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ASYMMETRIC SYNTHESIS OF PANAXYDOL AND ITS STEREOISOMERS

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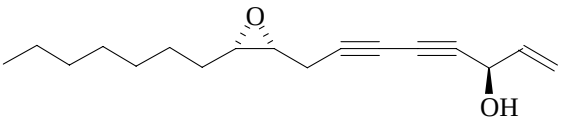
Abstract –A facile synthesis of four possible stereoisomers of panaxydol was described. The configurations of C-3 and C-9, C-10 positions were established by enantioselective reduction and Sharpless asymmetric dihydroxylation, respectively.

INTRODUCTION

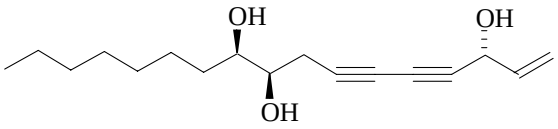
Renshen, the dried root of *Panax ginseng* (Araliaceae), is one of the most important medicinal plants used in traditional Chinese medicine and has been used for more than two thousand years as a general tonic in the Eastern world.[1-3] It contains a large number of different constituents and approximately two hundred substances have been isolated and characterized so far. Among them, several types of diacetylenic alcohols have shown to suppress *in vitro* growth of cultured tumor cells.[4-11] Panaxydol (**1**) is one of these diacetylenic alcohols and its structure was elucidated as 9,10-epoxyheptadec-1-ene-4,6-diyn-3-ol.[11-13] After hydrolysis in acidic solution, it was converted to panaxytriol (**2**), in which the 3*R* configuration was determined by the modified Mosher's method and 9*R*,10*R* configurations were defined by CD spectral analysis. Therefore, the C-3 configuration of panaxydol was determined to be *R* as panaxytriol. The absolute configuration of the epoxy moiety was assigned as 9*R*,10*S* by ^{13}C NMR spectral analysis and Mass-analyzed Ion Kinetic Energy Spectrometry (MIKES) study of FAB-MS of panaxytriol and ^{18}O-labeled panaxytriol obtained from the hydrolysis of panaxydol in ^{18}O-labeled water.[14]

In 1998, Cai *et al*. synthesized (3*R*,9*R*,10*S*)-panaxydol (**1**) in more than twenty steps with D-xylose and diethyl L-tartrate as the starting materials.[15] The unsymmetric diyne skeleton of **1** was constructed by

the Cadiot-Chodkiewicz coupling of a terminal alkyne prepared from D-xylose and a bromoalkyne derived from diethyl L-tartrate. In 2002, Yadav and Maiti synthesized panaxydol using the Yamaguchi method to couple an epoxide component and a diacetylenic component in near twenty steps.[16] These two components were prepared from D-arabinose and *trans*-2-decen-1-ol, respectively. Herein, we report a facile stereoselective synthesis of four possible stereoisomers of panaxydol in only nine steps.



1



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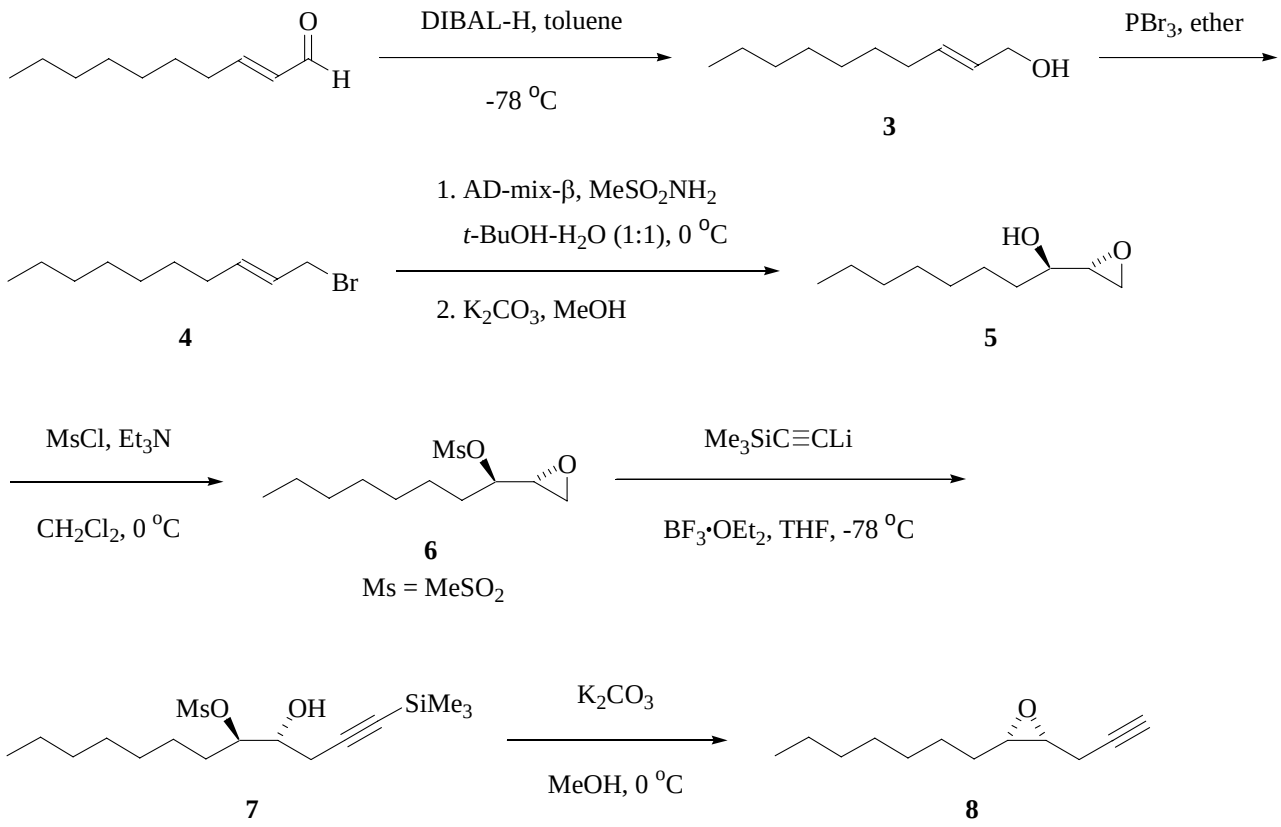
RESULTS AND DISCUSSION

In our approach, panaxydol and its stereoisomers were synthesized by the Cadiot-Chodkiewicz coupling of a terminal alkyne with a bromoalkyne.[17] The preparation of the terminal alkyne, 2-heptyl-3-(2-propynyl)oxirane, is shown in Scheme 1 starting from *trans*-2-decenal. This α,β-unsaturated aldehyde was reduced by diisobutylaluminum hydride or sodium borohydride to give *trans*-2-decen-1-ol (**3**), which was transformed to *trans*-1-bromo-2-decene (**4**) with phosphorus tribromide. Sharpless asymmetric dihydroxylation[18] with AD-mix-β at 0 °C converted the allyl bromide to (2*S*,3*R*)-1-bromo-2,3-decanediol, which subsequently epoxized by an S_N2 displacement in basic solution to afford (1*R*)-1-[(2*R*)-2-oxiranyl)-1-octanol (**5**). On the other hand, (1*S*)-1-[(2*S*)-2-oxiranyl)]-1-octanol (**5a**) was provided when AD-mix-α was used. In order to determine the enantiomeric excess of **5**, its (*R*)-MTPA ester was prepared and analyzed by ^{1}H-NMR spectrum. The area ratios between signals at 2.67, 2.86, 3.09 ppm and 2.57, 2.77, 3.04 ppm due to the oxiranyl protons of two diastereomers indicated an enantiomeric excess of 98%. Besides, the (*R*)-MTPA ester of **5a** was also prepared and showed the same enantiomeric excess. After mesylation with methanesulfonyl chloride, epoxy alcohol **5** reacted with lithium trimethylsilylacetylide in the presence of boron trifluoride diethyl etherate to afford **7**.[19] Under basic condition, the hydroxyl group of **7** displaced mesylate ion to form an epoxide and the trimethylsilyl group was also removed; thus, (2*S*,3*R*)-2-heptyl-3-(2-propynyl)oxirane (**8**) was obtained.

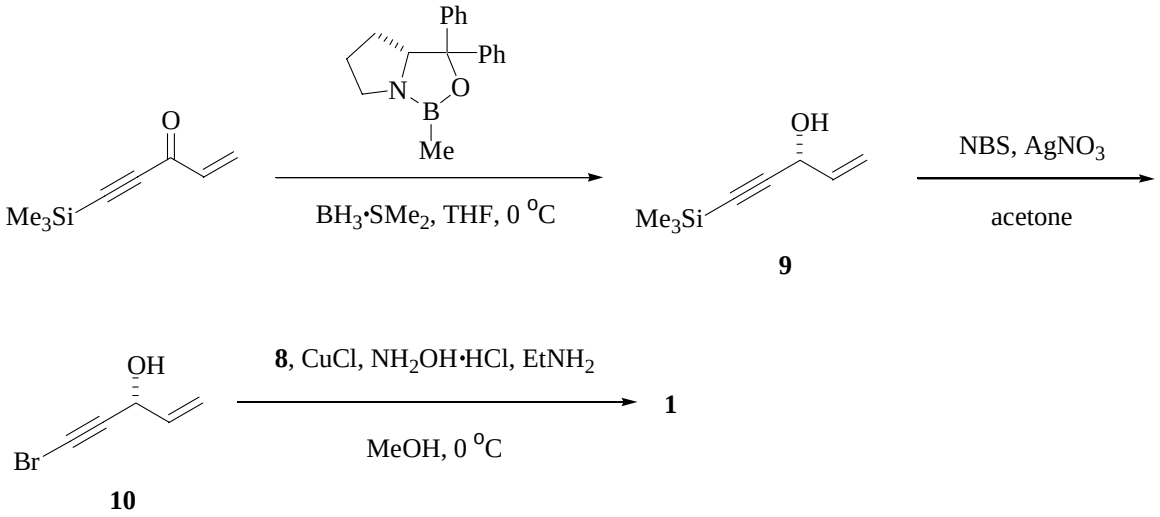
The synthesis of the bromoalkyne as shown in Scheme 2 started from 5-trimethylsilyl-1-penten-4-yn-3-one,[20] which was prepared through nucleophilic addition of acrolein with lithium trimethylsilylacetylide followed by oxidation with Jones reagent. We attempted the enantioselective reduction of the ketone with several reducing agents including Alpine-Borane,[21] BINAL-H,[22] $LiAlH_4$-Chirald,[23] and $BH_3 \cdot SMe_2$–chiral oxazaborolidine,[24,25] and found that borane–dimethyl sulfide complex was most efficient to reduce 5-trimethylsilyl-1-penten-4-yn-3-one in

the presence of (*R*)-2-methyl-CBS-oxazaborolidine to afford (*R*)-

Scheme 1



Scheme 2



5-trimethylsilyl-1-penten-4-yn-3-ol (**9**). In order to confirm the absolute configuration and determine the enantiomeric excess, both (*R*)- and (*S*)-MTPA esters of **9** were prepared. The ^{1}H-NMR spectra exhibited that the olefinic protons (δ 5.83, 5.52, and 5.31) of the (*S*)-MTPA ester appeared at higher field than those (δ 5.92, 5.59, and 5.36) of the (*R*)-MTPA ester, which confirmed the *R* configuration based on

the general rule of the Mosher's method. The enantiomeric excess was also determined to be 90%. Furthermore, (*S*)-5-trimethyl-1-penten-4-yn-3-ol was prepared by using (*S*)-2-methyl-CBS-oxazaborolidine as the chiral ligand. Treatment of **9** with *N*-bromosuccinimide and silver nitrate in acetone provided (*R*)-5-bromo-1-penten-4-yn-3-ol (**10**),[26] which was finally coupled with **8** through Cadiot-Chodkiewicz reaction to afford panaxydol with 3*R*,9*R*,10*S* configuration.

In addition, the (3*R*,9*S*,10*R*)-, (3*S*,9*R*,10*S*)-, (3*S*,9*S*,10*R*)-panaxydol stereoisomers were also synthesized by the similar approach. The optical rotations $[\alpha]_D$ in chloroform of (3*R*,9*R*,10*S*)-, (3*R*,9*S*,10*R*)-, (3*S*,9*R*,10*S*)-, (3*S*,9*S*,10*R*)-stereoisomers were –103° (*c* = 2.6) {lit. $[\alpha]_D^{22}$ –81.8° (*c* = 1.52, $CHCl_3$),[14] $[\alpha]_D$ –96.1° (*c* = 1.30, $CHCl_3$),[15] $[\alpha]_D^{25}$ –86.3° (*c* = 1.5, $CHCl_3$)[16]}, +51.2° (*c* = 1.7), –57.7° (*c* = 1.6), and +103° (*c* = 3.0), respectively.

In conclusion, panaxydol and its stereoisomers were obtained in nine steps starting from *trans*-2-decenal and 5-trimethylsilyl-1-penten-4-yn-3-one.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources and used as received. THF, ether, and toluene were dried and distilled from sodium benzophenone ketyl under N_2 atmosphere. Dichloromethane was dried by distillation under N_2 atmosphere from calcium hydride. ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 126 MHz in $CDCl_3$ on a Varian Unity Inova 500 spectrometer. Chemical shifts are reported relative to residual chloroform (δ = 7.24) for ^{1}H NMR and are referred to the $CDCl_3$ resonance (δ = 77.00) for ^{13}C NMR spectra. ^{19}F NMR spectra were recorded at 470 MHz in $CDCl_3$ and chemical shifts are reported relative to the internal standard $CFCl_3$. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrophotometer and peaks are reported in cm^{-1}. HRMS spectra were recorded on JEOL SX-102A and Finnigan MAT-95XL instruments. Optical rotations were taken on a JASCO DIP-370 polarimeter.

***trans*-2-Decen-1-ol (3).** To a solution of *trans*-2-decenal (1.00 g, 6.48 mmol) in 70 mL of dry toluene at –78 °C was added diisobutylaluminum hydride (DIBAL-H, 13.6 mL, 1.0 M solution in heptane, 13.6 mmol) dropwise under N_2 atmosphere. After 2.5 h, the reaction was quenched with 0.4 mL of methanol and allowed to warm to rt. The mixture was then diluted with EtOAc, and washed with 1 N HCl, water, and brine. After drying over $MgSO_4$ and solvent evaporation, the residue was chromatographed on a silica gel column using hexanes–EtOAc (5:1) as the eluant to furnish 1.01 g (quantitative) of oily *trans*-2-decen-1-ol: ^{1}H NMR δ 5.62 (2H, m, H-2 and H-3), 4.04 (2H, dd, *J* = 5.5, 1.0 Hz, H-1), 2.00 (2H, q, *J* = 7.0 Hz, H-4), 1.68 (1H, s, OH), 1.34 (2H, m, H-5), 1.24 (8H, m, H-6~H-9), 0.85 (3H, t, J = 7.0 Hz, H-10); ^{13}C NMR δ 133.49 (C-13), 128.77 (C-2), 63.73 (C-1), 32.17 (C-4), 31.78, 29.10 (3C), 22.61, 14.03 (C-10); IR (film) 3331, 2957, 2925, 2855, 1465, 1090, 1003, 969.

***trans*-1-Bromo-2-decene (4).** To a solution of *trans*-2-decen-1-ol (0.913 g, 5.84 mmol) in 14 mL of anhydrous ether was added dropwise a solution of phosphorus tribromide (0.639 g, 2.36 mmol) in 6 mL of anhydrous ether at 0 °C under N_2 atmosphere. After 10 min, the reaction mixture was allowed to stir at rt for 1 h and then 6 mL of saturated aqueous $NaHCO_3$ was added at 0 °C. The product was extracted into ether and the extract was washed with water and brine. After drying over $MgSO_4$ and solvent evaporation, the crude product was purified by column chromatography on silica gel using hexanes as the eluant to afford 1.13 g (88%) of *trans*-1-bromo-2-decene as an oil[27]: ^{1}H NMR δ 5.75 (1H, m, H-3), 5.66 (1H, m, H-2), 3.93 (2H, d, *J* = 7.5 Hz, H-1), 2.03 (2H, q, *J* = 7.0 Hz, H-4), 1.35 (2H, m, H-5), 1.25 (8H, m, H-6~H-9), 0.86 (3H, t, *J* = 6.8 Hz, H-10); ^{13}C NMR δ 136.78 (C-3), 126.23 (C-2), 33.65 (C-1), 32.05 (C-4), 31.77, 29.09, 29.06, 28.80, 22.63, 14.07 (C-10); IR (film) 2957, 2926, 2855, 1466, 1203, 964.

(1*R*)-1-[(2*R*)-2-Oxiranyl]-1-octanol (5). After 8.81 g of AD-mix-β was added to a mixture of *t*-BuOH–H_2O (1:1, 50 mL) and stirred vigorously at rt for 5 min, 0.583 (6.13 mmol) of methanesulfonamide was added. The mixture was then cooled to 0 °C and 1.39 g (6.34 mmol) of *trans*-1-bromo-2-decene was added. After stirring at 0 °C overnight, 9.4 g of sodium sulfite was added; the mixture allowed to warm to rt and stirred for 1 h. The dihydroxylation product was extracted into EtOAc and the extract was washed with 2 N KOH, water, and brine. After drying over $MgSO_4$ and solvent evaporation, the residue was dissolved in 110 mL of methanol and 2.88 g of K_2CO_3 powder was added. The mixture was stirred at rt for 1 h and subsequently 3 mL of saturated aqueous NH_4Cl was added. The epoxy alcohol was extracted into ether and the extract was washed with water and brine. After drying over $MgSO_4$ and solvent evaporation, the residue was chromatographed on a silica gel column using 2:1 hexanes–EtOAc as the eluant to give 0.830 g (76%) of (1*R*)-1-[(2*R*)-2-oxiranyl]-1-octanol as an oil[28,29]: $[\alpha]_D^{25}$ –4.3° (*c* = 1.4, $CHCl_3$); ^{1}H NMR δ 3.38 (1H, dt, *J* = 7.5, 5.5 Hz, H-1), 2.94 (1H, ddd, *J* = 5.5, 4.5, 3.0 Hz, H-2'), 2.78 (1H, dd, *J* = 5.0, 4.0 Hz, H-3'β), 2.67 (1H, dd, *J* = 5.0, 2.5 Hz, H-3'α), 2.12 (1H, br s, OH), 1.62–1.50 (2H, m, H-2), 1.48–1.18 (10H, m, H-3~H-7), 0.84 (3H, t, *J* = 7.0 Hz, H-8); ^{13}C NMR δ 71.72 (C-1), 55.45 (C-2'), 45.15 (C-3'), 34.30 (C-2), 31.72 (C-6), 29.51 (C-4 or C-5), 29.14 (C-4 or C-5), 25.25 (C-3), 22.58 (C-7), 14.01 (C-8); IR (film) 3417, 2927, 2856, 1466, 1378, 1088, 1058, 919, 896.

(1*S*)-1-[(2*S*)-2-Oxiranyl]-1-octanol (5a). The oily epoxy alcohol was prepared from *trans*-1-bromo-2-decene according to the method described for **5** with AD-mix-α.[28-30] $[\alpha]_D^{25}$ +4.8° (*c* = 1.5, $CHCl_3$); ^{1}H NMR δ 3.39 (1H, q, *J* = 6.0 Hz, H-1), 2.95 (1H, ddd, *J* = 5.5, 4.0, 2.5 Hz, H-2'), 2.79 (1H, t, *J* = 4.5 Hz, H-3'β), 2.68 (1H, dd, *J* = 5.0, 2.5 Hz, H-3'α), 2.04 (1H, br s, OH), 1.62–1.50 (2H, m, H-2), 1.48–1.18 (10H, m, H-3~H-7), 0.85 (3H, t, *J* = 7.0 Hz, H-8); ^{13}C NMR δ 71.71 (C-1), 55.42 (C-2'), 45.18 (C-3'), 34.34 (C-2), 31.75 (C-6), 29.53 (C-4 or C-5), 29.15 (C-4 or C-5), 25.26 (C-3), 22.60 (C-7), 14.04

(C-8); IR (film) 3416, 2927, 2856, 1467, 1379, 1086, 1055, 920, 896.

(*R*)-MTPA ester of (1*R*)-1-[(2*R*)-2-oxiranyl]-1-octanol. To a solution of (1*R*)-1-[(2*R*)-2-oxiranyl]-1-octanol (20 mg, 0.12 mmol) in 5 mL of CH_2Cl_2 was added (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-MTPA, 54 mg, 0.23 mmol], dicyclohexylcarbodiimide (110 mg, 0.53 mmol), and 4-(dimethylamino)pyridine (14 mg) under N_2 atmosphere. The resulting mixture was stirred overnight and then treated with ice water. The (*R*)-MTPA ester was extracted into CH_2Cl_2 and the organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated. After preparative TLC on silica gel with 2:1 hexanes–EtOAc as the developing solvent, 20 mg (43%) of the ester was obtained as an oil: $[\alpha]_D^{25}$ +38.5° (*c* = 0.78, $CHCl_3$); ^{1}H NMR δ 7.57–7.53 (2H, m, H-2, H-6 of Ph), 7.41–7.37 (3H, m, H-3~H-5 of Ph), 4.81 (1H, dt, *J* = 7.0, 5.5 Hz, H-1), 3.59 (3H, s, OCH_3), 3.09 (1H, ddd, *J* = 7.0, 4.0, 2.5 Hz, H-2'), 2.86 (1H, dd, *J* = 5.0, 4.0 Hz, H-3'β), 2.67 (1H, dd, *J* = 5.0, 2.5 Hz, H-3'α), 1.80–1.53 (2H, m, H-2), 1.30–1.18 (10H, m, H-3~H-7), 0.86 (3H, t, *J* = 7.0 Hz, H-8); ^{13}C NMR δ 166.06 (C=O of MTPA), 132.31 (C-1 of Ph), 129.61 (C-4 of Ph), 128.38 (C-3, C-5 of Ph), 127.31 (C-2, C-6 of Ph), 123.32 (q, *J* = 289 Hz, CF_3), 84.68 (q, *J* = 26.9 Hz, *C*CF_3), 77.85 (C-1), 55.54 (OCH_3), 52.59 (C-2'), 45.43 (C-3'), 31.61 (C-6), 31.06 (C-2), 29.22 (C-4 or C-5), 28.97 (C-4 or C-5), 24.71 (C-3), 22.57 (C-7), 14.02 (C-8); ^{19}F NMR δ –71.96; IR (film) 2928, 2855, 1750, 1666, 1498, 1452, 1267, 1252, 1188, 1169, 1122, 1019, 717.

(*R*)-MTPA ester of (1*S*)-1-[(2*S*)-2-oxiranyl]-1-octanol. The oily ester was prepared from (1*S*)-1-[(2*S*)-2-oxiranyl]-1-octanol according to the method described for the (*R*)-MTPA ester of (1*R*)-1-[(2*R*)-2-oxiranyl]-1-octanol. $[\alpha]_D^{25}$ +33.3° (*c* =1.6, $CHCl_3$); ^{1}H NMR δ 7.56–7.53 (2H, m, H-2, H-6 of Ph), 7.41–7.37 (3H, m, H-3~H-5 of Ph), 4.87 (1H, q, *J* = 6.5 Hz, H-1), 3.55 (3H, s, OCH_3), 3.04 (1H, ddd, *J* = 6.0, 4.0, 2.5 Hz, H-2'), 2.77 (1H, t, *J* = 5.0 Hz, H-3'β), 2.57 (1H, dd, *J* = 5.0, 2.5 Hz, H-3'α), 1.80–1.65 (2H, m, H-2), 1.40–1.17 (10H, m, H-3~H-7), 0.86 (3H, t, *J* = 7.0 Hz, H-8); ^{13}C NMR δ 165.99 (C=O of MTPA), 132.10 (C-1 of Ph), 129.62 (C-4 of Ph), 128.35 (C-3, C-5 of Ph), 127.48 (C-2, C-6 of Ph), 123.25 (q, *J* = 289 Hz, CF_3), 84.74 (q, *J* = 27.0 Hz, *C*CF_3), 77.34 (C-1), 55.47 (OCH_3), 52.51 (C-2'), 44.88 (C-3'), 31.63 (C-6), 31.08 (C-2), 29.26 (C-4 or C-5), 28.99 (C-4 or C-5), 25.04 (C-3), 22.56 (C-7), 14.02 (C-8); ^{19}F NMR δ –72.17; IR (film) 2933, 2857, 1751, 1665, 1499, 1452, 1252, 1168, 1121, 1019, 997, 721.

(1*R*)-1-[(2*R*)-2-Oxiranyl]octyl methanesulfonate (6). To a solution of **5** (0.830 g, 4.82 mmol) and triethylamine (1.27 g, 12.6 mmol) in 14 mL of CH_2Cl_2 was added a solution of methanesulfonyl chloride (0.662 g, 5.78 mmol) in 3 mL of CH_2Cl_2 at 0 °C under N_2 atmosphere. The resulting solution was stirred for 2 h and the reaction was subsequently quenched by water. The product was extracted into CH_2Cl_2 and the extract was washed with water and brine. After drying over $MgSO_4$ and solvent evaporation, the residue was chromatographed on a silica gel column using 4:1 hexanes–EtOAc as the

eluant to afford 0.966 g (80%) of **6** as an oil: $[\alpha]_D^{25}$ +8.6° (*c* = 1.4, $CHCl_3$); ^{1}H NMR δ 4.21 (1H, dt, *J* = 5.5, 7.5 Hz, H-1), 3.12 (1H, m, H-2'), 3.11 (3H, s, CH_3 of Ms), 2.90 (1H, t, *J* = 4.5 Hz, H-3'β), 2.68 (1H, dd, *J* = 4.5, 2.5 Hz, H-3'α), 1.85–1.66 (2H, m, H-2), 1.50–1.19 (10H, m, H-3~H-7), 0.85 (3H, t, *J* = 7.0 Hz, H-8); ^{13}C NMR δ 85.50 (C-1), 52.91 (C-2'), 45.39 (C-3'), 38.74 (CH_3 of Ms), 32.33 (C-2), 31.66 (C-6), 29.18 (C-4 or C-5), 28.96 (C-4 or C-5), 24.82 (C-3), 22.56 (C-7), 14.01 (C-8); IR (film) 2925, 2855, 1464, 1357, 1174, 977, 931; HREIMS calcd for $C_{11}H_{22}O_4S$: 250.1239, found: 250.1260.

(1*S*)-1-[(2*S*)-2-Oxiranyl]octyl methanesulfonate (6a). The oily mesylate was prepared from (1*S*)-1-[(2*S*)-2-oxiranyl]-1-octanol according to the method described for **6**. $[\alpha]_D^{25}$ –9.43° (*c* = 1.1, $CHCl_3$); ^{1}H NMR δ 4.20 (1H, dt, *J* = 6.0, 8.0 Hz, H-1), 3.12 (1H, m, H-2'), 3.11 (3H, s, CH_3 of Ms), 2.90 (1H, t, *J* = 4.5 Hz, H-3'β), 2.68 (1H, dd, *J* = 4.5, 2.5 Hz, H-3'α), 1.85–1.66 (2H, m, H-2), 1.50–1.19 (10H, m, H-3~H-7), 0.85 (3H, t, *J* = 7.0 Hz, H-8); ^{13}C NMR δ 85.51 (C-1), 52.90 (C-2'), 45.37 (C-3'), 38.71 (CH_3 of Ms), 32.30 (C-2), 31.64 (C-6), 29.16 (C-4 or C-5), 28.94 (C-4 or C-5), 24.80 (C-3), 22.54 (C-7), 14.00 (C-8); IR (film) 2930, 2857, 1468, 1359, 1175, 978, 931.

(1*R*,2*R*)-1-Heptyl-2-hydroxy-5-(1,1,1-trimethylsilyl)-4-pentynyl methanesulfonate (7). To a solution of trimethylsilylacetylene (0.412 g, 4.19 mmol) in 18 mL of THF was added dropwise a solutionof *n*-butyllithium (2.0 M in cyclohexane, 2.1 mL, 4.2 mmol) at –78 °C under N_2 atmosphere. After stirring at –78 °C for 30 min, a solution of **6** (0.700 g, 2.80 mmol) in 5 mL of THF and 0.595 g boron trifluoride diethyl etherate were added successively and the resulting mixture was stirred at –78 °C for 30 min. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (4 mL) and the mixture allowed to warm up to rt. The product was extracted into ether and the organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated. After column chromatography on silica gel using 2:1 hexanes–EtOAc as the eluant, 0.504 g (52%) of **7** was obtained as an oil: $[\alpha]_D^{25}$ +1.5° (*c* = 1.3, $CHCl_3$); ^{1}H NMR δ 4.71 (1H, dt, *J* = 8.0, 5.5 Hz, H-1), 3.82 (1H, q, *J* = 6.0 Hz, H-2), 3.08 (3H, s, CH_3 of Ms), 2.50 (1H, dd, *J* = 17.0, 6.0 Hz, H-3), 2.47 (1H, dd, *J* = 17.0, 6.0 Hz, H-3), 2.08 (1H, br s, OH), 1.81–1.63 (2H, m, H-1'), 1.44–1.20 (10H, m, H-2'~H-6'), 0.85 (3H, t, *J* = 7.0 Hz, H-7'), 0.14 (9H, s, $SiMe_3$); ^{13}C NMR δ 101.26 (C-4), 88.87 (C-5), 84.67 (C-1), 70.21 (C-2), 38.61 (CH_3 of Ms), 31.69 (C-5'), 30.93 (C-1'), 29.18 (C-3' of C-4'), 29.02 (C-3' or C-4'), 25.30 (C-3), 24.97 (C-2'), 22.56 (C-6'), 14.02 (C-7'), –0.11 ($SiMe_3$); IR (film) 3519, 2959, 2926, 2858, 2177, 1352, 1250, 1171, 917, 841, 761.

(1*S*,2*S*)-1-Heptyl-2-hydroxy-5-(1,1,1-trimethylsilyl)-4-pentynyl methanesulfonate (7a). The title compound was prepared as an oil from (1*S*)-1-[(2*S*)-2-oxiranyl]octyl methanesulfonate according to the method described for **7**. $[\alpha]_D^{25}$ –1.4° (*c* = 1.4, $CHCl_3$); ^{1}H NMR δ 4.71 (1H, dt, *J* = 8.0, 5.5 Hz, H-1), 3.83 (1H, q, *J* = 6.0 Hz, H-2), 3.08 (3H, s, CH_3 of Ms), 2.52 (1H, dd, *J* = 17.0, 5.5 Hz, H-3), 2.49 (1H, dd, *J* = 17.0, 6.5 Hz, H-3), 1.81–1.63 (2H, m, H-1'), 1.44–1.20 (10H, m, H-2'~H-6'), 0.85 (3H, t, *J* = 7.0 Hz,

H-7'), 0.14 (9H, s, $SiMe_3$); ^{13}C NMR δ 101.24 (C-4), 88.90 (C-5), 84.67 (C-1), 70.22 (C-2), 38.63 (CH_3 of Ms), 31.71 (C-5'), 30.94 (C-1'), 29.20 (C-3' of C-4'), 29.04 (C-3' or C-4'), 25.32 (C-3), 24.98 (C-2'), 22.58 (C-6'), 14.03 (C-7'), –0.10 ($SiMe_3$); IR (film) 3515, 2957, 2927, 2858, 2177, 1346, 1250, 1172, 916, 844, 761.

(2*S*,3*R*)-2-Heptyl-3-(2-propynyl)oxirane (8). To a solution of **7** (0.272 g, 0.780 mmol) in 25 mL of methanol was added 0.56 g (4.1 mmol) of K_2CO_3 powder at 0 °C under N_2 atmosphere. After stirring at 0 °C for 30 min, the mixture allowed to stir at rt for 2 h. Saturated aqueous NH_4Cl (1 mL) was then added and the mixture was extracted with ether. The ethereal extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel using 20:1 hexanes–EtOAc as the eluant to provide 96 mg (68%) of **8** as an oil: $[\alpha]_D^{25}$ –53.8° (*c* = 1.1, $CHCl_3$); ^1H NMR δ 3.12 (1H, ddd, *J* = 7.0, 5.5, 4.0 Hz, H-3), 2.94 (1H, dt, *J* = 4.0, 6.0 Hz, H-2), 2.56 (1H, ddd, *J* = 17.0, 5.5, 2.5 Hz, H-1"), 2.26 (1H, ddd, *J* = 17.0, 7.0, 2.5 Hz, H-1''), 2.03 (1H, t, *J* = 2.5 Hz, H-3'), 1.54–1.22 (10H, m, H-2'~H-6'), 0.86 (3H, t, *J* = 7.0 Hz, H-7'); ^{13}C NMR δ 79.45 (C-2"), 70.29 (C-3"), 57.00 (C-2), 54.77 (C-3), 31.72 (C-5'), 29.40 (C-3' or C-4'), 29.16 (C-3' or C-4'), 27.51 (C-1'), 26.43 (C-2'), 22.60 (C-6'), 18.48 (C-1"), 14.06 (C-7'); IR (film) 3313, 2957, 2926, 2857, 2123, 1464, 1381, 1293, 1267, 817, 783; HREIMS calcd for $C_{12}H_{20}O$: 180.1509, found: 180.1517.

(2*R*,3*S*)-2-Heptyl-3-(2-propynyl)oxirane (8a). The title compound was prepared as an oil from (1*S*,2*S*)-1-heptyl-2-hydroxy-5-(1,1,1-trimethylsilyl)-4-pentynyl methanesulfonate according to the method described for **8**. $[\alpha]_D^{25}$ +53.9° (*c* = 1.2, $CHCl_3$); ^1H NMR δ 3.13 (1H, ddd, *J* = 7.0, 5.5, 4.5 Hz, H-3), 2.94 (1H, dt, *J* = 4.5, 6.0 Hz, H-2), 2.56 (1H, ddd, *J* = 17.0, 5.5, 2.5 Hz, H-1"), 2.26 (1H, ddd, *J* = 17.0, 7.0, 2.5 Hz, H-1''), 2.03 (1H, t, *J* = 2.5 Hz, H-3'), 1.54–1.22 (10H, m, H-2'~H-6'), 0.86 (3H, t, *J* = 7.0 Hz, H-7'); ^{13}C NMR δ 79.44 (C-2"), 70.29 (C-3"), 56.99 (C-2), 54.76 (C-3), 31.71 (C-5'), 29.40 (C-3' or C-4'), 29.15 (C-3' or C-4'), 27.51 (C-1'), 26.43 (C-2'), 22.59 (C-6'), 18.47 (C-1"), 14.06 (C-7'); IR (film) 3313, 2957, 2927, 2857, 2123, 1463, 1381, 1293, 1267, 817, 783.

(*R*)-5-Trimethylsilyl-1-penten-4-yn-3-ol (9). (*R*)-2-Methyl-CBS-oxazaborolidine (6.6 mL, 1.0 M solution in toluene) and borane–dimethyl sulfide (3.3 mL, 2M solution in THF) were introduced to 15 mL of THF at 0 °C under N_2 atmosphere. After 5 min, a solution of 5-trimethylsilyl-1-penten-4-yn-3-one (1.0 g, 6.6 mmol) in 7 mL of THF was added dropwise and the resulting solution was stirred at 0 °C for 15 min. The reaction was quenched by addition of methanol (15 mL) at 0 °C and the solution was stirred at rt for 15 min. The product was extracted into ether and the extract was washed with water and brine. After drying over $MgSO_4$ and solvent evaporation, the residue was chromatographed on a silica gel column using 8:1 hexanes–EtOAc as the eluant to give 0.66 g (65%) of (*R*)-5-trimethylsilyl-1-penten-4-yn-3-ol as an oil: $[\alpha]_D^{25}$ –21.1° (*c* = 1.2, $CHCl_3$); ^1H NMR δ 5.93 (1H, ddd, *J* = 17.0, 10.0, 5.0 Hz, H-2), 5.44 (1H, d, *J* = 17.0 Hz, H-1a), 5.20 (1H, d, *J* = 10.0 Hz, H-1b), 4.84

(1H, d, *J* = 5.0 Hz, H-3), 2.14 (1H, br s, OH), 0.15 (9H, s, $SiMe_3$); ^{13}C NMR δ 136.71 (C-2), 116.52 (C-1), 104.07 (C-4), 91.08 (C-5), 63.50 (C-3), –0.24 ($SiMe_3$); IR (film) 3334, 2962, 2174, 1642, 1407, 1251, 1115, 1024, 986, 930, 886, 848, 761, 700.

(*S*)-5-Trimethylsilyl-1-penten-4-yn-3-ol (9a). The title compound was prepared as an oil from 5-trimethylsilyl-1-penten-4-yn-3-one according to the method described for **9** with (*S*)-2-methyl-CBS-oxazaborolidine as the chiral ligand. $[\alpha]_D^{25}$ +20.7° (*c* = 1.2, $CHCl_3$); ^1H NMR δ 5.93 (1H, ddd, *J* = 17.5, 10.0, 5.5 Hz, H-2), 5.44 (1H, d, *J* = 17.5 Hz, H-1a), 5.19 (1H, d, *J* = 10.0 Hz, H-1b), 4.84 (1H, d, *J* = 5.5 Hz, H-3), 2.11 (1H, s, OH), 0.16 (9H, s, $SiMe_3$); ^{13}C NMR δ 136.68 (C-2), 116.54 (C-1), 104.06 (C-4), 91.10 (C-5), 63.49 (C-3), –0.24 ($SiMe_3$); IR (film) 3353, 2962, 2174, 1642, 1407, 1251, 1115, 1022, 987, 931, 886, 846, 761, 701.

(*R*)-MTPA ester of (*R*)-5-trimethylsilyl-1-penten-4-yn-3-ol. To a solution of (*R*)-5-trimethylsilyl-1-penten-4-yn-3-ol (30 mg, 0.19 mmol) in 6 mL of CH_2Cl_2 was added (*R*)-MTPA (90 mg, 0.38 mmol), dicyclohexylcarbodiimide (96 mg, 0.47 mmol), and 4-(dimethylamino)pyridine (12 mg) under N_2 atmosphere. The resulting mixture was stirred overnight and then treated with ice water. The (*R*)-MTPA ester was extracted into CH_2Cl_2 and the organic extract was washed with water and brine, dried over $MgSO_4$ and concentrated. After preparative silica gel TLC with 12:1 hexanes–EtOAc as the developing solvent, 48 mg (68%) of the ester was obtained as an oil: $[\alpha]_D^{25}$ +24.1° (*c* = 1.4, $CHCl_3$); ^1H NMR δ 7.52 (2H, m, H-2 and H-6 of Ph), 7.39 (3H, m, H-3, H-4, and H-5 of Ph), 6.03 (1H, d, *J* = 6.0 Hz, H-3), 5.92 (1H, ddd, *J* = 17.5, 10.0, 6.0 Hz, H-2), 5.59 (1H, d, *J* = 17.5 Hz, H-1a), 5.36 (1H, d, *J* = 10.0 Hz, H-1b), 3.54 (3H, s, OCH_3), 0.15 (9H, s, $SiMe_3$); ^{13}C NMR δ 165.29 (C=O), 131.99 (C-1 of Ph), 131.63 (C-2), 129.63 (C-4 of Ph), 128.34 (C-3 and C-5 of Ph), 127.45 (C-2 and C-6 of Ph), 123.16 (q, *J* = 288 Hz, CF_3), 120.45 (C-1), 98.56 (C-4), 93.62 (C-5), 84.69 (q, *J* = 27.8 Hz, *C*CF_3), 66.76 (C-3), 55.50 (OCH_3), –0.42 ($SiMe_3$); ^{19}F NMR δ –72.45; IR (film) 2960, 2182, 1755, 1452, 1252, 1171, 1123, 1018, 991, 846, 763, 720.

(*S*)-MTPA ester of (*R*)-5-trimethylsilyl-1-penten-4-yn-3-ol. The oily ester was prepared from (*R*)-5-trimethylsilyl-1-penten-4-yn-3-ol according to the method described for the (*R*)-MTPA ester of (*R*)-5-trimethylsilyl-1-penten-4-yn-3-ol with (*S*)-MTPA. $[\alpha]_D^{25}$ –19.9° (*c* = 1.6, $CHCl_3$); ^1H NMR δ 7.53 (2H, m, H-2 and H-6 of Ph), 7.38 (3H, m, H-3, H-4, and H-5 of Ph), 6.06 (1H, d, *J* = 5.5 Hz, H-3), 5.83 (1H, ddd, *J* = 17.0, 10.5, 5.5 Hz, H-2), 5.51 (1H, d, *J* = 17.0 Hz, H-1a), 5.31 (1H, d, *J* = 10.5 Hz, H-1b), 3.58 (3H, s, OCH_3), 0.17 (9H, s, $SiMe_3$); ^{13}C NMR δ 165.37 (C=O), 132.25 (C-1 of Ph), 131.49 (C-2), 129.65 (C-4 of Ph), 128.35 (C-3 and C-5 of Ph), 127.36 (C-2 and C-6 of Ph), 123.21 (q, *J* = 289 Hz, CF_3), 120.00 (C-1), 98.82 (C-4), 93.72 (C-5), 84.48 (q, *J* = 27.6 Hz, *C*CF_3), 66.39 (C-3), 55.46 (OCH_3), –0.41 ($SiMe_3$); ^{19}F NMR δ –72.16; IR (film) 2960, 2182, 1755, 1453, 1251, 1171, 1122, 1018, 992, 846, 762, 722.

(*R*)-5-Bromo-1-penten-4-yn-3-ol (10). To a solution of (*R*)-5-trimethylsilyl-1-penten-4-yn-3-ol (0.351g, 2.28 mmol) in 15 mL of acetone was added 0.486 g (2.73 mmol) of *N*-bromosuccinimide and 22 mg of silver nitrate and the reaction mixture was stirred overnight at rt in the dark. The mixture was treated with water at 0 °C and extracted with ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and concentrated to give 0.365 g of crude (*R*)-5-bromo-1-penten-4-yn-3-ol as an oil.

(*S*)-5-Bromo-1-penten-4-yn-3-ol (10a). The title compound was prepared as an oil from (*S*)-5-trimethylsilyl-1-penten-4-yn-3-ol according to the method described for **10**.

(3*R*,9*R*,10*S*)-Panaxydol (1). (*R*)-5-Bromo-1-penten-4-yn-3-ol (120 mg, 0.75 mmol) was added to a solution of **8** (56 mg, 0.31 mmol), copper(I) chloride (31 mg), and hydroxylamine hydrochloride (13 mg) in methanol (4 mL) and 70% ethylamine (0.9 mL) at 0 °C. After 1 h, the mixture was diluted with water and extracted with ether. The ethereal extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a silica gel column using 1:1 hexanes–EtOAc as the eluant to give 66 mg (81%) of oily (3*R*,9*R*,10*S*)-panaxytriol: $[\alpha]_D^{25}$ –103° (*c* = 2.6, $CHCl_3$); ^{1}H NMR δ 5.91 (1H, ddd, *J* = 17.0, 10.5, 5.5 Hz, H-2), 5.44 (1H, dd, *J* = 17.0, 1.0 Hz, H-1a), 5.22 (1H, d, *J* = 10.0 Hz, H-1b), 4.89 (1H, d, *J* = 5.0 Hz, H-3), 3.12 (1H, ddd, *J* = 7.0, 5.5, 4.0 Hz, H-9), 2.94 (1H, dt, *J* = 4.0, 6.0 Hz, H-10), 2.67 (1H, dd, *J* = 17.5, 5.5 Hz, H-8a), 2.36 (1H, dd, *J* = 17.5, 7.0 Hz, H-8b), 2.18 (1H, br s, OH) 1.50–1.20 (12H, m, H-11~H-16), 0.86 (3H, t, *J* = 7.0 Hz, H-17); ^{13}C NMR δ 136.01 (C-2), 117.09 (C-1), 76.66 (C-7), 74.92 (C-4), 70.79 (C-5), 66.26 (C-6), 63.41 (C-3), 56.97 (C-10), 54.30 (C-9), 31.70 (C-15), 29.37 (C-13 or C-14), 29.14 (C-13 or C-14), 27.46 (C-11), 26.42 (C-12), 22.59 (C-16), 19.40 (C-8), 14.05 (C-17); IR (film) 3411, 2954, 2927, 2856, 2236, 1674, 1464, 1380, 1274, 1023, 983; HREIMS calcd for $C_{17}H_{23}O_2$ (M^+–H): 259.1698, found: 259.1690.

(3*R*,9*S*,10*R*)-Panaxydol. The title compound was prepared as an oil from (2*R*,3*S*)-2-heptyl-3-(2-propynyl)oxirane and (*R*)-5-bromo-1-penten-4-yn-3-ol according to the method described for **1**. $[\alpha]_D^{25}$ +51.2° (*c* = 1.7, $CHCl_3$); ^{1}H NMR δ 5.92 (1H, ddd, *J* = 17.0, 10.0, 5.5 Hz, H-2), 5.44 (1H, d, *J* = 17.0 Hz, H-1a), 5.23 (1H, d, *J* = 10.0 Hz, H-1b), 4.89 (1H, br d, *J* = 3.5 Hz, H-3), 3.12 (1H, ddd, *J* = 7.5, 6.0, 4.0 Hz, H-9), 2.94 (1H, dt, *J* = 4.0, 6.0 Hz, H-10), 2.68 (1H, dd, *J* = 18.0, 5.5 Hz, H-8a), 2.36 (1H, ddd, *J* = 17.5, 7.5, 1.0 Hz, H-8b), 2.12 (1H, br s, OH) 1.53–1.20 (12H, m, H-11~H-16), 0.86 (3H, t, *J* = 7.0 Hz, H-17); ^{13}C NMR δ 136.01 (C-2), 117.12 (C-1), 76.69 (C-7), 74.91 (C-4), 70.81 (C-5), 66.26 (C-6), 63.43 (C-3), 56.97 (C-10), 54.29 (C-9), 31.71 (C-15), 29.38 (C-13 or C-14), 29.14 (C-13 or C-14), 27.47 (C-11), 26.43 (C-12), 22.60 (C-16), 19.42 (C-8), 14.05 (C-17); IR (film) 3418, 2959, 2927, 2856, 2260, 1645, 1464, 1381, 1289, 1021, 985.

(3*S*,9*R*,10*S*)-Panaxydol. The title compound was prepared as an oil from (2*S*,3*R*)-2-heptyl-3-(2-propynyl)oxirane and (*S*)-5-bromo-1-penten-4-yn-3-ol according to the method

described for **1**. $[\alpha]_D^{25}$ –57.7° (*c* = 1.6, $CHCl_3$); ^{1}H NMR δ 5.92 (1H, ddd, *J* = 17.0, 10.5, 5.5 Hz, H-2), 5.44 (1H, dd, *J* = 17.0, 1.5 Hz, H-1a), 5.22 (1H, dt, *J* = 10.0, 1.0 Hz, H-1b), 4.89 (1H, d, *J* = 5.0 Hz, H-3), 3.12 (1H, ddd, *J* = 7.0, 5.5, 4.0 Hz, H-9), 2.94 (1H, dt, *J* = 4.0, 6.0 Hz, H-10), 2.66 (1H, dd, *J* = 17.5, 5.0 Hz, H-8a), 2.36 (1H, ddd, *J* = 17.5, 7.5, 1.0 Hz, H-8b), 2.15 (1H, br s, OH) 1.53–1.20 (12H, m, H-11~H-16), 0.86 (3H, t, *J* = 7.0 Hz, H-17); ^{13}C NMR δ 136.00 (C-2), 117.10 (C-1), 76.67 (C-7), 74.92 (C-4), 70.79 (C-5), 66.25 (C-6), 63.42 (C-3), 56.97 (C-10), 54.29 (C-9), 31.70 (C-15), 29.37 (C-13 or C-14), 29.14 (C-13 or C-14), 27.46 (C-11), 26.42 (C-12), 22.59 (C-16), 19.40 (C-8), 14.05 (C-17); IR (film) 3407, 2954, 2927, 2857, 2237, 1673, 1463, 1381, 1276, 1023, 985.

(3*S*,9*S*,10*R*)-Panaxydol. The title compound was prepared as an oil from (2*R*,3*S*)-2-heptyl-3-(2-propynyl)oxirane and (*S*)-5-bromo-1-penten-4-yn-3-ol according to the method described for **1**. $[\alpha]_D^{25}$ +103° (*c* = 3.0, $CHCl_3$); ^{1}H NMR δ 5.91 (1H, ddd, *J* = 17.0, 10.5, 5.5 Hz, H-2), 5.44 (1H, dd, *J* = 17.0, 1.5 Hz, H-1a), 5.22 (1H, dt, *J* = 10.5, 1.0 Hz, H-1b), 4.89 (1H, d, *J* = 5.0 Hz, H-3), 3.12 (1H, ddd, *J* = 7.0, 5.5, 4.5 Hz, H-9), 2.94 (1H, dt, *J* = 4.5, 6.0 Hz, H-10), 2.67 (1H, dd, *J* = 18.0, 5.5 Hz, H-8a), 2.36 (1H, ddd, *J* = 18.0, 7.5, 1.0 Hz, H-8b), 2.24 (1H, br s, OH) 1.53–1.20 (12H, m, H-11~H-16), 0.86 (3H, t, *J* = 7.0 Hz, H-17); ^{13}C NMR δ 136.01 (C-2), 117.07 (C-1), 76.63 (C-7), 74.94 (C-4), 70.75 (C-5), 66.26 (C-6), 63.39 (C-3), 56.97 (C-10), 54.30 (C-9), 31.69 (C-15), 29.36 (C-13 or C-14), 29.13 (C-13 or C-14), 27.45 (C-11), 26.40 (C-12), 22.58 (C-16), 19.39 (C-8), 14.04 (C-17); IR (film) 3417, 2959, 2926, 2856, 2257, 1644, 1463, 1381, 1291, 1023, 986.

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