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Synthesis of A New Type of Antitumour Agent Panaxytriol:Synthesis of Its Four Diastereomers#

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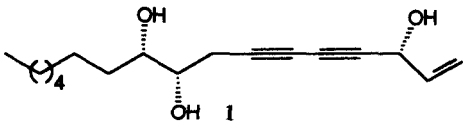
Abstract: Synthesis of four diastereomers of panaxytriol has been described. The basic objective is to create two acetylenic precursors followed by cuprous chloride mediated C-C bond coupling reaction.

Key words: Polyynes; panaxytriol; stereochemistry; asymmetric hydroxylation.

Introduction

The roots of Panax ginseng C.A. Meyer have been employed in Asia for many centuries, as an analeptic, stomachic, and erythropoietic agent [1]. The crude extract of panax ginseng forms part of a traditional oriental medicine in Japan and is presently available as a commercial medicinal formulation [2]. The many types of polyacetylenic compounds [3-5], including panaxytriol (**1**), present in the panax species, suppress the in vitro growth of cultured tumour cells.



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These compounds also exhibit strong neurotoxicity, antifungal activity and cytotoxic activity against leukemia cells (L-1210) in tissue cultures as well as against tumours [6-11]. Panaxytriol also suppressed the growth of B-16 melanoma transplanted into mice [12] and showed stimulative effect on the antitumour activity of mitomycin-C in cultured tumour cells [13]. A highly sensitive enzyme linked immunosorbent assay (ELISA) for panaxytriol was reported by Katano et al [14].

Panaxytriol (**1**) was isolated as a characteristic constituent of the red ginseng in 1983, and its plain structure was elucidated in 1987 [15,16]. In 1995, Kobayashi et al [17] proposed the absolute configuration of 1 to be 3R,9R,10R. The 3R configuration was determined by the modified Mosher's method while 9R and 10R stereocenters were established by CD analysis of the di-*p*-bromobenzoate derivative and the CD exciton chirality method. During the course of our investigations on the synthesis of panaxytriol, Fujimoto et al [18] revised the stereo-chemistry of **1** as 3R,9S,10S. Their interpretations were based on synthesis of panaxytriol derivatives starting from D (-)- and L (+)-diethyl tartrate followed by comparing optical rotations and NMR

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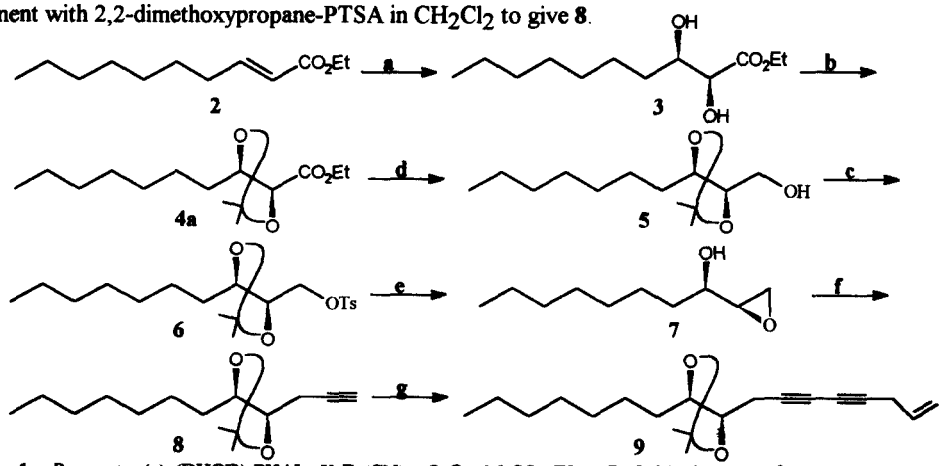
spectra with similar derivatives derived from the natural product. Recently, Kobayashi et al [19] reiterated their findings and reproposed 3R,9R,10R configuration for panaxytriol. They disputed Fujimoto's interpretation based on Hudson's rule. We realised that both the groups agreed upon the 3R configuration for **1** but provide evidence to propose opposite configurations for C-9 and C-10 centres. In this report, we disclose the synthesis of four diastereomeric structures of panaxytriol, compare their optical rotation values and NMR spectral data with those reported for the natural product.

Results and Discussion:

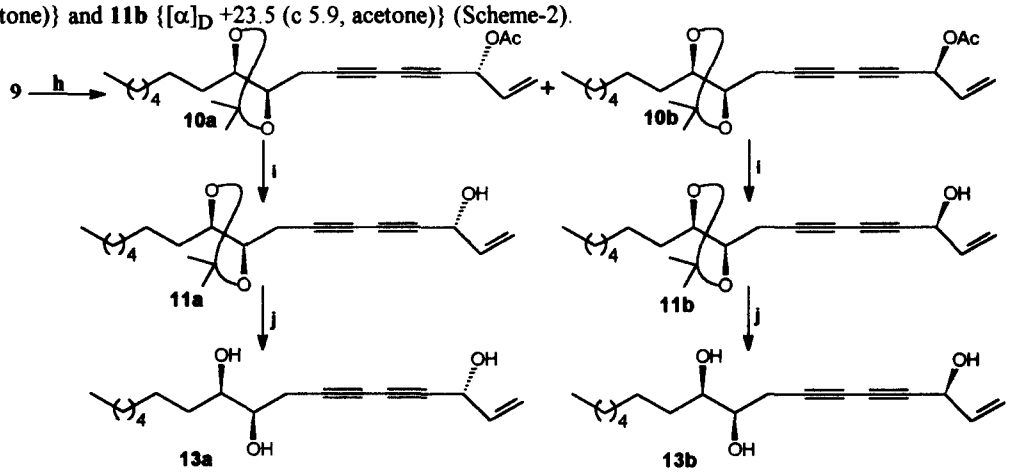
In the first instance we proposed to synthesise (3R,9R,10R)-panaxytriol. The Sharpless asymmetric dihydroxylation[20] of α,β-unsaturated esters using cinchona alkaloid dimers provides an excellent approach to *cis* diols with high enantiomeric excess. Application of this reaction to ethyl (E)-2-decenoate (**2**) using $(DHQD)_2PHAL$ as a chiral ligand at 0°C for 5h provided the corresponding ethyl (2S,3R)-2,3-dihydroxy decanoate (**3a**) (Scheme 1). Subsequent protection of the diol with 2,2-dimethoxypropane and catalytic PTSA gave the isopropylidene derivative **4a** in 92% yield. The conversion of the ester **4a** into alcohol **5** was effected with $LiAlH_4$ in THF at room temperature for 6h. Transformation of **5** into the corresponding tosylated derivative **6** was then executed using TsCl in pyridine. Displacement of the tosylate group in **6** with lithium acetylide ethylenediamine complex in the presence of HMPA in THF at 0°C - RT proved futile.

To overcome this problem, compound **6** was hydrolysed using aq. HCl in ethanol to give the corresponding diol which was consequently treated with potassium carbonate in ethanol to give the epoxide derivative **7**. Ring opening reaction of the epoxide with lithium acetylide ethylenediamine complex in THF at 0°C for 7 h gave (4R,5R)-1-dodecyne-4,5-diol, the free hydroxyl groups of which were protected as acetonide by treatment with 2,2-dimethoxypropane-PTSA in CH_2Cl_2 to give **8**.



Scheme 1. *Reagents*: (a) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, OsO_4, $MeSO_2NH_2$, *t*-BuOH-H_2O (1:1), 0°C, 5h, 70%; (b) $Me_2C(OMe)_2$, TsOH (cat), CH_2Cl_2, RT, 3h, 92%; (c) LAH, THF, 0°C-RT, 6h, 68%; (d) TsCl, Py, 0°C, 2h, 91%; (e) 1N HCl, EtOH, rt, 1h, then, K_2CO_3, RT, 61%; (f) (I) Li-acetylide complex, THF-HMPA, 0°C, 7h; (ii) $Me_2C(OMe)_2$, TsOH (cat), CH_2Cl_2, RT, 3h, 65% (two steps); (g) 1-Penten-4-yn-3-ol, Cu(I)Cl, O_2, TMEDA, MeCOMe, RT, 3h, 56%.

The ^{1}H NMR spectrum of **8** showed a characteristic triplet due to the acetylenic proton at δ 1.96. Compound **8** was coupled[21,22] with 1-penten-4-yn-3-ol[23] in the presence of Cu(I)Cl, TMEDA and oxygen in acetone to give a diastereomeric mixture of diacetylenes **9** in 56% yield. The diastereomeric mixture could not be separated by chromatography whereas separation of the acetates **10** (1:1 mixture) was accomplished by preparative HPLC on CHIRALCEL OD with 1.5% isopropanol in n-hexane as the mobile phase. The acetates **10a** and **10b** were then deacetylated using methanolic sodium methoxide to give **11a** {$[\alpha]_D$ +4.1 (c 4.1, sacetone)} and **11b** {$[\alpha]_D$ +23.5 (c 5.9, acetone)} (Scheme-2).



Scheme 2 *Reagents*: (h) (i) Ac_2O, Py, 0°C, 1h, 96%; (ii) HPLC separation; (I) NaOMe, MeOH, RT, 15min. 91%; (j) 1N HCl, MeOH, RT, 1h, 85%.

Mosher's ester method is a reliable technique to establish the absolute stereochemistry of secondary alcohols and therefore we decided to establish the stereochemistry at C-3 by using this method which is summarised in figure-I. Based on these findings, we propose 3R and 3S configurations for **11a** and **11b** respectively. Fujimoto *et al*[18] had described comparison studies of the ^{1}H NMR spectra of R(+)-MTPA esters of (3S,9S,10S)-panaxytriol acetonide and (3R,9S,10S)-panaxytriol acetonide with that of the R(+)-MTPA ester obtained from natural panaxytriol in order to assign the absolute configuration at C-3. We reasoned that the ^{1}H NMR spectral analysis of the S(-)-MTPA esters **12a** and **12b** of the antipodes (3R,9R,10R)-**11a** and (3S,9R,10R)-**11b** respectively on similar lines would be adequate for reconfirming the absolute stereochemistry at C-3 of our compounds.

For example, the ^{1}H NMR spectra of the (S)-MTPA esters **12a** (from **11a**) and **12b** (from **11b**) were analysed, wherein, the vinylic proton signals [δ 5.39, 5.59 (H1) and 5.91 (H2)] of **12a** appeared downfield compared to those values [δ 5.34, 5.52 (H1) and 5.82 (H2)] of **12b**. This was in agreement with Fujimoto's observations.

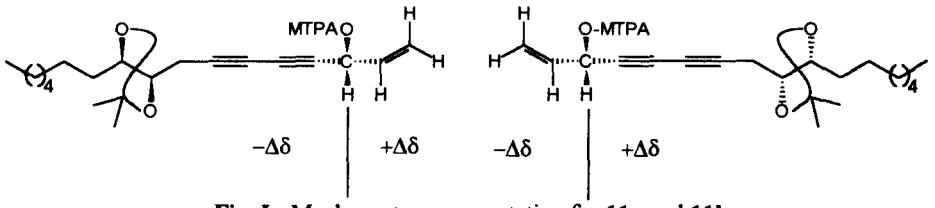
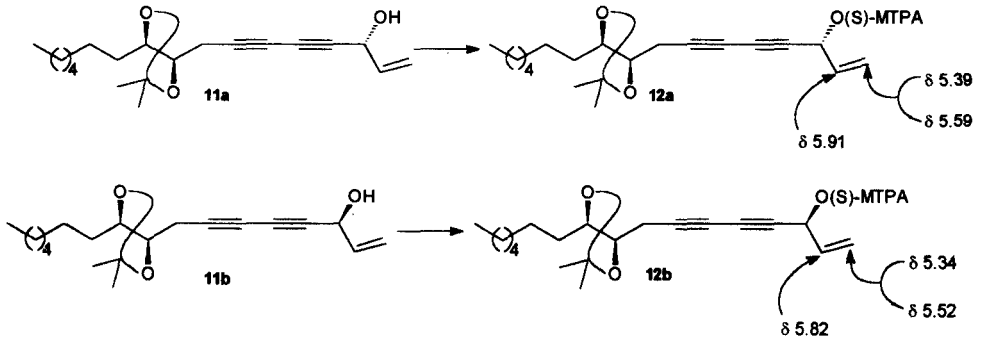
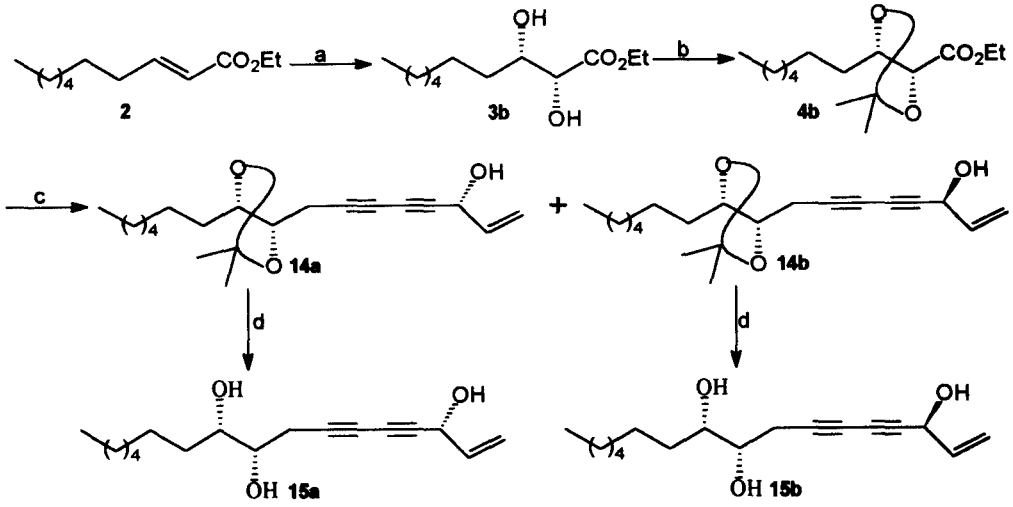


Fig. I : Mosher ester representation for **11a** and **11b**



The isopropylidine group was removed individually from (3R,9R,10R)-**11a** and (3S,9R,10R)-**11b** with aq. HCl in methanol to provide (3R,9R,10R)-**13a** {$[\alpha]_D$ -12.3 (c 0.75, $CHCl_3$)} and (3S,9R,10R)-**13b** {$[\alpha]_D$ +25.3 (c 3.9, $CHCl_3$)} respectively. The optical rotations for naturally occurring panaxytriol {$[\alpha]_D$ -25.4 (c 1.54, $CHCl_3$)} and its acetonide derivative {$[\alpha]_D$ -22.5 (c 1.2, acetone)} do not correlate with (3R,9R,10R)-**13a** and (3R,9R,10R)-**11a**. On the otherhand, the diastereomeric panaxytriol (3S,9R,10R)-**13b** and its acetonide derivative (3S,9R,10R)-**11b** showed comparable rotations with the corresponding naturally occurring derivatives, however, with opposite sign.

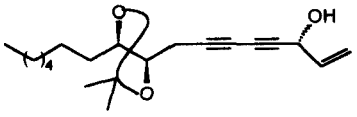
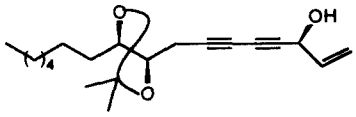
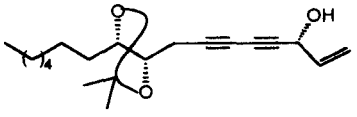
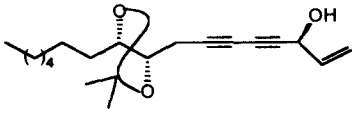
Further, we also synthesised the (3R,9S,10S)- and (3S,9S,10S)-panaxytriol diastereomers (Scheme 3) by a similar approach. For example the Sharpless asymmetric dihydroxylation of ethyl-(E)-2-decenoate (**2**) with $(DHQ)_2PHAL$ as the chiral ligand followed by the same sequence of reactions reported earlier provided the acetonide derivatives (3R,9S,10S)- **14a** {$[\alpha]_D$ -28 (c 0.49, acetone)} and (3S,9S,10S)- **14b** {$[\alpha]_D$ -3.9 (c 0.61, acetone)}. The ^1H NMR spectral data of **14a** was in complete agreement with the data reported [17,19] for the authentic acetonide derivative derived from naturally occurring panaxytriol. Separate cleavage of the isopropylidine group in **14a** and **14b** with aq. HCl in methanol gave (3R,9S,10S)-**15a** {$[\alpha]_D$ -25.5^0 (c 0.98, $CHCl_3$)} and (3S,9S,10S)-**15b** {$[\alpha]_D$ +18.7^0 (c 0.21, $CHCl_3$)}.



Scheme 3. *Reagents*: (a) $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, OsO_4, $MeSO_2NH_2$, *t*-BuOH-H_2O (1:1), 0°C, 5h, 70%; (b) $Me_2C(OMe)_2$, TsOH (cat), CH_2Cl_2, RT, 3h, 92%; (c) refer scheme 1 reagents (c) to (g) and scheme 2 reagents (h) and (I) (d) 1N HCl, MeOH, RT, 1h, 85%.

The optical rotation values of the synthetic panaxytriol acetonide derivatives are given in table-I.

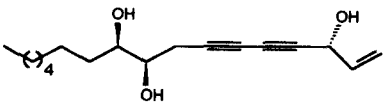
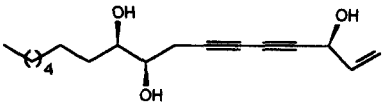
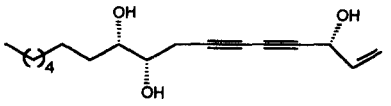
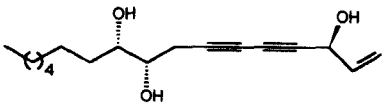
Table-I

Cpd. No.	Structure	Configuration	$[\alpha]_D$ (in acetone)	$[\alpha]_D$ of natural derivative
11a		**3R,9R,10R**	**+4.1** (c 4.14)	**-22.5** (c 1.2)
11b		**3S,9R,10R**	**+23.4** (c 5.86)	
14a		**3R,9S,10S**	**-28** (c 0.73)	
14b		**3S,9S,10S**	**-3.9** (c 0.61)	

It is conspicuous from the above values, that the optical rotations of synthetic (3R,9R,10R) and (3S,9S,10S)- acetonide derivatives (**11a** and **14b**)do not correlate with the reported value. While the synthetic (3R,9S,10S)- and (3S,9R,10R)-acetonide derivatives (**14a** and **11b**) have comparable optical rotations with that

reported for the acetonide derivative of the natural product. The optical rotation values of the synthetic panaxytriol isomers are tabulated below (Table-II).

Table-II

Cpd. No.	Structure	Configuration	$[\alpha]_D$ (in $CHCl_3$)	$[\alpha]_D$ of natural derivative
13a		**3R,9R,10R**	**-12.3** (c 0.75)	**-25.4** (c 1.54)
13b		**3S,9R,10R**	**+25.3** (c 3.88)	
15a		**3R,9S,10S**	**-25.5** (c 0.98)	
15b		**3S,9S,10S**	**+18** (c 0.21)	

Conclusions:

Based on the correlation of optical rotation and ^1H NMR spectral data of **14a** and **15a** with the natural product and its acetonide derivative, we propose that naturally occurring panaxytriol has 3R,9S,10S configuration.

While the manuscript was under preparation, Lu et al. reported [24, 25] the absolute configuration of the natural product to be 3R,9R,10R based on the correlation of the optical rotation of the synthetic derivative with that of the natural product. We feel that it could be erroneous in comparing the optical rotations of the synthetic diastereomeric derivatives of the natural product, because the optical rotation of the natural product itself has been reported to have varying values ranging from -18 to –25.4.

Experimental: General Remarks

All non-aqueous reactions were performed under an atmosphere of dry nitrogen. Proton magnetic resonance spectra were recorded on Varian FT-200 MHz (Gemini) and Varian Unity-400 MHz spectrometers in chloroform-d_1 using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on the same spectrometer at 50 MHz in chloroform-d_1. Chemical shifts have been expressed in ppm units downfield from TMS. Mass spectra were recorded on a CEC-21-110B, Finnigan Mat 1210 or MICROMASS 7070 spectrometers at 70 eV using a direct inlet system. HRMS were recorded on a VG AUTOSPEC M at 70 eV using a direct inlet system in electron impact (EI) or fast atom bombardment (FAB) mode. Optical rotations were measured using a JASCO DIP 370 digital polarimeter with specific rotations determined at 25°C. Chromatography refers to flash column chromatography and was carried out using silica gel (60-120 mesh) as the stationary phase.

Light petroleum refers to the fraction which distils between 40°C and 60°C and THF refers to tetrahydrofuran. All solvents were dried and distilled, using standard literature procedures, before use. All reactions were monitored by thin layer chromatography and was performed on 0.25 mm E. Merck silica gel plates (60F-254) and visualised by UV light or anisaldehyde-sulphuric acid spray.

Ethyl (4S,5R)-5-hexyl-2,2-dimethyl-1,3-dioxolane (4a):

To a solution of $(DHQD)_2PHAL$ ligand (0.15 g, 0.2 mmol), potassium ferricyanide (19.0 g, 57.6 mmol), potassium carbonate (8.1 g, 57.6 mmol) and OsO_4 in a 1:1 mixture of $tBuOH:H_2O$ (200 ml) was added methanesulfonamide (1.8 g, 19.2 mmol) at room temperature. The mixture was stirred at room temperature for 10 min., cooled to 0° C and ethyl (E)-2-decenoate (**2**) (3.8 g, 19.2 mmol) was added in one portion and the reaction mixture was stirred vigorously at 0° C for 5h. Sodium sulphite (29 g) was then added and after 45 min. at room temperature, it was extracted with ethyl acetate, washed with 2N KOH solution, water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate-light petroleum (1:1.5) to give **3a** (3.12 g, 70%) as a thick syrup; $[\alpha]_D$ +10.1 (c 1.42, $CHCl_3$); ^1H NMR ($CDCl_3$): 0.86 (t, 3H, J=7.0 Hz), 1.18-1.44 (m, 13H), 1.54 (m, 2H), 2.36 (brs, 1H), 3.36 (brs, 1H), 3.8 (m, 1H), 4.0 (m, 1H), 4.26 (q, 2H, J=7.0 Hz); HRMS : Calcd. 159.1385; Found: 159.1383 (M^+-CO_2Et).

Compound **3a** (2.4 g, 10.3 mmol), 2,2-dimethoxypropane (2 ml, 15.5 mmol) and PTSA (catalytic) in CH_2Cl_2 were stirred at room temperature for 3h. The reaction was neutralised with triethylamine, concentrated and purified by silica gel chromatography with ethyl acetate-light petroleum (1:19) as eluent to yield **4a** (2.5 g, 92%) as an oil; $[\alpha]_D$ +13.5 (c 5.04, $CHCl_3$); ^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.24-1.48 (m, 19H), 1.68 (m, 2H), 4.06 (m, 2H), 4.22 (q, 2H, J=7.0 Hz); Mass : 257 (M^+-15).

(4R,5R)-5-Heptyl-2,2-dimethyl-1,3-dioxolan-4-yl methanol (5):

To a suspension of LAH (0.5 g, 13.0 mmol) in dry THF (10 ml) was added a solution of compound **4a** (2.4 g, 8.8 mmol) in dry THF (20 ml) at 0°C. The reaction mixture was stirred at room temperature for 6h. The reaction was quenched with a saturated solution of sodium sulphate, filtered, washed with ethyl acetate and the combined organics were concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum (1:9) as the eluent to afford **5** (1.38 g, 68%) as a syrup; $[\alpha]_D$ +21.1 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.2-1.6 (m, 12H), 1.40 (s, 6H), 1.88 (bt, 1H, J=7.0 Hz), 3.5-3.9 (m, 4H); HRMS: Calcd. 215.1647; Found: 215.1646 (M^+-15).

(4R,5R)-5-Heptyl-2,2-dimethyl-1,3-dioxolan-4-yl-methyl-4-methyl-1-benzenesulfonate (6):

A solution of compound **5** (1.3 g, 5.6 mmol), pyridine (1.8 ml, 22.6 mmol) and DMAP (10 mg) in CH_2Cl_2 (15 ml) was cooled to 0° C and PTS-Cl (1.4 g, 7.35 mmol) was added. After 2h, the reaction mixture was washed with 2% HCl, water, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography with ethyl acetate-light petroleum (1:20) as eluent to give **6** (1.97 g, 91%) as a colourless oil; $[\alpha]_D$ +9.15 (c 1.95, $CHCl_3$); ^1H NMR ($CDCl_3$): 0.9 (t, 3 , J=7.5 Hz), 1.2-1.65 (m, 18H), 2.47 (s, 3H), 3.74 (m, 2H), 4.06 (m, 2H), 7.35 (d, 2H, J=8.0 Hz), 7.8 (d, 2H, J=8.0 Hz); Mass : 370 (M^+-15).

1-[(2R)-Oxiran-2-yl]-(1R)-octan-1-ol (7):

The above product **6** (1.8 g, 4.7 mmol) and 1N HCl (0.5 ml) in ethanol (10 ml) was stirred at room temperature for 1h and neutralised with potassium carbonate. More potassium carbonate was then added to the reaction mixture and the pH adjusted to around 8-9. The reaction mixture was vigorously stirred at room temperature for 8h. Ethanol was removed, the residue extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography with ethyl acetate-light petroleum (1:1.5) as eluent to give **7** (0.49 g, 61%) as an oil; $[\alpha]_D$ -5.6 (c 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$): 0.9 (t, 3H, J=7.0 Hz), 1.2-1.7 (m, 12H), 1.75 (d, 1H, J=6.0 Hz), 2.7 (dd, 1H, J=3.0 Hz, 4.5 Hz), 2.8 (dd, 1H, J=4.5 Hz), 2.95 (m, 1H), 3.42 (m, 1H); ^{13}C NMR ($CDCl_3$): 13.98, 22.54, 25.22, 29.10, 29.47, 31.69, 34.18, 45.13, 55.50, 71.75; Mass : 172 (M^+).

(4R,5R)-4-Heptyl-2,2-dimethyl-5-(2-propynyl)-1,3-dioxolane (8):

To a solution of lithiumacetylide-ethylenediamine complex (1.7 g, 18.8 mmol) in dry THF (10 ml) and dry HMPA (0.8 ml), compound **7** (1.1 g, 6.3 mmol) in THF (5 ml) was added. The reaction mixture was stirred at 0°C for 7 h, quenched with a saturated solution of ammonium chloride and concentrated. The residue was

extracted with ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue (0.86 g), 2,2-dimethoxypropane (1 ml) and PTSA (10 mg) in CH_2Cl_2 (10 ml) was stirred at room temperature. After 3 h the reaction mixture was neutralised with triethylamine, concentrated and purified by silica gel chromatography with ethyl acetate-light petroleum (1:20) as eluent to yield **8** (0.98 g, 65%) as a thick syrup; $[\alpha]_D$ +12.5 (c 2.97, $CHCl_3$); ^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.22-1.64 (m, 12H), 1.38 (s, 6H), 1.96 (t, 1H, J=3.0 Hz), 2.46 (m, 2H), 3.6-3.9 (m, 2H); ^{13}C NMR ($CDCl_3$): 14.18, 22.72, 22.82, 26.09, 27.20, 27.55, 29.26, 29.71, 31.89, 33.23, 70.62, 78.36, 79.83, 80.62, 108.33; HRMS: Calcd. 223.1698; Found: 223.1696 (M^+-15).

(4R,5R)-6-[5-Heptyl-2,2-dimethyl-1,3-dioxolan-4-yl]-1-vinyl-2,4-hexadiynyl alcohol (9):

To a solution of copper (I) chloride (0.05 g, 0.5 mmol), TMEDA (0.2 ml, 1.3 mmol) in acetone (5 ml), a mixture of 1-penten-4-yn-3-ol (1.0 g, 12 mmol) and compound **8** (0.48 g, 2 mmol) in dry acetone (10 ml) were added dropwise. Oxygen gas was bubbled through the reaction mixture for 3h and quenched by adding a saturated solution of NH_4Cl. The reaction mixture was extracted with ethyl acetate and filtered. The filtrate was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography with ethyl acetate - light petroleum (1:10) as eluent to afford **9** (0.36 g, 56%) as a colourless oil; ^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.2-1.7 (m, 12H), 1.40 (s, 6H), 1.85 (brs, 1H), 2.57 (m, 2H), 3.6-3.85 (m, 2H), 4.87 (dd, 1H, J=5.0, 7.0 Hz), 5.23 (d, 1H, J=10.0 Hz), 5.45 (d, 1H, J=17.0 Hz), 5.94 (ddd, 1H, J=17.0, 10.0, 5.0 Hz); Mass : 303 (M^+-15).

(4R,5R)-6-[5-Heptyl-2,2-dimethyl-1,3-dioxolan-4-yl]-1-vinyl-hexadiynyl acetate (10):

A solution of compound **9** (0.32 g, 1.0 mmol), acetic anhydride (0.36 ml, 2.4 mmol), pyridine (0.36 ml) in CH_2Cl_2 (2 ml) was stirred at 0°C for 1h. After usual work up, the residue was purified by silica gel chromatography with ethyl acetate-light petroleum (1:50) as eluent to give **10** (0.35 g, 96%) as an oil; ^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.20-1.62 (m, 12H), 1.40 (s, 6H), 2.08 (s, 3H), 2.58 (d, 2H, J=5.0 Hz), 3.6-3.82 (m, 2H), 5.32 (d, 1H, J=10.0 Hz), 5.52 (d, 1H, J=16.0 Hz), 5.70-5.92 (m, 2H); HRMS: Calcd. 360.2300; Found: 360.2312 (M^+).

Panaxytriol acetonide (11a):

A solution of compound **10a** (30 mg, 0.080 mmol) and 1M methanolic sodium methoxide (0.1 ml) in MeOH (1 ml) were stirred at room temperature for 30 min and quenched by adding solid carbon dioxide and concentrated. The residue was purified by silica gel chromatography with ethyl acetate-light petroleum (1:10) as eluent to give **11a** (20 mg, 91%) as a colourless oil; $[\alpha]_D$ +4.1 (c 4.1, acetone); ^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz),

1.2-1.60 (m, 12H), 1.38 (s, 6H), 2.57 (m, 2H), 3.6-3.80 (m, 2H), 4.85 (brs, 1H), 5.23 (d, 1H, J=10.0 Hz), 5.45 (d, 1H, J=17.5 Hz), 5.94 (ddd, 1H, J=17.5, 10.0, 5.0 Hz); HRMS: Calcd. 303.1960; Found: 303.1968 (M^+-15).

Panaxytriol acetonide (11b):

Compound **10b** (30 mg) was subjected to deacetylation as described above to give **11b** (20 mg, 91%) as a colourless oil; $[\alpha]_D$ +23.5 (c 5.9, acetone); ^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.26-1.60 (m, 12H), 1.40 (s, 6H), 2.58 (d, 2H, J=5.0 Hz), 3.62-3.80 (m, 2H), 4.88 (brs, 1H), 5.26 (d, 1H, J=10.0 Hz), 5.45 (d, 1H, J=17.2 Hz), 5.93 (ddd, 1H, J=17.2, 10.0, 5.0 Hz); ^{13}C NMR ($CDCl_3$): 14.09, 22.63, 23.53, 25.95, 27.02, 27.39, 29.14, 29.62, 31.78, 32.87, 63.48, 66.41, 70.89, 74.59, 77.21, 78.07, 80.41, 108.70, 117.14, 136.02 ; HRMS: Calcd. 303.1960; Found: 303.1968 (M^+-15).

3-O-S-(-)-MTPA ester (12a):

A solution of **11a** (5 mg, 0.0157 mmol) in dry CH_2Cl_2 (1 ml) was treated with S-(-)-MTPA (14.7 mg, 0.063 mmol) and the mixture was stirred at room temperature for 20h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. Purification of the product by silica gel column chromatography with ethyl acetate - light petroleum (1:10) as eluent afforded the 3-O-S-(-)-MTPA ester **12a** (6.8 mg) as a colourless glassy oil.

^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.22-1.29 (m, 10H), 1.34 (s, 6H), 1.51 (m, 2H), 2.57 (d, 2H, J=5.1 Hz), 3.52 (s, 3H), 3.68 (m, 2H), 5.39 (d, 1H, J=10.2 Hz), 5.59 (d, 1H, J=17.0 Hz), 5.91 (ddd, 1H, J=5.4, 10.2, 17.0 Hz), 6.07 (d, 1H, J=5.7 Hz), 7.41 (m, 3H), 7.50 (m, 2H).

The 3-O-R(+)-MTPA ester of **11a** was prepared from **11a** (5 mg) and R-(+)-MTPA (14.7 mg) through the same procedure as described above.

^1H NMR ($CDCl_3$): 0.88 (t, 3H, J=6.8 Hz), 1.20-1.34 (m, 10H), 1.39 (s, 6H), 1.54 (m, 2H), 2.58 (d, 2H, J=5.0 Hz), 3.59 (s, 3H), 3.68 (m, 2H), 5.34 (d, 1H, J=10.2 Hz), 5.52 (d, 1H, J=17.0 Hz), 5.82 (ddd, 1H, J=5.5, 10.2, 17.0 Hz), 6.1 (d, 1H, J=5.7 Hz), 7.41 (m, 3H), 7.5 (m, 2H).

3-O-S(-)-MTPA ester (12b):

A solution of **11b** (10 mg, 0.0314 mmol) in dry CH_2Cl_2 (1 ml) was treated with S-(-)-MTPA (22 mg, 0.094 mmol), DCC (23 mg, 0.111 mmol) and DMAP (5 mg) and the reaction mixture was stirred at room temperature for 20h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. Purification of the product by silica gel chromatography with ethyl acetate - light petroleum (1:10) as eluent afforded the 3-O-S-(-)-MTPA ester **12b** (13.5 mg) as a colourless glassy oil.

^{1}H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.23-1.35 (m, 10H), 1.39 (s, 6H), 1.57 (m, 2H), 2.60 (d, 2H, J=5.0 Hz), 3.60 (s, 3H), 3.75 (m, 2H), 5.34 (d, 1H, J=10.5 Hz), 5.52 (d, 1H, J=17.0 Hz), 5.82 (ddd. 1H, J=5.6, 10.5, 17.0 Hz), 6.1 (d, 1H, J=6.0 Hz), 7.43 (m, 3H), 7.52 (m, 2H).

The 3-O-R-(+)-MTPA ester of **11b** was prepared from **11b** (10 mg) and R-(+)-MTPA (22 mg) through the same procedure as described above.

^{1}H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.24-1.34 (m, 10H), 1.40 (s, 6H), 1.55 (m, 2H), 2.58 (d, 2H, J=5.0 Hz), 3.54 (s, 3H), 3.68 (m, 2H), 5.40 (d, 1H, J=9.5 Hz), 5.60 (d, 1H, J=16.7 Hz), 5.90 (ddd, 1H, J=5.4, 10.4, 16.8 Hz), 6.06 (d, 1H, J=6.0 Hz), 7.39 (m, 3H), 7.49 (m, 2H).

(3R,9R,10R)-Panaxytriol (13a):

Compound **11a** (0.02 g, 0.063 mmol) and 1N HCl (0.1 ml) in methanol (2 ml) was stirred at room temperature for 1h, neutralised with triethylamine and concentrated. The residue was purified by silica gel chromatography with ethyl acetate-light petroleum (1:2.5) as eluent to afford **13a** (0.015 g, 85%) as a colourless glassy solid.

$[\alpha]_D$ -12.2 (c 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 0.88 (t, 3H, J=7.0 Hz), 1.2-1.75 (m, 12H), 2.04 (brs, 1H), 2.38 (brs, 1H), 2.62 (d, 2H, J=6.0 Hz), 3.64 (m, 2H), 4.94 (brd, 1H, J=5.5 Hz), 5.28 (d, 1H, J=10.0 Hz), 5.40 (d, 1H, J=17.0 Hz), 5.98 (ddd, 1H, J=17.0, 10.0, 5.5 Hz); ^{13}C NMR ($CDCl_3$): 14.07, 22.62, 24.93, 25.54, 29.19, 29.50, 31.77, 33.53, 63.45, 66.46, 70.87, 72.10, 73.05, 74.69, 78.09, 117.18, 135.96; HRMS: Calcd. 279.1960; Found: 279.1966 (M^++1).

(3S,9R,10R)-1-Heptadecen-4,6-diyne-3,9,10-triol [(3S,9R,10R)-Panaxytriol] (13b):

Compound **11b** (20 mg, 0.063 mmol) and 1N HCl (0.1 ml) in methanol (2 ml) was stirred at room temperature for 1h, neutrlised with triethylamine and concentrated. The residue was purified by silica gel chromatography with ethyl acetate-light petroleum (1:2.5) as eluent to afford **13b** (17 mg) as a colourless glassy solid; $[\alpha]_D$ +25.3 (c 3.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 0.89 (t, 3H, J=7.0 Hz), 1.18-1.60 (m, 12H), 2.04 (brs, 1H), 2.34 (brs, 1H), 2.61 (d, 2H, J=6.0 Hz), 3.62 (m, 2H), 4.94 (brd, 1H, J=5.5 Hz), 5.26 (d, 1H, J=10.0 Hz), 5.48 (d, 1H, J=17.5 Hz), 5.96 (ddd, 1H, J=17.5, 10.0, 5.5 Hz); ^{13}C NMR ($CDCl_3$): 14.05, 22.61, 24.97, 25.54, 29.18, 29.51, 31.77, 33.57, 63.47, 66.49, 70.88, 72.10, 73.06, 74.74, 78.10, 117.12, 136.02; HRMS: Calcd. 279.1960; Found: 279.1966 (M^++1).

Data for the synthesis of (3R,9S,10S) and (3S,9S,10S)-panaxytriol

Ethyl (4R,5S)-5-hexyl-2,2-dimethyl-1,3-dioxolane (4b):

To a solution of $(DHQ)_2PHAL$ ligand (0.15 g, 0.2 mmol), potassium ferricyanide (19.0 g, 57.6 mmol), potassium carbonate (8.1 g, 57.6 mmol) and OsO_4 in a 1:1 mixture of tBuOH:H_2O (200 ml) was added methanesulfonamide (1.8 g, 19.2 mmol) at room temperature. The mixture was stirred at room temperature for 10 min., cooled to 0°C and ethyl (E)-2-decenoate (**2**) (3.8 g, 19.2 mmol) was added in one portion and the reaction mixture was stirred vigorously at 0°C for 5h. Sodium sulphite (29 g) was then added and after 45 min. at room temperature, it was extracted with ethyl acetate, washed with 2N KOH solution, water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate-light petroleum (1:1.5) to give **3b** (3.12 g, 70%) as a thick syrup; $[\alpha]_D$ -9.9 (c 1.46, $CHCl_3$).

Compound **3b** (2.4 g, 10.3 mmol), 2,2-dimethoxypropane (2 ml, 15.5 mmol) and PTSA (catalytic) in CH_2Cl_2 were stirred at room temperature for 3h. The reaction was neutralised with triethylamine, concentrated and purified by silica gel chromatography with ethyl acetate-light petroleum (1:19) as eluent to yield **4b** (2.5 g, 92%) as an oil; $[\alpha]_D$ -13.5 (c 5.04, $CHCl_3$).

(4S,5S)-5-Heptyl-2,2-dimethyl-1,3-dioxolan-4-yl methanol :

$[\alpha]_D$ -19.6 (c 1.59, $CHCl_3$).

(4S,5S)-5-Heptyl-2,2-dimethyl-1,3-dioxolan-4-yl-methyl-4-methyl-1-benzenesulfonate :

$[\alpha]_D$ -9.4 (c 1.95, $CHCl_3$).

1-[(2S)-Oxiran-2-yl]-(1S)-octan-1-ol :

$[\alpha]_D$ +3.9 (c 1.42, $CHCl_3$).

(4S,5S)-4-Heptyl-2,2-dimethyl-5-(2-propynyl)-1,3-dioxolane :

$[\alpha]_D$ -15.1 (c 2.97, $CHCl_3$).

Panaxytriol acetonide (14a):

$[\alpha]_D$ -28 (c 0.73, acetone).

Panaxytriol acetonide (14b):

$[\alpha]_D$ -3.9 (c 0.61, acetone).

(3R,9S,10S)-1-Heptadecen-4,6-diyne-3,9,10-triol[(3S,9R,10R)-Panaxytriol] (15a):

$[\alpha]_D$ -25.5 (c 0.98, $CHCl_3$).

(3S,9S,10S)-Panaxytriol (15b):

$[\alpha]_D$ +18.7 (c 0.21, $CHCl_3$).

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