $(HCHO)_n$ (0.24 g, 8.0 mmol) was added and stirring was continued for 10 min at 0°C and 2.5 h at room temperature. Saturated NH_4Cl solution was added to the reaction mixture and the reaction product was extracted with ethyl acetate. The extract was washed with water, brine, dried and concentrated at reduced pressure. Column chromatographed of the crude product gave 0.81 g of propargyl alcohol **7** in 82% yield. R_f=0.25 (10% EtOAc/hexane; A: green); $[\alpha]_D^{25}$=+24.12 (*c* 1.08, $CHCl_3$); IR (film) ν_{max} 3490, 3330, 2210, 1455, 1375, 1250, 1092, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31, 1.39, 1.42, 1.45 (4s, 12H, 2×C(CH_3)$_2$), 3.88–4.12 (series m, 4H), 4.30 (d, *J*=10.0 Hz, 2H, CH_2OH), 4.61 (m, 1H, C≡CC*H*(O)); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.86, 25.89, 26.28, 26.64, 50.20, 66.32, 67.92, 75.67, 81.67, 82.45, 84.84, 109.67, 110.57; Mass (*m*/*z*) 256 (M^+), 238 (M^+-H_2O); HRMS Calcd for $C_{13}H_{20}O_5$: 256.3013. Found: 256.3010.

1.1.3. 4-(3-Chloro-1-propynyl)-5-[2,2-dimethyl-(4*R*)-1,3-di-oxolano-4-yl]-2,2-dimethyl-(4*R*,5*S*)-1,3-dioxolane (8). A mixture of propargyl alcohol **7** (0.8 g, 3.12 mmol), triphenylphosphine (1.64 g, 6.24 mmol) and sodium bicarbonate (0.1 g) in carbon tetrachloride (15 mL) was heated at reflux for 4 h. The solid was filtered, and the solvent was evaporated and the residue was purified by chromatography to give propargyl chloride **8** 0.82 g in 96% yield as a colorless liquid. R_f=0.7 (10% EtOAc/hexane; A: green); $[\alpha]_D^{25}$=+1.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3420, 2220, 1450, 1380, 1269, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36, 1.39, 1.42, 1.48 (4s, 12H, 2×C(CH_3)$_2$), 3.85–4.10 (series m, 4H), 4.15 (s, 2H, CH_2Cl), 4.61 (m, 1H, C≡CC*H*(O)); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.90, 26.02, 26.27, 26.66, 34.32, 66.38, 67.92, 75.68, 80.34, 81.02, 82.55, 109.70, 110.37; Mass (*m*/*z*) 276 (M^++2), 274 (M^+); HRMS Calcd for $C_{13}H_{19}{}^{35}ClO_4$: 274.7469. Found: 274.7482.

1.1.4. 1-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-(1*S*)-2,4-pentadiyn-1ol (3). To a stirred suspension of lithium amide (prepared from 0.1 g, 14.28 mg atom of Li) in liquid ammonia (20 mL), propargyl chloride **8** (1.0 g, 3.64 mmol) in THF/HMPA (5:1, 2 mL) was added and stirred for 30 min. The reaction was quenched with solid ammonium chloride (1 g) and excess ammonia was evaporated. The residue was dissolved in water and extracted with ether. The organic layer was washed, dried, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent: 15% ethyl acetate in hexane) to afford diacetylenic alcohol **3** (0.55 g, 85%) as a colorless oil. R_f=0.48 (25% EtOAc in hexane); $[\alpha]_D^{25}$=+8.3 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3450, 3310, 2220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35, 1.42 (2s, 6H, C(CH_3)$_2$), 2.11 (s, 1H, C≡C*H*), 2.20 (br s, 1H, O*H*, exchangeable with D_2O), 4.0–4.2 (series m, 3H), 4.33 (m, 1H, C*H*OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.73, 26.96, 63.89, 64.84, 66.09, 66.59, 69.27, 69.43, 74.54, 111.02; Mass (*m*/*z*) 165 (M^+-CH_3, 30), 101 (100), 43 (100); Anal. Calcd for $C_{10}H_{12}O_3$: C 66.65, H 6.71. Found: C 66.62, H 6.79.

1.1.5. 1-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-(1*S*)-2,4-pentadiyn-1-ol (3a). TBDPSCl (0.85 mL, 3.34 mmol) was added dropwise over 1 min to a stirred solution of diacetylenic alcohol **3** (0.5 g, 2.78 mmol) and imidazole (0.58 g, 8.5 mmol) in dry DCM (10 mL) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 24 h. The mixture was then diluted with DCM and washed with water, brine, dried over Na_2SO_4, filtered and concentrated giving a residue that was purified by chromatography. Elution with ethyl acetate/hexane 1:9 gave compound **3a** (1.05 g, 88%) as a colorless liquid. R_f=0.62 (25% EtOAc/hexane); $[\alpha]_D^{25}$=+89.36 (*c* 2.87, $CHCl_3$); IR (film) ν_{max} 3280, 3050, 2210, 2064, 1590, 1470, 1380, 1260, 1111, 1074, 820, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 9H, SiC(CH_3)$_3$), 2.08 (s, 1H, C≡C*H*), 3.70 (m, 2H, CH_2(O)), 3.82 (m, 1H, CH_2(O)C*H*(O)), 4.45 (d, *J*=2.3 Hz, 1H, C*H*OTBDPS), 7.38 (m, 6H, aromatic *H*), 7.69 (m, 4H, aromatic *H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.36, 25.28, 26.41, 26.82, 26.90 (2C), 64.77, 65.88, 67.43, 68.21, 70.40, 74.83, 78.49, 110.09, 127.52 (2C), 127.69 (2C), 129.94 (2C), 132.67, 135.86, 135.91, 135.99, 136.12 (2C); Mass (*m*/*z*) 441 (M^++Na); Anal. Calcd for $C_{26}H_{30}O_3Si$: C 74.60, H 7.22. Found: C 74.48, H 7.26.

1.1.6. 3-(4-Methoxybenzyloxy)-(2*S*,3*R*)-decane-1,2-diol (10). To a stirred solution of epoxy alcohol **9** (4.0 g, 23.25 mmol) and PMBOH (5.49 g, 46.5 mmol) in toluene (100 mL), Ti(O^{i}Pr)$_4$ (10.4 mL, 34.9 mmol) was added under nitrogen at room temperature. The reaction mixture was then refluxed for 2 h. The solvent was removed under reduced pressure and the reaction mixture diluted with ether. Then 10% NaOH solution (25 mL) in brine was added to this and stirred overnight. Next this was filtered through a pad of Celite, washed with $CHCl_3$, dried and concentrated. The crude product was chromatographed to afford 6.1 g of diol **10** in 84% yield as a colorless oil. R_f=0.55 (70% EtOAc/hexane); $[\alpha]_D^{25}$=−6.41 (*c* 2.64, $CHCl_3$); IR (film) ν_{max} 3416, 2950, 2875, 1612, 1513, 1462, 1377, 1248, 1176, 1038, 822, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H, CH_3), 1.20–1.70 (series m, 12H, 6×CH_2), 2.50 and 2.89 (m, 2H, 2×O*H*),

3.45–3.78 (series m, 4H, CH_2(O)CH(O)C*H*(O)), 3.79 (s, 3H, OCH_3), 4.42, 4.55 (2d, *J*=8.9 Hz, 2H, Benzylic CH_2), 6.81 (d, *J*=6.2 Hz, 2H, aromatic *H*), 7.20 (d, *J*=6.2 Hz, 2H, aromatic *H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.97, 22.52, 25.26, 29.14, 29.63, 30.36, 31.70, 55.11, 63.30, 72.16, 72.63, 80.63, 113.73 (2C), 129.40 (2C), 130.25, 158.99; Mass (*m*/*z*): 292 (M^+-H_2O); Anal. Calcd for $C_{18}H_{30}O_4$: C 69.64, H 9.74. Found: C 69.62, H 9.80.

1.1.7. 3-(4-Methoxybenzyloxy)-1-*tert*-butyldimethylsilyloxy-(2*S*,3*R*)-decan-2-ol (11). TBDMSCl (2.67 g, 17.8 mmol) was added portionwise over 5 min to a stirred solution of diol **10** (5.0 g, 16.13 mmol) and imidazole (1.65 g, 24.2 mmol) in dry DCM (50 mL) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 6 h. The mixture was then diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to give mono silylated product **11** (6.1 g, 88%) as a colorless liquid. R_f=0.65 (25% EtOAc/hexane); $[\alpha]_D^{25}=-1.63$ (*c* 1.7, $CHCl_3$); IR (film) ν_{max} 3565, 2872, 1613, 1585, 1513, 1467, 1302, 1256, 1119, 1074, 939, 831, 777 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.05 (s, 6H, Si(CH_3)$_2$), 0.89 (t, *J*=7.0 Hz, 3H, CH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 1.20–1.60 (series m, 12H, 6×CH_2), 2.30 (br s, 1H, CHO*H* exchangeable with D_2O), 3.35 (m, 1H), 3.54–3.71 (series m, 3H), 3.69 (s, 3H, OCH_3), 4.47 (s, 2H, Benzylic CH_2), 6.82 (d, *J*=6.2 Hz, 2H, aromatic *H*), 7.25 (d, *J*=6.2 Hz, 2H, aromatic *H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.44, −5.42, 14.03, 18.20, 22.57, 25.16, 25.31, 25.61, 25.89, 29.74, 30.14, 31.61, 31.70, 55.16, 63.87, 71.91, 72.93, 79.01, 113.73 (2C), 129.67 (2C), 130.81, 159.18; Mass (*m*/*z*) 409 (M^+-CH_3); Anal. Calcd for $C_{24}H_{44}O_4Si$: C 67.88, H 10.44. Found: C 67.62, H 10.31.

1.1.8. Nonyl-1-(*tert*-butyldimethylsilyloxymethyl)-(2*R*)-(4-methoxy-benzyloxy)-(1*R*)-4-methyl-benzenesulfonate (12). TsCl (2.5 g, 13.2 mmol) was added portionwise to a stirred solution of **11** (5.0 g, 11.79 mmol) and Et_3N (2.5 mL, 17.97 mmol) in dry DCM at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 48 h. The mixture was then diluted with DCM and washed with water, brine and dried over Na_2SO_4. Organic layer was concentrated, and purified by flash column chromatography elution with EtOAc/hexane 1:50 to give **12** (5.45 g, 80%) as a colorless oil. R_f=0.65 (10% EtOAc/hexane); $[\alpha]_D^{25}=-14.62$ (*c* 0.95, $CHCl_3$); IR (film) ν_{max} 2929, 2857, 1612, 1513, 1463, 1367, 1300, 1251, 1177, 1096, 1036, 911, 839, 779 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.05 (s, 6H, Si(CH_3)$_2$), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.89 (t, *J*=6.9 Hz, 3H, CH_3), 1.15–1.40 (series m, 12H, 6×CH_2), 2.42 (s, 3H, C_6H_4–CH_3), 3.65 (m, 1H), 3.81 (s, 3H, OCH_3), 3.89 (series m, 2H), 4.40, 4.50 (2d, *J*=8.6 Hz, 2H, Benzylic CH_2), 4.55 (m, 1H), 6.82 (d, *J*=7.2 Hz, 2H, aromatic *H*), 7.15 (d, *J*=7.2 Hz, 2H, aromatic *H*), 7.29 (d, *J*=6.8 Hz, 2H, aromatic *H*), 7.80 (d, *J*=6.8 Hz, 2H, aromatic *H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.58, −5.50, 14.02, 18.18, 21.49, 22.58, 25.48, 25.78 (3C), 29.10, 29.39, 30.73, 31.75, 55.18, 61.39, 72.36, 77.31, 84.12, 113.67 (2C), 127.89 (2C), 129.47 (2C), 129.54 (2C), 130.40, 134.34, 144.34, 159.20; Anal. Calcd for $C_{31}H_{50}O_6SSi$: C 64.32, H 8.71. Found: C 64.26, H 9.01.

1.1.9. 2-[1-(4-Methoxybenzyloxy)-(1*R*)-octyl]-(2*R*)-oxirane (4). To a solution of **12** (5.0 g, 8.62 mmol) in dry THF (50 mL) was added Bu_4NF (1.0 M solution in THF, 34.5 mL, 34.5 mmol) at 0°C with vigorous stirring and was allowed to warm to room temperature. The reaction mixture was stirred for 3 h. Saturated NH_4Cl solution (10 mL) was added and resulting mixture was stirred for few minutes. Then the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash chromatography gave epoxide **4** (2.3 g, 92%) as a colorless liquid. R_f=0.52 (25% EtOAc/hexane); $[\alpha]_D^{25}=+19.2$ (*c* 2.3, $CHCl_3$); IR (film) ν_{max} 2928, 2857, 1612, 1587, 1513, 1463, 1248, 1175, 1090, 1037, 919, 821, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H, CH_3), 1.35 (m, 12H, 6×CH_2), 2.40 (dd, *J*=4.8, 2.9 Hz, 1H, Oxirane *H*), 2.71 (dd, *J*=4.8, 4.2 Hz, 1H, Oxirane *H*), 2.90–3.01 (series m, 2H, C*H*(O)C*H*(O)), 3.79 (s, 3H, OCH_3), 4.58, 4.61 (2d, *J*=8.6 Hz, 2H, Benzylic CH_2), 6.83 (d, *J*=8.7 Hz, 2H, aromatic *H*), 7.25 (d, *J*=8.7 Hz, 2H, aromatic *H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.78, 22.25, 25.25, 28.92, 29.30, 31.55, 32.11, 42.81, 54.80, 54.92, 71.06, 79.79, 113.46 (2C), 129.09 (2C), 130.65, 158.90; Anal. Calcd for $C_{18}H_{28}O_3$: C 73.94, H 9.65. Found: C 73.67, H 9.98.

1.1.10. 1-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4yl]-8-(4-methoxybenzyloxy)-1-*tert*-butyldiphenylsilyloxy-(1*S*,7*R*,8*R*)-2,4-pentadecadiyn-7ol (13). A solution of diacetylene **3a** (1.0 g, 2.39 mmol) in 10 mL THF was stirred at −78°C. A solution of BuLi (0.95 mL, 2.4 M solution in hexane, 2.3 mmol) was added dropwise. The resulting dark brown mixture was stirred for 30 min and then to this $BF_3{\cdot}OEt_2$ (0.23 mL, 2.3 mmol) was added. After another 30 min a solution of epoxide **4** (0.82 g, 2.8 mmol) in 3 mL THF was added dropwise and stirred for 1 h at −78°C. After that, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The extract was washed with water, brine and dried over Na_2SO_4, then concentrated under reduced pressure, purified by column chromatography to afford 1.28 g, 75% of **13** as a colorless oil. R_f=0.35 (25% EtOAc/hexane); $[\alpha]_D^{25}=+12.8$ (*c* 1.07, $CHCl_3$); IR (film) ν_{max} 3437, 2930, 2858, 2256, 1612, 1513, 1463, 1427, 1374, 1249, 1073, 821, 771, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H, CH_3), 1.08 (s, 3H, CCH_3), 1.09 (s, 9H, SiC(CH_3)$_3$), 1.30 (m, 10H, 5×CH_2), 1.35 (s, 3H, CCH_3), 1.60 (m, 2H, CH_2CHOPMB), 2.27 (d, *J*=7.1 Hz, 1H, CHO*H*), 2.49 (m, 2H, C≡CCH_2), 3.45 (dt, *J*=6.1, 3.7 Hz, 1H, C*H*(OPMB)CH_2), 3.69 (m, 1H, C*H*H(O)CH(O)CH(OTBDPS)), 3.80 (s, 3H, OCH_3), 3.90 (m, 1H, CH*H*(O)CH(O)CH(OTBDPS)), 4.01 (ddd, *J*=11.8, 8.2, 2.1 Hz, 1H, C*H*OH), 4.18 (m, 1H, C*H*(O)CH (OTBDPS)), 4.41 (d, *J*=2.1 Hz, 1H, C*H*OTBDPS), 4.50, 4.52 (2d, *J*=10.1 Hz, 2H, benzylic CH_2), 6.88 (d, *J*=8.6 Hz, 2H, aromatic *H*), 7.25 (d, *J*=8.6 Hz, 2H, aromatic *H*), 7.40 (m, 6H, aromatic *H*), 7.71 (m, 4H, aromatic *H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.04, 19.31, 22.60, 24.69, 25.23, 25.29, 26.35, 26.86 (3C), 29.18, 29.75, 30.31, 31.75, 55.19, 64.73, 65.80, 66.26, 70.89, 71.04, 72.34, 74.44, 77.51, 78.59, 79.67, 109.94, 113.83 (2C), 127.39 (2C), 127.58 (2C), 129.52 (2C), 129.72, 129.82, 130.20, 132.75, 135.87 (2C), 135.97, 136.10 (2C), 159.30;

Mass (*m*/*z*) 734 (M^++Na), 712 (M^++1); HRMS Calcd for $C_{44}H_{59}O_6Si$: 712.0216. Found: 712.0260.

1.1.11. 4-[8-(4-Methoxybenzyloxy)-1,7-di(*tert*-butyldiphenylsilyloxy)-(1*S*,7*R*,8*R*)-2,4-hexadecadiynyl]-2,2-dimethyl-(4*R*)-1,3-dioxolane (14). TBDPSCl (0.48 mL, 1.9 mmol) was added portionwise over 5 min to a stirred solution of alcohol **13** (1.1 g, 1.55 mmol) and imidazole (0.68 g, 10.0 mmol) in dry DCM (5 mL) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 6 h. The mixture was then diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography giving **14** (1.34 g 91%) as a colorless liquid. R_f=0.69 (10% EtOAc/hexane); $[\alpha]_D^{25}$=+11.86 (*c* 2.02, $CHCl_3$); IR (film) ν_{max} 2925, 2860, 2250, 1613, 1376, 1219, 1107, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J*=7.0 Hz, 3H, C*H*$_3$), 1.06 (s, 3H, CC*H*$_3$), 1.07 (s, 9H, Si(C*H*$_3$)$_3$), 1.09 (s, 9H, Si(C*H*$_3$)$_3$), 1.22 (m, 10H, 5×C*H*$_2$), 1.35 (s, 3H, CC*H*$_3$), 1.65 (m, 2H, C*H*$_2$CHOPMB), 2.43 (dd *J*=17.2, 7.1 Hz, 1H, C≡CC*H*H), 2.45 (dd *J*=17.2, 7.1 Hz, 1H, C≡CCH*H*), 3.17 (dt, *J*=8.8, 3.1 Hz 1H, C*H*OPMB), 3.77 (s, 3H, OC*H*$_3$), 3.96–4.20 (series m, 6H), 4.42 (d, *J*=5.1 Hz, 1H, C≡CC*H*OTBDPS), 6.78 (d, *J*=8.6 Hz, 2H, aromatic *H*), 7.04 (d, *J*=8.6 Hz, 2H, aromatic *H*), 7.37 (m, 12H, aromatic *H*), 7.71 (m, 8H, aromatic *H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.09, 18.96, 22.63, 25.31, 26.12, 26.36, 26.52 (4C), 26.92 (2C), 26.97 (2C), 28.56, 29.26, 29.59, 31.79, 55.19, 64.61 (2C), 65.71, 65.91, 71.38, 71.67, 73.71, 78.72, 79.62, 80.59, 109.94, 113.59 (2C), 127.44, 127.57 (2C), 127.62 (2C), 127.66 (3C), 129.27 (2C), 129.59 (2C), 129.77, 130.67, 132.78, 132.94, 133.32, 133.84, 134.76 (4C), 135.16, 135.89 (2C), 136.12 (2C), 159.01; Anal. Calcd for $C_{60}H_{76}O_6Si_2$: C 75.90, H 8.07. Found: C 75.69, H 8.20.

1.1.12. 10-(4-Methoxybenzyloxy)-2,9-di(*tert*-butyldiphenylsilyloxy)-(2*R*,3*S*,9*R*,10*R*)-4,6-heptadecadinyne-1,2-diol (15). To a stirred solution of **14** (1.1 g, 1.16 mmol) in 5 mL acetonitrile, crystals of $CuCl_2{\cdot}2H_2O$ (0.4 g, 2.35 mmol) was added at 0°C. The solution was allowed to warm to room temperature and stirred for 3 h. After completion of the reaction most of the solvent was removed at room temperature under vacuum. The crude was taken in ether and washed with aq. $NaHCO_3$ solution, brine and dried over Na_2SO_4. Solvent was removed and purified over silica gel to give diol **15** (0.99 g, 94%) as a colorless liquid. R_f=0.25 (25% EtOAc/hexane); $[\alpha]_D^{25}$=+23.2 (*c* 2.35, $CHCl_3$); IR (film) ν_{max} 3480, 3072, 2930, 2858, 2255, 1612, 1589, 1513, 1466, 1428, 1375, 1249, 1109, 822, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.08 Hz, 3H, C*H*$_3$), 1.06 (s, 9H, Si(C*H*$_3$)$_3$), 1.10 (s, 9H, Si(C*H*$_3$)$_3$), 1.25 (m, 10H, 5×C*H*$_2$), 1.64 (m, 2H, C*H*$_2$CHOPMB), 1.83 (br s, 1H, CH$_2$O*H*), 2.41 (dd, *J*=17.0, 7.3 Hz, 1H, C≡CC*H*H), 2.43 (dd, *J*=17.0, 7.3 Hz, 1H, C≡CCH*H*), 2.43 (d, *J*=5.4 Hz, 1H, CHO*H*), 3.15 (dt, *J*=9.0, 3.3 Hz, 1H, C*H*OPMB), 3.66 (m, 2H, C*H*$_2$OH), 3.76 (s, 3H, OC*H*$_3$), 3.83 (m, 1H, C*H*OH), 3.95 (dt, *J*=7.3, 4.3 Hz, 1H, CH$_2$C*H*OTBDPS), 4.0, 4.09 (2d, *J*=8.8 Hz, 2H, benzylic C*H*$_2$), 4.46 (d, *J*=4.6 Hz, 1H, C≡CC*H*OTBDPS), 6.73 (d, *J*=8.6 Hz, 2H, aromatic *H*), 6.98 (d, *J*=8.6 Hz, 2H, aromatic *H*), 7.36 (m, 12H, aromatic *H*), 7.67 (m, 8H, aromatic *H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.10, 19.31, 19.34, 22.64, 26.13, 26.94 (7C), 28.57, 29.26, 29.59, 31.80, 55.20, 62.99, 65.63 (3C), 71.84 (2C), 72.56, 72.81, 74.41, 80.17, 113.54 (2C), 127.55 (2C), 127.60 (2C), 127.64 (3C), 127.83 (3C), 129.29, 129.73, 129.80, 129.97, 130.10, 130.64, 132.33, 132.44, 133.36, 133.73, 135.80 (2C), 135.94 (2C), 136.02 (2C), 136.13, 159.03; Mass (*m*/*z*) 914 (M^++Na−H_2O).

1.1.13. 1-[1-Heptyl-2,8-di(*tert*-butyldiphenylsilyloxy)-(1*R*,2*R*,8*R*)-9-decen-4,6-diynyloxymethyl]-4-methoxybenzene (16). The diol **15** (0.9 g, 0.99 mmol), PPh_3 (1.0 g, 4.0 mmol) and imidazole (0.272 g, 4.0 mmol) were refluxed in toluene (10 mL) with stirring. I_2 (0.76 g, 3.0 mmol) was added in small portions. After 3 h, the reaction mixture was cooled and decanted into excess aqueous sodium bicarbonate and sodium thiosulfate in a separating funnel. The residue in the flask was extracted with several portions of toluene, and the combined toluene extract was shaken with thiosulfate until a colorless solution appeared. The organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography to afford olefin **16** (0.77 g, 89%) as a colorless liquid. R_f=0.76 (25% EtOAc/hexane); $[\alpha]_D^{25}$=+7.84 (*c* 2.01, $CHCl_3$); IR (film) ν_{max} 2926, 2855, 2256, 1613, 1592, 1512, 1465, 1426, 1302, 1247, 1108, 821, 772, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.08 Hz, 3H, C*H*$_3$), 1.07 (s, 9H, Si(C*H*$_3$)$_3$), 1.09 (s, 9H, Si(C*H*$_3$)$_3$), 1.26 (m, 10H, 5×C*H*$_2$), 1.65 (m, 2H, C*H*$_2$CHOPMB), 2.43 (dd, *J*=17.2, 7.1 Hz, 1H, C≡CC*H*H), 2.46 (dd, *J*=17.2, 7.1 Hz, 1H, C≡CCH*H*), 3.18 (dt, *J*=3.1, 9.0 Hz, 1H, CH$_2$C*H*OPMB), 3.77 (s, 3H, OC*H*$_3$), 3.99 (m, 1H, CH$_2$C*H*OTBDPS), 4.05, 4.09 (2d, *J*=10.2 Hz, 2H, benzylic C*H*$_2$), 4.83 (dt, *J*=5.3, 1.3 Hz, 1H, CH$_2$=CHC*H*OTBDPS), 5.11 (dt, *J*=10.1, 1.3 Hz, 1H, olefinic *H*), 5.26 (dt, *J*=16.9, 1.3 Hz, 1H, olefinic *H*), 5.85 (ddd, *J*=16.9, 10.1, 5.3 Hz, 1H, olefinic *H*), 6.77 (d, *J*=8.6 Hz, 2H, aromatic *H*), 7.03 (d, *J*=8.6 Hz, 2H, aromatic *H*), 7.37 (m, 12H, aromatic *H*), 7.70 (m, 8H, aromatic *H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.02, 19.33, 22.61, 22.76, 26.16, 26.85, 27.01 (4C), 28.68, 29.24 (2C), 29.61 (2C), 31.79, 55.19, 65.07 (3C), 71.86 (2C), 74.56, 79.81, 80.73, 113.65 (2C), 115.62, 127.53 (9C), 129.22 (2C), 129.72 (4C), 130.81, 133.05, 133.42, 133.95, 135.77 (2C), 135.93 (4C), 136.14 (2C), 136.93, 159.08; Anal. Calcd for $C_{57}H_{70}O_4Si_2$: C 78.21, H 8.07. Found: C 78.18, H 8.20.

1.1.14. 1-Heptyl-2,8-di(*tert*-butyldiphenylsilyloxy)-(1*R*,2*R*,8*R*)-9decen-4,6-diynyl-alcohol (17). Compound **16** (0.75 g, 0.86 mmol) was taken in 4 mL aq. DCM (DCM/H_2O 19:1), DDQ (0.295 g, 1.3 mmol) was added to it and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was filtered off and the filtrate was washed with 5% $NaHCO_3$ solution, brine, and dried over Na_2SO_4. Purified by column chromatography gave 0.53 g of **17** in 82% yield. R_f=0.76 (25% EtOAc/hexane); $[\alpha]_D^{25}$=−4.79 (*c* 0.90, $CHCl_3$); IR (film) ν_{max} 3450, 2930, 2853, 2250, 1522, 1430, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.08 Hz, 3H, C*H*$_3$), 1.06 (s, 9H, Si(C*H*$_3$)$_3$), 1.08 (s, 9H, Si(C*H*$_3$)$_3$), 1.25 (m, 12H, 6×C*H*$_2$), 1.91 (m, 1H, O*H* exchangeable with D_2O), 2.43 (dd, *J*=16.9, 7.3 Hz, 1H, C≡CC*H*H), 2.43 (dd, *J*=16.9, 7.3 Hz, 1H, C≡CCH*H*), 3.60 (m, 2H, C*H*(O)C*H*(O)), 4.78

(dt, J=5.5, 1.4 Hz, 1H, C=CC*H*(OTBDPS)), 5.10 (dt, J=10.2, 1.4 Hz, 1H, olefinic *H*), 5.22 (dt, J=17.2, 1.4 Hz, 1H, olefinic *H*), 5.80 (ddd, J=17.2, 10.2, 5.5 Hz, 1H, olefinic *H*), 7.35 (m, 12H, aromatic *H*), 7.70 (m, 8H, aromatic *H*); Anal. Calcd for $C_{49}H_{62}O_3Si_2$: C 77.94, H 8.28. Found: C 77.99, H 8.40.

1.1.15. (3*R*,9*R*,10*R*)-1-Heptadecen-4,6-diyne-3,9,10-triol (1). To a solution of **17** (0.25 g, 0.33 mmol) in dry THF 4 mL was added Bu_4NF (1.0 M solution in dry THF, 1.2 mL, 1.2 mmol) at 0°C under nitrogen and the resulting solution was allowed to attain room temp. The mixture was stirred for 3 h and next quenched with 2 mL of NH_4Cl solution. Then diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried and evaporated under reduced pressure. The crude product was purified by flash chromatography gave **1** (84 mg, 91%) as a white glassy wax. R_f=0.42 (50% EtOAc/hexane); $[\alpha]_D^{25}=-20.1$ (c 1.54, $CHCl_3$). All other data are in agreement with the earlier report.[5]

1.1.16. 1-Heptyl-2,8-di(*tert*-butyldiphenylsilyloxy)-(1*R*, 2*R*,8*R*)-9-decen-4,6-diynyl-4-methyl-1-benzenesulfonate (18). TsCl (95 mg, 0.5 mmol) was added portion wise to a stirred solution of **17** (250 mg, 0.33 mmol), Et_3N (0.2 mL, 1.5 mmol) and catalytic DMAP in dry DCM at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 48 h. The mixture was then diluted with DCM and washed with water, brine and dried over Na_2SO_4. Organic layer was concentrated and purified by flash column chromatography to give **18** 240 mg, 81% as a colorless oil. R_f=0.25 (10% EtOAc/hexane, B: red); $[\alpha]_D^{25}=+1.02$ (c 0.85, $CHCl_3$); IR (film) ν_{max} 2930, 2857, 2255, 1613, 1513, 1462, 1370, 1258, 1180, 1090 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J=7.0 Hz, 3H, CH_3), 1.07 (s, 9H, Si(CH_3)$_3$), 1.09 (s, 9H, Si(CH_3)$_3$), 1.26 (m, 10H, 5×CH_2), 1.65 (m, 2H, CH_2CHOTs), 2.35 (m, 2H, C≡CCH_2), 2.40 (s, 3H, aromatic CH_3), 3.91–4.08 (series m, 2H, C*H*(O)C*H*(O)), 4.81 (m, 1H, CH_2=CHC*H*OTBDPS), 5.17 (dt, J=9.8, 1.1 Hz, 1H, olefinic *H*), 5.26 (dt, J=16.9, 1.1 Hz, 1H, olefinic *H*), 5.85 (ddd, J=16.9, 9.8, 5.3 Hz, 1H, olefinic *H*), 7.26–7.43 (m, 14H, aromatic *H*), 7.61–7.81 (m, 10H, aromatic *H*); Anal. Calcd for $C_{56}H_{68}O_5SSi_2$: C 73.95, H 7.56. Found: C 73.59, H 7.64.

1.1.17. 8-[3-Heptyl-(2*R*,3*S*)-oxiran-2-yl]-(3*R*)-1-octen-4,6-diyn-3-ol (2). To a solution of **18** (0.24 g, 0.26 mmol) in dry THF 4 mL was added Bu_4NF (1.0 M solution in dry THF, 1.5 mL, 1.5 mmol) at 0°C under nitrogen and the resulting solution was allowed to attain room temperature. The mixture was stirred for 3 h and next quenched with 2 mL of NH_4Cl solution. Then diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried and evaporated under reduced pressure. The crude product was purified by flash chromatography gave **2** (51 mg, 76%) as a colorless oil. R_f=0.25 (10% EtOAc/hexane, B: red); $[\alpha]_D^{25}=-86.3$ (c 1.5, $CHCl_3$). All other data are in agreement with the earlier report.[5]

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