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The Absolute Stereostructures of the Polyacetylenic Constituents of Ginseng Radix Rubra

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Abstract : The absolute stereostructures of panaxytriol (**1**) and panaxydol (**2**), two polyacetylenic constituents of the oriental medicine, Ginseng Radix Rubra, were determined by applying the modified Mosher method, CD exciton chirality method, and chemical conversion to be expressed 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. Panaxytriol (**1**), the characteristic constituent of Ginseng Radix Rubra, was presumed to be formed from panaxydol (**2**), during the processing of the crude drug, *via* a regioselective hydrolysis of the epoxy moiety in **2**.
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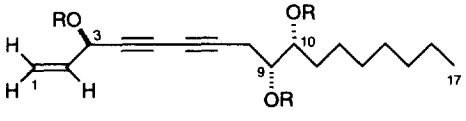
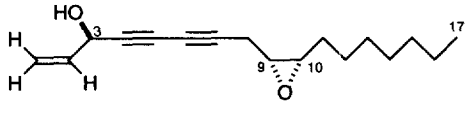
Ginseng Radix Rubra (Red Ginseng) is a processed ginseng root (*Panax ginseng* C.A., MEYER, Araliaceae), which is used distinguishably and for different purposes from the white ginseng in oriental medicinal practices.[2] The biologically active constituents of these ginsengs have been pursued extensively and, recently, some of the constituents have received attention as a potential new type of antitumor agent.[3] During our comparison studies on the chemical constituents of the white and red ginsengs, we isolated a polyacetylenic alcohol, panaxytriol (**1**), as one of the characteristic constituents of the red ginseng and its plane structure was elucidated,[4] while its related compounds, panaxydol (**2**) and panaxynol (**3**), were found in both ginsengs. Furthermore, panaxytriol (**1**) was presumed to be formed during the processing of the crude drug from its epoxidal analogue, panaxydol (**2**). In continuation of our chemical studies on the constituents of Ginseng Radix Rubra, we investigated the absolute stereostructures of panaxytriol (**1**)[5] and panaxydol (**2**), as well as their metabolic pathways.

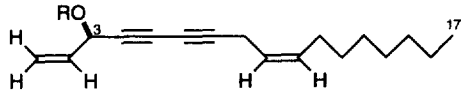


panaxytriol (**1**) : R= H

5 : R= *S*-(-)-MTPA [**6** : R= *R*-(+)-MTPA]

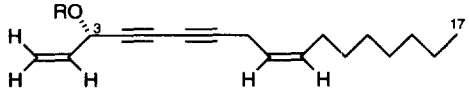


panaxydol (**2**)



panaxynol (**3**) : R= H

7 : R= *p*-Br-Bz



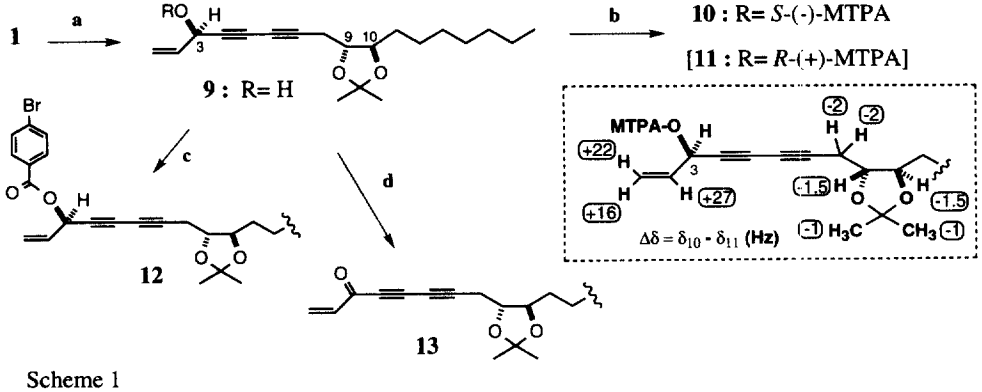
falcarinol (**4**) : R= H

8 : R= *p*-Br-Bz

The methanol extract of Ginseng Radix Rubra (6 years old) was partitioned into an Et_2O:MeOH:H_2O (3:1:2) mixture to give an Et_2O-soluble portion and a water-soluble portion. The Et_2O-soluble portion was further partitioned into an *n*-hexane-90% aq. MeOH mixture to provide an *n*-hexane-soluble portion (9.75 g) and a methanol-soluble portion (13.2 g). The methanol-soluble portion was then subjected to silica gel column chromatography, reversed-phase silica gel column chromatography, Sephadex LH-20 column chromatography, and reversed-phase HPLC to isolate panaxytriol (**1**, 0.039 % from Ginseng Radix Rubra), panaxydol (**2**, 0.002 %), and panaxynol (**3**, 0.018 %).

Since panaxytriol (**1**) was presumed to be produced from the hydrolysis to the epoxy moiety in panaxydol (**2**), it is possible that **1** consists of an epimeric mixture at the C-9 and C-10 positions. Therefore, in order to confirm the diastereomeric purity of panaxytriol (**1**), both the 3,9,10-*O*-tri-*S*-MTPA ester (**5**) and the 3,9,10-*O*-tri-*R*-MTPA ester (**6**) of **1** were prepared and the purities of these compounds were analyzed by ^{1}H-NMR. Thus, the clear distinctive ^{1}H-NMR spectra of both compounds suggested that panaxytriol (**1**) is a single and optically pure compound.

In order to determine the absolute configuration at C-3 of panaxytriol (**1**), both the 3-*O*-*R*- and 3-*O*-*S*-MTPA esters (**10** and **11**) of **1** were first prepared from the 9,10-acetonide derivative **9**. Detailed examination of the proton NMR spectra of **10** and **11**, of which the $\Delta\delta$ values (δ_S-δ_R) are illustrated in Scheme 1, has led us to assign a 3*R* configuration to **10** and **11**.

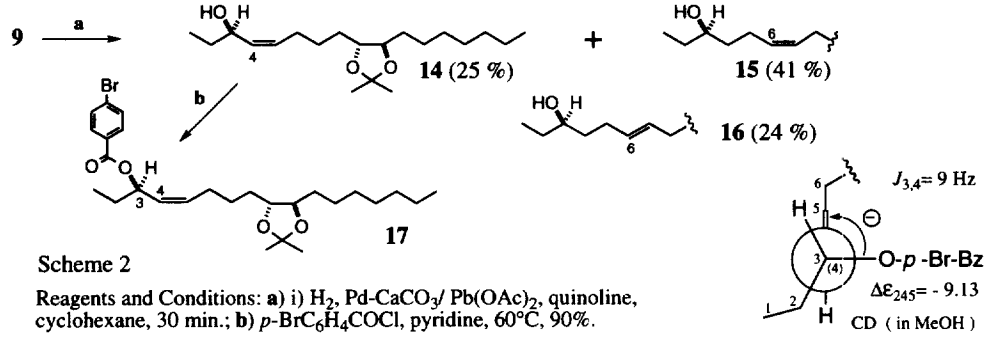


Scheme 1

Reagents and Conditions: **a**) $Me_2C(OMe)_2$, Dowex 50w x 8, r.t., 86%; **b**) *S*-(-)-MTPA [or *R*-(+)-MTPA], DCC, DMAP, r.t., 95%; **c**) *p*-BrC_6H_4COCl, pyridine, 70°C, 96%; **d**) MnO_2, 92%.

Partial hydrogenation of **9** using Lindlar catalyst[6] furnished three products, **14**, **15**, and **16**. Of these, **14** was further converted to *p*-bromobenzoate **17**, to which the CD exciton chirality method is unequivocally applicable. The CD spectrum of **17** showed a negative maximum at 245 nm ($\Delta\varepsilon$ = - 9.1) and, thus, the absolute configuration of C-3 in panaxytriol (**1**) has been reconfirmed to be *R*.[5]

Concerning the absolute stereostructures at C-3 of the polyacetylenic constituents of the ginseng radix, previously Shim *et al.* applied the CD exciton chirality method[7] to the *p*-bromobenzoate derivative **7** of panaxynol (**3**) and concluded that panaxynol (**3**) possessed a 3*S* configuration.[8] However, Bernart *et al.*[9] claimed that panaxynol (**3**) must possess a 3*R* configuration after they defined the 3*S* configuration to (+)-farcarinol (**4**), which is a known enantiomer of panaxynol (**3**), by means of the modified Mosher method,[10] and that the CD exciton chirality method applied to secondary allylic alcohols was not applicable to secondary alcohols flanked by two unsaturated chromophores as seen in **3**.



Scheme 2

Reagents and Conditions: **a**) i) H_2, Pd-$CaCO_3$/ $Pb(OAc)_2$, quinoline, cyclohexane, 30 min.; **b**) *p*-BrC_6H_4COCl, pyridine, 60°C, 90%.

For comparison purposes, the 3-*O*-*p*-bromobenzoate derivative **12** of **1** was prepared. The CD spectrum of **12** showed a negative CD maximum [249 nm ($\Delta\varepsilon$ = - 7.9)], which was similar to that of **7** (Fig. 1). As regards the sign of CD maximum of the 3-*O*-*p*-bromobenzoate derivative **7** of panaxynol (**3**) reported by Shim, as well as the 3-*O*-*p*-bromobenzoate derivative **12**, it can be explained that the interaction between the benzoate and diyne chromophore is more dominant than the interaction between the benzoate and double-bond chromophore in **7** and **12**, while the CD allylbenzoate exciton chirality seems to be unaffected by an isolated triple bond adjacent to the benzoate moiety as shown in the study on the stereochemistry of marine polyacetylene alcohol, petrosynol.[11]

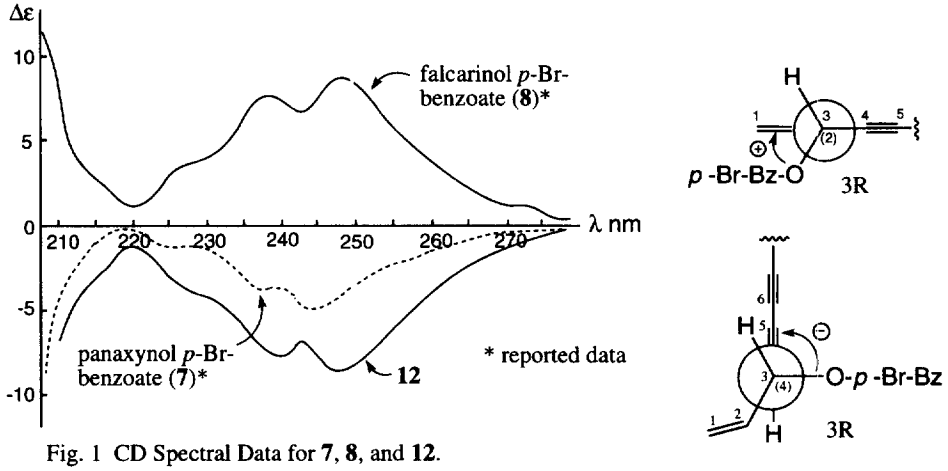


Fig. 1 CD Spectral Data for **7**, **8**, and **12**.

Next, we investigated the absolute stereochemistry of the vicinal glycol moiety at C-9 and C-10 of panaxytriol (**1**). The relative configuration of the vicinal glycol was defined as *syn* by the NOE experiment of acetonide **9** as illustrated in Fig. 2. Furthermore, the coupling constant (8 Hz) between 9-H and 10-H as well as the isopropylidene methyl proton signals observed at δ 1.40 (6H, s) supported the *syn*-acetonide structure in **9**.[12]

Based on the CD analysis of the di-*p*-bromobenzoate **18**, which showed a negative exciton split [255 nm ($\Delta\varepsilon$ = - 6.5) and 239 nm ($\Delta\varepsilon$ = + 10.6)], the absolute configurations of C-9 and C-10 were defined as 9*R*, 10*R*.[13]

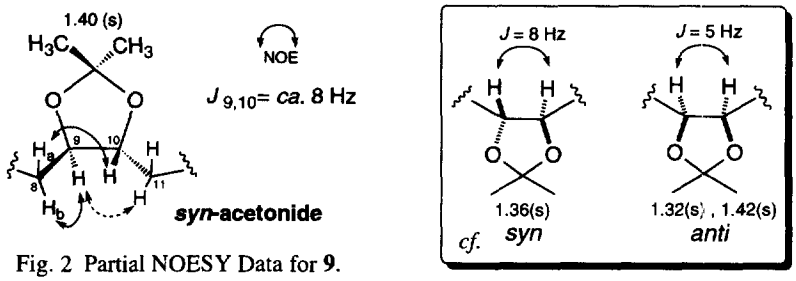
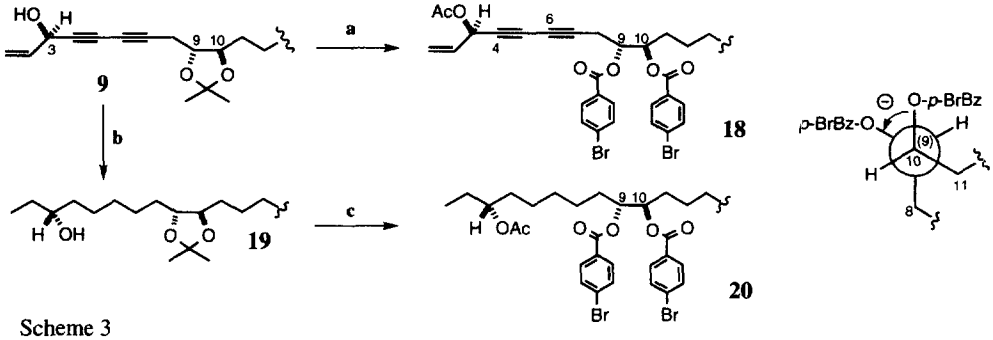


Fig. 2 Partial NOESY Data for **9**.



Scheme 3

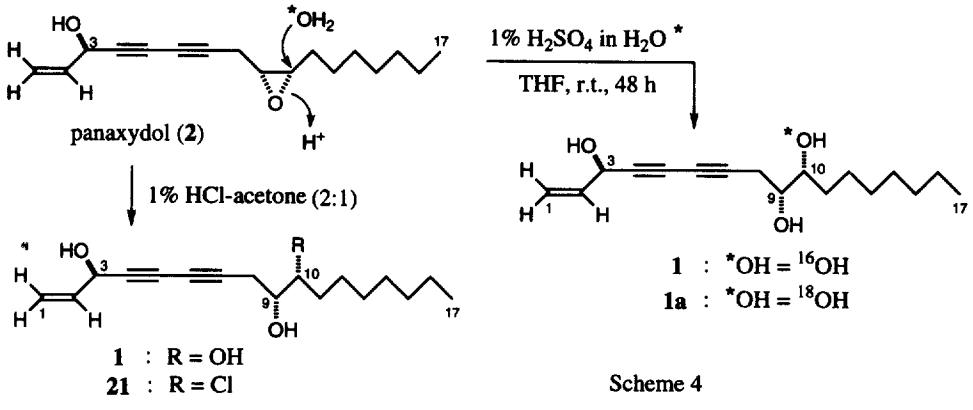
Reagents and Conditions: **a**) i) Ac_2O, pyridine, r.t., ii) 80% aq. AcOH, 60°C, iii) *p*-BrC_6H_4COCl, pyridine, 60°C, 3 steps 60%; **b**) H_2, Pd-$CaCO_3$/ $Pb(OAc)_2$, cyclohexane, 90%; **c**) i) Ac_2O, pyridine, r.t., ii) 80% aq. AcOH, 60°C, iii) *p*-BrC_6H_4COCl, pyridine, 60°C, 3 steps 61%.

In order to eliminate the effect of the 4,6-diyne chromophore adjacent to the C-9 benzoate chromophore, we further prepared a saturated di-*p*-bromobenzoate derivative **20**. Here again, the CD spectrum of **20** showed a clear exciton split with similar amplitude [first Cotton at 255 nm ($\Delta\varepsilon$ = - 6.5); second Cotton at 239 nm ($\Delta\varepsilon$ = + 7.1)] and, thus, the 9*R* and 10*R* configurations were confirmed unambiguously.

Very recently, Fujimoto and his group[14] reported that the absolute stereostructure of panaxytriol (**1**) has 9*S* and 10*S* configurations on the basis of synthetic study. They synthesized a diastereomeric mixture at C-3 of (9*S*,10*S*)-panaxytriol ([α]D -13.5°) and (9*S*,10*S*)-3-oxopanaxytriol acetonide (= 9*S*,10*S*-analog of **13**)([α]D -15.3°) from *L*-(+)-diethyl tartarate. They also converted the natural panaxytriol ([α]D -16.3°) to (9*S*,10*S*)-3-oxopanaxytriol acetonide ([α]D -16.0°) by Swern oxidation. However, by taking [α]D value (-34.6°) of panaxynol (**3**)[15] into account, it is very difficult to explain the correlation of these compounds by Hudson's rule.[16] In order to reconfirm their result, we also prepared the 3-oxo derivative **13** by MnO_2 oxidation of the acetonide **9** from **1**.[17] Compound **13** showed positive optical rotation ([α]D +20.3° (*c*=2.20, MeOH). This result supported the 9*R*, 10*R* configurations of panaxytriol (**1**). Consequently, the absolute stereostructure of panaxytriol (**1**) was confirmed to be (3*R*,9*R*,10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol.

Previously, we have reported that panaxydol (**2**) was hydrolyzed with 1% aq. HCl-acetone (2:1) to give panaxytriol (**1**)(20 %) and a chlorine-containing acetylene **21** (70 %) as the major product.[4] In treatment with 1% aq. H_2SO_4 and tetrahydrofuran (1:2), panaxydol (**2**) was selectively hydrolyzed to give panaxytriol (**1**) in good yield, which was identical with the authentic sample including the [α]D value. Thus, the C-3 stereochemistry of panaxydol (**2**) was also defined as 3*R*. Furthermore, to determine the absolute

configuration of the 9, 10-epoxy moiety in **2**, ^{18}O isotope-labeled water (95 % enriched $H_2{}^{18}O$) was used in the hydrolysis reaction and **2** was converted to ^{18}O-labeled panaxytriol (**1a**).



Scheme 4

Comparative Mass-analyzed Ion Kinetic Energy Spectrometry (MIKES)[18] study of FAB-MS of **1** and **1a** clearly showed the ^{18}O-enrichment in **1a**, where the characteristic fragment ions at *m/z* 186 and *m/z* 188 were observed for **1** and **1a**, respectively, and the common fragment ion at *m/z* 156 was observed for both compounds (Fig. 3). These evidence suggested that the C-10 hydroxyl group in **1a** was labeled with ^{18}O isotope.

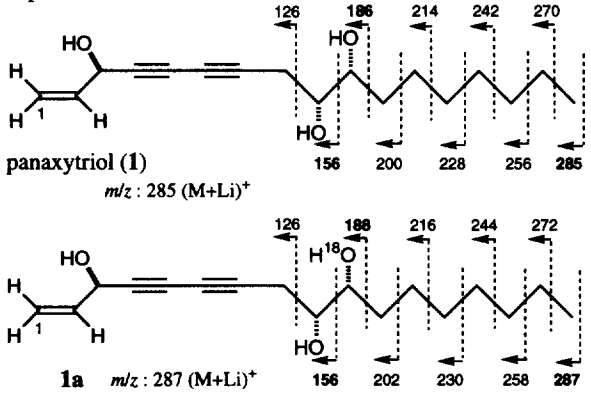


Fig. 3 MIKES Fragmentation Patterns of Panaxytriol (**1**) and ^{18}O-Enriched Derivative **1a**.

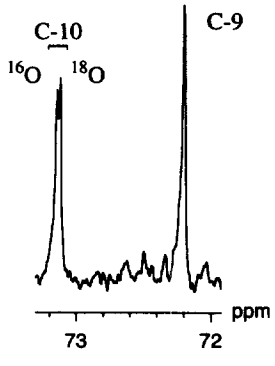


Fig. 4 ^{18}O Isotope Effect in ^{13}C-NMR Spectrum of **1a'** (50 % enriched ^{18}O).

Moreover, we analyzed the ^{13}C-NMR spectrum of ^{18}O-labeled panaxytriol (**1a'**), which was prepared from the hydrolysis of **2** by using 50% enriched $H_2{}^{18}O$. Owing to the ^{18}O isotope effect[19], the C-10 carbinol carbon attached to the ^{18}O-labeled hydroxyl group shifted to upfield (0.023 ppm), and the C-10 carbon signal in **1a'** was observed as two peaks (Fig. 4).

Hence, it became clear that panaxytriol (**1**) was obtained from panaxydol (**2**), *via* a S_N2-type regioselective epoxy ring-opening from the C-10 position in **2**, and the absolute configuration of C-9 and C-10 in **2** should be 9*R*, 10*S*.

In conclusion, panaxytriol (**1**) was presumed to be formed from panaxydol (**2**), during the processing of the crude drug, *via* a regioselective hydrolysis of the epoxy moiety in **2**, and the absolute stereostructures of panaxytriol (**1**) and panaxydol (**2**) were determined to be (3*R*,9*R*,10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol and (9*R*,10*S*)-9,10-epoxy-heptadec-1-ene-4,6-diyn-3-ol, respectively.

EXPERIMENTAL

The UV spectra were obtained with a Hitachi 330 spectrophotometer, and the IR spectra were taken with a JASCO FT/IR-5300 spectrometer (by a diffusion-reflection method on KBr powder). The EI-MS were taken on a JEOL JMS-D300 spectrometer, while the FAB-MS were taken on a JEOL SX-102 double-focused high-resolution mass spectrometer with a JMA DA-6000 data system by a direct inlet method. The ^{1}H-NMR and ^{13}C-NMR spectra were measured with a JEOL JNM EX-270 spectrometer and a JEOL GX-500 Spectrometer. Optical rotations were measured in a 0.5 dm length cell with a JASCO DIP-370 digital polarimeter. The CD spectra were obtained with a JASCO J-500A spectropolarimeter equipped with a 501N data processor. For HPLC, a JASCO 887-PU Intelligent Prep. Pump was used with a JASCO 875-UV Intelligent UV/VIS detector, and Cosmosil 5C18-AR 250 x 10 mm i.d. (Nacalai Tesque) column. Column chromatography was carried out using Kieselgel 60 (70-230 mesh, Merck) or Sephadex LH-20. Thin-layer chromatography (TLC) was conducted on precoated Kieselgel 60 F_{254} plates (0.25 mm, Merck) and detection of the spots was carried out by spraying 1% $Ce(SO_4)_2$/10% H_2SO_4 on the TLC plates followed by heating.

All chemical reactions were carried out under an Argon atmosphere unless otherwise indicated.

Isolation of Panaxytriol (1), Panaxydol (2), and Panaxynol (3) The methanol extract of Ginseng Radix Rubra (2.3 kg, 6 years old) imported from China was partitioned into a Et_2O:MeOH:H_2O (3:1:2) mixture to give a Et_2O-soluble portion (24 g) and a water-soluble portion (280 g). The Et_2O-soluble portion was then partitioned into a *n*-hexane-90% aq.MeOH mixture to give a *n*-hexane-soluble portion (9.75 g) and a methanol-soluble portion (13.2 g). The methanol-soluble portion was subjected to silica gel (SiO_2) column chromatography (*n*-hexane:AcOEt = 5:1~2:1 → MeOH) to give 6 fractions [fr. 1 (0.23 g), fr. 2 (1.02 g), fr. 3 (0.55 g), fr. 4 (0.67 g), fr. 5 (2.01 g), and fr. 6 (8.01 g)]. Fr. 5 was then purified by column chromatography (SiO_2, *n*-hexane:AcOEt = 2:1 → AcOEt) and Sephadex LH-20 column chromatography (MeOH) to give panaxytriol (**1**, 0.039 % yield from the Ginseng Radix Rubra). Fr. 3 was repeatedly subjected to column chromatography (SiO_2, n-hexane: AcOEt = 4:1 → AcOEt) and reversed-phase HPLC (Cosmosil 5C_{18} AR 250 x 10 mm i.d., 80 % aq. MeOH) to give panaxydol (**2**, 0.002 %). On the other hand, fr. 2 was subjected to reversed-phase silica gel column chromatography [(Cosmosil 75C18-OPN, 75 % aq. MeOH → 85 % aq. MeOH → MeOH) to give panaxynol (**3**, 0.018 %) .

Panaxytriol (**1**) : A colorless glassy solid, $[\alpha]_D$ -25.4° (*c* = 1.54, $CHCl_3$, 22 ° C). IR ν_{max} (KBr) cm^{-1} : 3325, 2256. FAB-MS *m/z* : 301 $(M+Na)^+$. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5.26 (1H, d, *J*= 10 Hz, 1-Ha), 5.47 (1H, d, *J*= 17 Hz, 1-Hb), 5.95 (1H, ddd, *J*= 17, 10, 5 Hz, 2-H), 4.92 (1H, dd, *J*= 6, 5 Hz, 3-H), 1.93 (1H, d, *J*= 6 Hz, 3-OH), 2.57 (1H, dd, *J*= 17, 6 Hz, 8-Ha), 2.61 (1H, dd, *J*= 17, 6 Hz, 8-Hb), 3.65 (1H, m, 9-H), 2.32 (1H, d, *J*= 6 Hz, 9-OH), 3.59 (1H, m, 10-H), 1.96 (1H, d, *J*= 6 Hz, 10-OH), 1.50 (2H, m, 11-H_2), 1.25~1.37 (10H, m), 0.89 (3H, t, *J*= 6 Hz, 17-H_3). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δc : 117.2 (C-1), 136.0 (C-2), 63.5 (C-3), 74.8 (C-4), 70.9 (C-5), 66.5 (C-6), 78.1 (C-7), 25.6 (C-8), 72.1 (C-9), 73.1 (C-10), 33.6 (C-11), 25.0 (C-12), 29.5 (C-13), 29.2 (C-14), 31.8 (C-15), 22.6 (C-16), 14.1 (C-17).

Panaxydol (**2**) : A colorless oil, $[\alpha]_D$ - 81.8 ° (*c* = 1.52, $CHCl_3$, 22 ° C). IR (KBr) cm^{-1} : 3410, 2256. FAB-MS *m/z* : 283 $(M+Na)^+$. HR FAB-MS *m/z* : Calcd for $C_{17}H_{24}O_2Na$: 283.1674. Found : 283.1695. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 5.26 (1H, d, *J*= 10 Hz, 1-Ha), 5.47 (1H, d, *J*= 17 Hz, 1-Hb), 5.95 (1H, ddd, *J*= 17, 10, 5 Hz, 2-H), 4.92 (1H, br d, *J*= *ca.* 5 Hz, 3-H), 2.38 (1H, dd, *J*= 18, 7 Hz, 8-Ha), 2.71 (1H, dd, *J*= 18, 6 Hz, 8-Hb), 3.13 (1H, ddd, *J*= 4, 5.5, 8 Hz, 9-H), 2.96 (1H, m, 10-H), 1.50 (2H, m, 11-H_2), 1.28~1.44 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3).

Panaxynol (**3**) : A colorless oil, $[\alpha]_D$ - 34.6 ° (*c* = 8.09, $CHCl_3$, 22 ° C). IR (KBr) cm^{-1} : 3337, 2256. FAB-MS *m/z* : 267 $(M+Na)^+$. HR FAB-MS *m/z* : Calcd for $C_{17}H_{24}ONa$: 267.1724. Found : 267.1747. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5.22 (1H, dd, *J*= 10, 1.7 Hz, 1-Ha), 5.45 (1H, dd, *J*= 17, 1.7 Hz, 1-Hb), 5.93 (1H, ddd, *J*= 17, 10, 5 Hz, 2-H), 4.90 (1H, d, *J*= 5 Hz, 3-H), 3.02 (2H, d, *J*= 7 Hz, 8-H_2), 5.36 (1H, dtt, *J*= 10, 7, 1.7 Hz, 9-H), 5.50 (1H, dtt, *J*= 10, 7, 1.7 Hz, 10-H), 2.02 (2H, br q, *J*= *ca.* 7 Hz, 11-H_2), 1.26~1.37 (10H, 12~16-H_2), 0.87 (3H, t, *J*= 7 Hz, 17-H_3).

Preparation of the 3,9,10-*O*-Tri-*S*-(-)-MTPA Ester (5) and 3,9,10-*O*-Tri-*R*-(+)-MTPA Ester (6) A solution of **1** (2 mg) in dry CH_2Cl_2 (1 ml) was treated with *S*-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) (18 mg), 1,3-dicyclohexylcarbodiimide (DCC) (26 mg), and 4-dimethylaminopyridine (DMAP) (3 mg), and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in a usual manner gave a product. Purification of the product by column chromatography (SiO_2, *n*-hexane-AcOEt=10:1) afforded the 3,9,10-*O*-tri-*S*-(-)-MTPA ester **5** (6 mg). The 3,9,10-*O*-tri-*R*-(+)-MTPA ester **6** (5.5 mg) was prepared from **1** (2 mg) and *R*-(+)-MTPA (18 mg) through the same procedure as described for the preparation of **5**.

5 : A colorless glassy solid, $[\alpha]_D$ - 65.6 ° (*c* = 0.37, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 2359, 2262, 1755, 1714, 1666. FAB-MS *m/z* : 927 $(M+H)^+$. HR FAB-MS *m/z* : Calcd for $C_{47}H_{48}O_9F_9$: 927.315. Found : 927.315. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5.42 (1H, d, *J*= 10 Hz, 1-Ha), 5.60 (1H, d, *J*= 17 Hz, 1-Hb), 5.93 (1H, ddd, *J*= 17, 10, 6 Hz, 2-H), 6.08 (1H, d, *J*= 6 Hz, 3-H), 2.32 (1H, dd, *J*= 17, 7 Hz, 8-Ha), 2.58 (1H, dd, *J*= 17, 7 Hz, 8-Hb), 5.23 (1H, td, *J*= 7, 5 Hz, 9-H), 5.26 (1H, td, *J*= 7, 5 Hz, 10-H), 1.58-1.78 (2H, m, 11-H_2), 1.19~1.28 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 3.49, 3.50, 3.54 (9H, OCH_3 x 3), 7.35-7.56 (15H, Ph x 3).

6 : A colorless glassy solid, $[\alpha]_D$ + 25.8 ° (*c* = 0.63, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 2359, 2262, 1753, 1714, 1666. FAB-MS *m/z* : 927 $(M+H)^+$. HR FAB-MS *m/z* : Calcd for $C_{47}H_{48}O_9F_9$: 927.315. Found : 927.316. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5.35 (1H, d, *J*= 10 Hz, 1-Hb), 5.51 (1H, d, *J*= 17 Hz, 1-Ha), 5.82 (1H, ddd, *J*= 17, 10, 6 Hz, 2-H), 6.10 (1H, d, *J*= 6 Hz, 3-H), 2.49 (1H, dd, *J*= 17, 7 Hz, 8-Ha), 2.58 (1H, dd, *J*= 17, 7 Hz, 8-Hb), 5.29 (1H, td, *J*= 7, 5 Hz, 9-H), 5.35 (1H, 10-H), 1.63-1.80 (2H, m, 11-H_2), 1.19~1.27 (10H, m), 0.87 (3H, t, *J*= 7 Hz, 17-H_3), 3.44, 3.46, 3.58 (9H, OCH_3 x 3), 7.38-7.56 (15H, Ph x 3).

Preparation of Acetonide Derivative 9 To a solution of panaxytriol (**1**, 9.8 mg) in 2,2-dimethoxypropane (0.36 ml), Dowex 50w x 8 (100 mg) was added and the reaction mixture was stirred at room temperature for 2 h. The resin was removed by filtration and the filtrate was subjected to silica gel column chromatography (SiO_2, *n*-hexane:AcOEt = 10:1) to afford **9** (9.6 mg, 86 %).

9 : A colorless oil, $[\alpha]_D$ - 22.5 ° (*c* = 1.2, acetone, 25 ° C). IR (KBr) cm^{-1} : 3431, 2349, 2237, 1647. FAB-MS *m/z* : 341 $(M+Na)^+$. HR FAB-MS *m/z* : Calcd for $C_{20}H_{30}O_3Na$: 341.2092. Found : 341.2085. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5.25 (1H, d, *J*= 10 Hz, 1-Ha), 5.47 (1H, d, *J*= 17 Hz, 1-Hb), 5.94 (1H, ddd, *J*= 17, 10, 5 Hz, 2-H), 4.92 (1H, dd, *J*= 7, 5 Hz, 3-H), 1.87 (1H, d, *J*= 7 Hz, 3-OH), 2.59 (1H, dd, *J*= 17, 5 Hz, 8-Ha), 2.63 (1H, dd, *J*= 17, 5 Hz, 8-Hb), 3.73 (1H, dt, *J*= 8, 5 Hz, 9-H), 3.80 (1H, td, *J*= 8, 4 Hz, 10-H), 1.58 (2H, m, 11-H_2), 1.25~1.37 (10H, m), 0.89 (3H, t, *J*= 7 Hz, 17-H_3), 1.40 (6H, s).

Preparation of the 3-*O*-*S*-(-)-MTPA Ester (10) and 3-*O*-*R*-(+)-MTPA Ester (11) A solution of **9** (1.8 mg) in dry CH_2Cl_2 (1 ml) was treated with *S*-(-)-MTPA (18 mg), DCC (13 mg), and DMAP (3 mg), and the mixture was stirred at room temperature for 24 h. The reaction mixture was worked up as described above. Purification of the product by column chromatography (SiO_2, *n*-hexane-AcOEt=10:1) afforded the 3-*O*-*S*-(-)-MTPA ester **10** (2.5 mg). The 3-*O*-*R*-(+)-MTPA ester **11** (2.5 mg) was prepared from **9** (1.8 mg) and *R*-(+)-MTPA (9 mg) through the same procedure as described for the preparation of **10**.

10 : A colorless glassy solid, $[\alpha]_D$ - 26.9 ° (*c* = 0.16, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 2361, 2260, 1755, 1714, 1666. FAB-MS *m/z* : 557 $(M+Na)^+$. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 5.40 (1H, d, *J*= 10 Hz, 1-Ha), 5.60 (1H, d, *J*= 17 Hz, 1-Hb), 5.96 (1H, ddd, *J*= 17, 10, 6 Hz, 2-H), 6.08 (1H, d, *J*= 6 Hz, 3-H), 2.61 (2H, d, *J*= 5 Hz, 8-H_2), 3.74 (2H, m, 9-H and 10-H), 1.57 (2H, m, 11-H_2), 1.26~1.37 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.40 (6H, s), 3.56 (3H, s, OCH_3), 7.40~7.55 (5H, m, Ph).

11 : A colorless glassy oil, $[\alpha]_D$ + 19.7 ° (*c* = 0.22, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 2361, 2258, 1755, 1666. FAB-MS *m/z* : 535 $(M+H)^+$. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 5.34 (1H, d, *J*= 10 Hz, 1-Ha), 5.51

(1H, d, *J*= 17 Hz, 1-Hb), 5.82 (1H, ddd, *J*= 17, 10, 6 Hz, 2-H), 6.10 (1H, d, *J*= 6 Hz, 3-H), 2.62 (2H, d, *J*= 5 Hz, 8-H_2), 3.75 (2H, m, 9-H and 10-H), 1.57 (2H, m, 11-H_2), 1.26~1.38 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.40 (6H, s), 3.42 (3H, s, OCH_3), 7.33~7.52 (5H, m, Ph).

Preparation of the *p*-Bromobenzoate Ester 12 from 9 A solution of **9** (2.9 mg) in dry pyridine (1 ml) was treated with *p*-bromobenzoyl chloride (15 mg), and stirred at 70 °C for 30 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in a usual manner gave a product. Purification of the product by column chromatography (SiO_2, *n*-hexane-AcOEt=15:1) afforded the *p*-bromobenzoate **12** (4.4 mg).

12 : A colorless glassy solid, $[\alpha]_D$ - 48.9 ° (*c* = 0.43, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 2260, 1730, 1591. FAB-MS *m/z* : 523 $(M+Na)^+$. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5.39 (1H, d, *J*= 10 Hz, 1-Ha), 5.79 (1H, d, *J*= 17 Hz, 1-Hb), 5.98 (1H, ddd, *J*= 17, 10, 5 Hz, 2-H), 6.14 (1H, d, *J*= 5 Hz, 3-H), 2.58 (1H, dd, *J*= 17, 5 Hz, 8-Ha), 2.63 (1H, dd, *J*= 17, 5 Hz, 8-Hb), 3.73 (1H, dt, *J*= 8, 5 Hz, 9-H), 3.79 (1H, td, *J*= 8, 4 Hz, 10-H), 1.57 (2H, m, 11-H_2), 1.26~1.33 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.40 (6H, s), 7.59, 7.92 (both 2H, d, *J*= 8.5 Hz, 3-*O*-*p*-Br-Bz). CD (*c* = 0.3 x 10^{-3}, MeOH, 20 ° C): $\Delta\varepsilon_{292}$ = 0; $\Delta\varepsilon_{249}$ = - 7.88 (neg. max.); $\Delta\varepsilon_{241}$ = - 6.36 (sh.); $\Delta\varepsilon_{222}$ = - 0.67 (neg. min.).

Preparation of the *p*-Bromobenzoate Ester 17 from 9 A solution of **9** (10 mg) in cyclohexane (0.5 ml) was treated with 5% Pd-$CaCO_3$/$Pb(OAc)_2$ (4 mg) and quinoline (0.5 mg), and stirred at room temperature under hydrogen atmosphere for 30 min. The reaction mixture was filtered to remove the catalyst and the product was subjected to reversed-phase HPLC (CAPCELL PAK C_{18}, CH_3CN:H_2O=7:3) to give **14** (2.1 mg), **15** (3.5 mg), and **16** (2.0 mg). The solution of **14** (0.6 mg) in pyridine (0.5 mg) was treated with *p*-bromobenzoyl chloride (15.1 mg), and the mixture was stirred at 70 °C for 30 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in a usual manner gave a product. Purification of the product by column chromatography (SiO_2, *n*-hexane-AcOEt=15:1) afforded the *p*-bromobenzoate **17** (0.8 mg).

14 : A colorless glassy solid, FAB-MS *m/z*: 349 $(M+Na)^+$. HR FAB-MS *m/z* : Calcd for $C_{20}H_{30}O_3Na$: 349.2718. Found : 349.2725. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 0.90 (3H, t, *J*= 7.5 Hz, 1-H_3), 1.62 (2H, m, 2-H_2), 4.34 (1H, dt, *J*= 8, 7 Hz, 3-H), 5.39 (1H, dd, *J*= 8, 11 Hz, 4-H), 5.50 (1H, dt, *J*= 11, 7 Hz, 5-H), 2.11 (4H, m, 6-H_2 and 7-H_2), 1.44~1.51 (4H, m, 8-H_2 and 11-H_2), 3.61 (2H, m, 9-H and 10-H), 1.14~1.24 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.38 (6H, s).

15 : A colorless glassy solid, FAB-MS *m/z*: 349 $(M+Na)^+$. HR FAB-MS *m/z* : Calcd for $C_{20}H_{30}O_3Na$: 349.2719. Found : 349.2729. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 0.94 (3H, t, *J*= 7.5 Hz, 1-H_3), 1.45~1.54 (6H, m, 2-H_2, 4-H_2 and 11-H_2), 3.62 (1H, m, 3-H), 2.13 (2H, m, 5-H_2), 5.48 (2H, m, 6-H and 7-H), 2.27 (2H, m, 8-H_2), 3.51 (2H, m, 9-H and 10-H), 1.25~1.29 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.38 (6H, s). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δc : 10.1 (C-1), 31.8 (C-2), 71.5 (C-3), 36.1 (C-4), 23.4 (C-5), 125.5 (C-6), 131.8 (C-7), 27.1 (C-8), 32.7, 30.5, 30.2, 29.7, 29.1, 22.6, 14.1 (C-17), 26.1, 27.2.

16 : A colorless glassy solid, FAB-MS *m/z*: 349 $(M+Na)^+$. HR FAB-MS *m/z* : Calcd for $C_{20}H_{30}O_3Na$: 349.2718. Found : 349.2710. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 0.95 (3H, t, *J*= 7.5 Hz, 1-H_3), 1.46~1.51 (4H, m, 2-H_2 and 11-H_2), 3.58 (1H, m, 3-H), 1.60 (2H, m, 4-H_2), 2.19 (2H, m, 5-H_2), 5.49 (2H, t, *J*= 6 Hz, 6-H and 7-H), 2.03 (2H, m, 8-H_2), 3.49 (2H, m, 9-H and 10-H), 1.25~1.28 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.37 (6H, s). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δc : 10.0 (C-1), 31.8 (C-2), 72.0 (C-3), 40.2 (C-4), 29.8 (C-5), 126.6 (C-6), 133.8 (C-7), 32.6 (C-8), 32.8, 29.7, 29.6, 29.4, 29.1, 22.6, 14.1 (C-17), 26.1, 27.2.

17 : A colorless glassy solid, $[\alpha]_D$ - 13.1 ° (*c* = 0.14, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 1722. FAB-MS *m/z* : 531 $(M+Na)^+$. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 0.95 (3H, t, *J*= 7 Hz, 1-H_3), 1.69 (1H, m, 2-Ha), 1.79 (1H, m, 2-Hb), 5.69 (1H, dt, *J*= 9, 7 Hz, 3-H), 5.42 (1H, dd, *J*= 11, 9 Hz, 4-H), 5.64 (1H, dt, *J*= 11, 7 Hz, 5-H), 2.25 (4H, m, 6-H_2 and 7-H_2), 1.41~1.49 (4H, m, 8-H_2 and 11-H_2), 3.61 (2H, m, 9-H and 10-H), 1.25~1.27 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.37 (6H, s), 7.57, 7.89 (both 2H, d, *J*= 8 Hz, 3-*O*-*p*-Br-Bz). CD (*c* = 0.1 x 10^{-3}, MeOH, 20 °C): $\Delta\varepsilon_{279}$ = 0; $\Delta\varepsilon_{245}$ = - 9.13 (neg. max.); $\Delta\varepsilon_{222}$ = - 1.26 (neg. min.).

Preparation of the 3-*O*-Acetyl-9,10-*O*-di-(*p*-bromobenzoyl)-panaxytriol (18) from 9 A solution of **9** (2.2 mg) in dry pyridine (0.15 ml) was treated with acetic anhydride and stirred at room temperature for 10 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the

AcOEt extract in a usual manner gave a product, which then dissolved in 80 % aq. acetic acid solution (0.5 ml) and stirred at 70 °C for 30 min. The solvent was then evaporated and the solution of the product in dry pyridine (0.2 ml) was treated with *p*-bromobenzoyl chloride (15 mg), and the mixture was stirred at 70 °C for 30 min. The reaction mixture was poured into ice-water and extracted with AcOEt. Work-up of the AcOEt extract in a usual manner gave a product. Purification of the product by column chromatography (SiO_2, *n*-hexane-AcOEt=10:1) afforded the 3-*O*-acetyl-9,10-*O*-*p*-bromobenzoate **18** (2.6 mg, 3 steps 60 %).

18 : A colorless glassy solid, $[\alpha]_D$ - 9.9 ° (*c* = 0.18, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 1728, 1589. FAB-MS *m/z* : 707 $(M+Na)^+$. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5.33 (1H, d, *J*= 10 Hz, 1-Ha), 5.49 (1H, d, *J*= 17 Hz, 1-Hb), 5.84 (1H, ddd, *J*= 16, 10, 6 Hz, 2-H), 5.87 (1H, d, *J*= 6 Hz, 3-H), 2.76 (1H, dd, *J*= 18, 6 Hz, 8-Ha), 2.83 (1H, dd, *J*= 18, 6 Hz, 8-Hb), 5.38 (1H, m, 9-H), 5.49 (1H, m, 10-H), 1.79 (2H, m, 11-H_2), 1.38 (2H, m, 12-H_2), 1.22~1.32 (8H, m, 13-H_2~16-H_2), 0.84 (3H, t, *J*= 7 Hz, 17-H_3), 2.10 (3H, s, 3-*O*-acetyl), 7.58, 7.89, 7.57, 7.88 (each 2H, d, *J*= 8.5 Hz, 10-*O*-*p*-Br-Bz). CD (*c* = 0.17 x 10^{-3}, MeOH, 20 °C): $\Delta\varepsilon_{274} = 0$; $\Delta\varepsilon_{255}$ = - 6.5 (neg. max.); $\Delta\varepsilon_{249} = 0$; $\Delta\varepsilon_{239}$ = + 10.6 (pos. max.); $\Delta\varepsilon_{220} = 0$.

Preparation of the 3-*O*-Acetyl-9,10-*O*-di-(*p*-bromobenzoyl)-heptadecane-3,9,10-triol (20) from 9 A solution of **9** (5 mg) in cyclohexane (0.5 ml) was treated with 5% Pd-$CaCO_3$/Pb$(OAc)_2$ (2 mg), and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 2 h. The reaction mixture was filtered and evaporated in vacuo to give **19** (4.7 mg). The solution of **19** (1.0 mg) in dry pyridine (0.5 ml) was treated with acetic anhydride (0.2 ml) and stirred at room temperature for 10 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in a usual manner gave a product, which was then dissolved in 80 % aq. acetic acid solution (0.5 ml) and stirred at 70 °C for 3 h. The solvent was then evaporated and the residue was treated with pyridine (0.2 mg) and *p*-bromobenzoyl chloride (17 mg), and the mixture was stirred at 70 °C for 30 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in a usual manner gave a product. Purification of the product by column chromatography (SiO_2, *n*-hexane-AcOEt=10:1) afforded **20** (1.4 mg).

19 : A colorless glassy solid, FAB-MS *m/z*: 351 $(M+H)^+$. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 0.94 (3H, t, *J*= 7.5 Hz, 1-H_3), 1.49~1.55 (8H, m, 2-H_2, 4-H_2, 8-H_2 and 11-H_2), 3.58 (1H, m, 3-H), 1.25~1.36 (16H, m, 5-H_2~7-H_2 and 12-H_2~16-H_2), 3.52 (2H, m, 9-H and 10-H), 0.88 (3H, t, *J*= 7 Hz, 17-H_3), 1.38 (6H, s).

20 : A colorless glassy solid, $[\alpha]_D$ + 12.8 ° (*c* = 0.07, $CHCl_3$, 20 ° C). IR (KBr) cm^{-1} : 1726, 1641. FAB-MS *m/z* : 719 $(M+Na)^+$. ^{1}H-NMR (270 MHz, $CDCl_3$) δ : 0.84 (6H, t, *J*= 7.5 Hz, 1-H_3 and 17-H_3), 1.49 (4H, m, 2-H_2, and 4-H_2), 4.75 (1H, m, 3-H), 1.25~1.36 (16H, m, 5-H_2~7-H_2 and 12-H_2~16-H_2), 1.68 (4H, m, 8-H_2 and 11-H_2), 5.34 (2H, m, 9-H and 10-H), 2.01 (3H, s, 3-*O*-acetyl), 7.56, 7.87 (both 4H, d, *J*= 8.5 Hz, 9,10-*O*-*p*-Br-Bz). CD (*c* = 0.6 x 10^{-4}, MeOH, 20 ° C): $\Delta\varepsilon_{287} = 0$; $\Delta\varepsilon_{255}$ = - 6.5 (neg. max.); $\Delta\varepsilon_{249} = 0$; $\Delta\varepsilon_{239}$ = + 7.1 (pos. max.); $\Delta\varepsilon_{220} = 0$.

Preparation of 3-Oxo Derivative 13 from 9 To a solution of **9** (25 mg) in methylenechloride (10 ml) MnO_2 was suspended, and the whole was stirred vigorously for 30 min at 22°C. The reaction mixture was then filtered and the solvent was evaporated. The residue was purified by HPLC (Cosmosil 5Sil, *n*-hexane-AcOEt=10:1) to afford **13** (23 mg, 92%).

13 : A colorless oil, $[\alpha]_D$ + 20.3 ° (*c* = 2.2, MeOH, 22 ° C). IR (KBr) cm^{-1} : 2235, 2154, 1649, 1610. FAB-MS *m/z* : 317 $(M+H)^+$. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.55 (1H, d, *J*= 16.5 Hz, 1-Ha), 6.40 (1H, dd, *J*= 16.5, 10 Hz, 2-H), 6.22 (1H, d, *J*= 10 Hz, 1-Hb), 3.77 (2H, m, 9,10-H), 2.73 (2H, m, 8-H_2), 1.58 (2H, m), 1.41 (6H, s), 1.25~1.40 (10H, m), 0.88 (3H, t, *J*= 7 Hz, 17-H_3). ^{13}C-NMR (125 MHz, $CDCl_3$)δc: 177.7 (s), 137.8 (d), 134.3 (t), 108.9 (s), 85.2 (s), 80.3 (s), 77.8 (s), 70.8 (d), 65.8 (d), 32.8 (t), 31.8 (t), 29.6 (t), 29.1 (t), 27.4 (t), 27.0 (t), 25.9 (t), 23.8 (q), 22.6 (q), 14.1 (q).

Conversion of Panaxydol (2) into Panaxytriol (1) **2** (5.2 mg) was dissolved in 1% aq. H_2SO_4-THF (1:2, 0.6 ml) and stirred at room temperature for 48 h. The reaction mixture was poured into sat. aq. NaCl and extracted with AcOEt. The solvent was then evaporated and the residue was purified by column chromatography (SiO_2, *n*-hexane:AcOEt=2:1) to afford **1** (3.5 mg, 63 %). The chemical structure of **1** was confirmed by comparison of its physical data (TLC, IR, ^{1}H-NMR, $[\alpha]_D$) with those of natural panaxytriol.

Conversion of Panaxydol (2) into 1a **2** (6.5 mg) was dissolved in 1 % aq. (95 % enriched $H_2{}^{18}O$) H_2SO_4-THF (1:2, 0.6 ml) and stirred at room temperature for 48 h. To the reaction mixture sat. aq. NaCl was added and the whole was extracted with AcOEt. The solvent was then evaporated and the residue was purified by column chromatography (SiO_2, *n*-hexane:AcOEt=2:1) to afford **1a** (5.5 mg, 63 %). 1 % Aq. (50% enriched $H_2{}^{18}O$) H_2SO_4-THF was used in preparing **1a'** for the ^{13}C-NMR analysis.

1a : A colorless glassy solid, $[\alpha]_D$ - 24.9 ° (*c* = 0.10, $CHCl_3$, 20 ° C). IR ν_{max} (KBr) cm^{-1} : 2854, 2256. FAB-MS *m/z*: 287 $(M+Li)^+$. ^1H-NMR (500 MHz, $CDCl_3$) δ : 5.26 (1H, d, *J*= 10 Hz, 1-Ha), 5.47 (1H, d, *J*= 17 Hz, 1-Hb), 5.95 (1H, ddd, *J*= 17, 10, 5 Hz, 2-H), 4.92 (1H, dd, *J*= 6, 5 Hz, 3-H), 1.93 (1H, d, *J*= 6 Hz, 3-OH), 2.57 (1H, dd, *J*= 17, 6 Hz, 8-Ha), 2.61 (1H, dd, *J*= 17, 6 Hz, 8-Hb), 3.65 (1H, m, 9-H), 2.32 (1H, d, *J*= 6 Hz, 9-OH), 3.59 (1H, m, 10-H), 1.96 (1H, d, *J*= 6 Hz, 10-OH), 1.50 (2H, m, 11-H_2), 1.25~1.37 (10H, m, 12-H_2~16-H_2), 0.89 (3H, t, *J*= 6 Hz, 17-H_3). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δc : 117.2 (C-1), 136.0 (C-2), 63.5 (C-3), 74.8 (C-4), 70.9 (C-5), 66.5 (C-6), 78.1 (C-7), 25.6 (C-8), 72.1 (C-9), 73.1 (C-10), 33.6 (C-11), 25.0 (C-12), 29.5 (C-13), 29.2 (C-14), 31.8 (C-15), 22.6 (C-16), 14.1 (C-17).

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