Synthesis of Panax Acetylenes: Chiral Syntheses of Acetylpanaxydol, PQ-3 and Panaxydiol

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Acetylpanaxydol (1-Ac), PQ-3 (2) and panaxydiol (3) and their optical isomers were synthesized from L-(+)-diethyl tartrate. The absolute configurations of 1-Ac, 2 and 3 were determined to be 1-Ac (3*R*,9*R*,10*S*), 2 (9*R*,10*S*) and 3 (3*R*,10*S*), respectively, by comparisons of their optical rotations and the NMR data of their MTPA esters with those of natural products.

Key words panaxydol; panaxydiol; panax species; polyacetylene; absolute configuration; enzyme mediated-acetylation

In previous papers we have reported the isolation and structural elucidation of eight C_{17}-polyacetylenes[1,2] including acetylpanaxydol (**1-Ac**), PQ-3 (**2**) and panaxydiol (**3**) as well as C_{14}-polyacetylene, PQ-8 (**4a**), from *Panax quinquefolium* and syntheses of **4a** and its optical isomer (**4b**) from L-(+)-diethyl tartrate (Chart 1).[3] Although synthesis[4,5] and absolute structure[6] of panaxydol have already been reported, the absolute configuration of natural acetylpanaxydol has not yet been determined. In this paper, we report the absolute structures and the syntheses of **1-Ac**, **2** and **3** from **4a**.

Reaction of **4a** or **4b** with acrolein in the presence of 1.3 eq of BuLi gave a diastereomeric mixture at C-3 of (9*R*,10*S*)-panaxydol (**1a**) or (9*S*,10*R*)-panaxydol (**1b**), while the reaction performed in the presence of 3.0 eq of BuLi afforded a diastereomeric mixture at C-3 of (10*S*)-panaxydiol (**3a**) or its (10*R*)-isomer (**3b**). Oxidation of **1a** and **1b** with manganese dioxide gave (9*R*,10*S*)-3-oxo-panaxydol (**2a**) and its (9*S*,10*R*)-isomer (**2b**), respectively (Chart 2). Comparison of

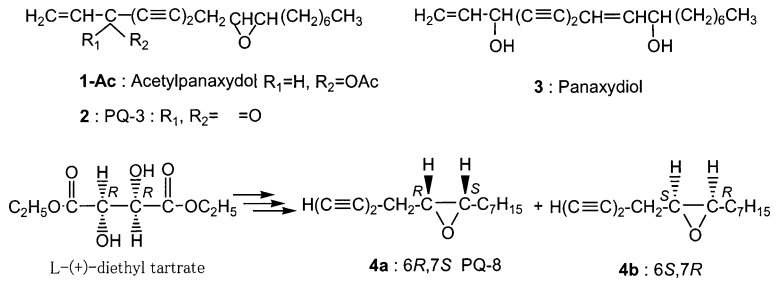

Chart 1

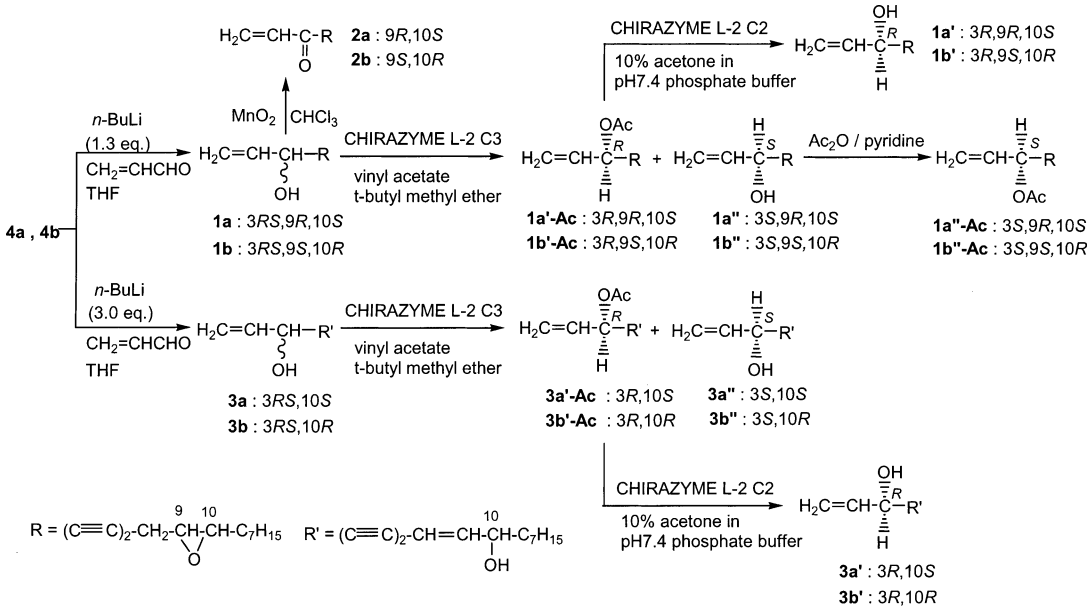

Chart 2

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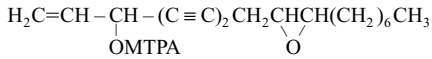
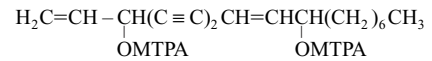
the optical rotation value of PQ-3 ($[\alpha]_D$ −79.2°) with those of **2a** ($[\alpha]_D$ −77.2°) and **2b** ($[\alpha]_D$ +78.0°) indicated that the absolute stereostructure of PQ-3 should be 9*R*, 10*S* (Table 2). Next, we attemped the separation of the diastereomeric mixtures (**3a**, **b**) using CHIRAZYME (Boehringer Mannheim Corp., Indianapolis, IN, U.S.A.) catalyzed acetylation and hydrolysis procedures.[7] Treatment of **3a** and **3b** with vinyl acetate in the presence of CHIRAZYME L-2, C3 (Boehringer Mannheim Corp., Indianapolis, IN, U.S.A.) gave the mixtures of acetates (**3a′-Ac**, **3b′-Ac**) and unreacted alcohols (**3a″**, **b″**), respectively, which were separated by high performance liquid chromatography (HPLC). The acetates (**3a′-Ac**, **3b′-Ac**) were hydrolyzed with CHIRAZYME L-2, C2 (Boehringer Mannheim Corp., Indianapolis, IN, U.S.A.) and phosphate buffer (pH 7.4) to give the alcohols (**3a′**, **b′**), respectively (Chart 2).[8] In order to determine the absolute configurations at C-3 by application of the modified Mosher method,[9] the alcohols (**3a′**, **a″** and **3b′**, **b″**) were converted into their (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) esters, respectively. The optical purities of the alcohols (**3a′**, **a″** and **3b′**, **b″**) were more than 99%, respectively, which were estimated on the basis of the ^{1}H-NMR spectra of their MTPA esters. The above results showed that only the alcohol (**3a′**, **b′**) having *R*-configuration were enantioselectively acetylated by the action of CHIRAZYME and vinyl acetate. As shown in Table 1, the signals due to H_2-1 and H-2 of **3a′**-(*R*)- and **3b′**-(*R*)-MTPA esters appeared at higher fields than those of **3a′**-(*S*)- and **3b′**-(*S*)-MTPA esters, respectively, thereby suggesting the stereochemistry at C-3 of **3a′** and **3b′** to be *R*-configuration. On the other hand, the signals due to H_2-1 and H-2 of **3a″**-(*R*)- and **3b″**-(*R*)-MTPA esters appeared at lower fields than those of **3a″**-(*S*)- and **3b″**-(*S*)-MTPA esters, respectively. Thus, the absolute configuration at C-3 of **3a″** and **3b″** could both be assigned as *S*-configurations.

Furthermore, the absolute configurations at C-10 of **3a′**, **3a″** and **3b′**, **3b″** were also determined to be 10*S* for **3a′**, **3a″** and 10*R* for **3b′**, **3b″**, respectively, by comparison of the NMR data of their MTPA esters (Table 1). As shown in Tables 1 and 2, comparison of the spectral data of MTPA esters and the optical rotation value of natural panaxydiol (**3**) with those of synthetic ones indicated that the absolute configuration of **3** could be concluded to be 3*R*, 10*S*. Similarly, the diastereomeric mixtures (**1a**, **b**) at C-3 of panaxydol were separated into 3*R*-isomers (**1a′**, **b′**) and 3*S*-isomers (**1a″**, **b″**) through CHIRAZYME catalyzed acetylation and hydrolysis procedures.

Table 1.



Panaxydol	H-1a	H-1b	H-2
1a′: 3*R*, 9*R*, 10*S*	+25	+40	+50
1b′: 3*R*, 9*S*, 10*R*	+30	+40	+50
1a″: 3*S*, 9*R*, 10*S*	−25	−40	−50
1b″: 3*S*, 9*S*, 10*R*	−25	−40	−50
Nat. product	+30	+40	+50



Panaxydiol	H-1a	H-1b	H-2	H-8	H-9
3a′: 3*R*, 10*S*	+30	+40	+50	+68	+35
3b′: 3*R*, 10*R*	+25	+40	+50	−68	−40
3a″: 3*S*, 10*S*	−35	−40	−50	+68	+45
3b″: 3*S*, 10*R*	−30	−40	−50	−68	−35
Nat. product	+30	+40	+50	+68	+40

$\Delta\delta$ ($=\delta_S-\delta_R$) values obtained from the MTPA esters of isomers (panaxydol, panaxydiol). $\Delta\delta$ values are expressed in Hz.

Table 2. Optical Rotation

Panaxydol				
3*R*, 9*R*, 10*S*	3*R*, 9*S*, 10*R*	3*S*, 9*R*, 10*S*	3*S*, 9*S*, 10*R*	Nat. product
−119.2° (c=0.65, $CHCl_3$)	+50.6° (c=0.63, $CHCl_3$)	−48.8° (c=1.06, $CHCl_3$)	+103.0° (c=1.28, $CHCl_3$)	−112.7° (c=0.47, $CHCl_3$)
Acetylpanaxydol				
3*R*, 9*R*, 10*S*	3*R*, 9*S*, 10*R*	3*S*, 9*R*, 10*S*	3*S*, 9*S*, 10*R*	Nat. product
−47.5° (c=0.60, $CHCl_3$)	+108.9° (c=0.73, $CHCl_3$)	−106.1° (c=0.43, $CHCl_3$)	+42.9° (c=0.52, $CHCl_3$)	−43.0° (c=1.15, $CHCl_3$)
Panaxydiol				
3*R*, 10*R*	3*R*, 10*S*	3*S*, 10*R*	3*S*, 10*S*	Nat. product
−57.5° (c=0.18, $CHCl_3$)	−33.7° (c=0.19, $CHCl_3$)	+30.3° (c=0.59, $CHCl_3$)	+45.3° (c=0.15, $CHCl_3$)	−33.4° (c=1.12, $CHCl_3$)
PQ-3				
9*R*, 10*S*	9*S*, 10*R*	Nat. product		
−77.2° (c=0.47, $CHCl_3$)	+78.0° (c=0.58, $CHCl_3$)	−79.2° (c=0.58, $CHCl_3$)		

Comparison of the optical rotation value of acetylpanaxydol with those of synthetic acetylpanaxydols (**1a′-Ac**, **1b′-Ac**, **1a″-Ac**, **1b″-Ac**) indicated that the absolute stereostructure of acetylpanaxydol should be 3*R*, 9*R*, 10*S* (Table 2).

Further studies on the synthesis of Panax acetylenes are now in progress.

Experimental

The ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-EX90 and a JEOL JNM-α500 spectrometer in $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a JEOL JMS-D 300 instrument. Waco-gel (C-300) was used for column chromatography. The optical rotations were measured on a JASCO DIP-370 polarimeter. Senshu pack (PEGASIL Silica 60-5, 10ϕ×250 mm) column was used for HPLC.

Diastereomeric Mixture (1a, b) at C-3 of Panaxydol *n*-Buli (1.60 mmol/ml) in hexane [400 μl (0.64 mmol)] was added dropwise to a stirred solution of **4a** or **4b** (98.6 mg, 0.48 mmol) in THF (2 ml) at −78 °C. After 30 min, acrolein (100 μl) was added and stirring was continued for 3 h at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution (1.0 ml) and then extracted with AcOEt (20 ml×2). The organic layer was washed with brine (10 ml×2), dried over $MgSO_4$ and concentrated under reduced pressure to leave an oil which was purified by HPLC (hexane : AcOEt=7 : 1) to give **1a** or **1b** (54.0—70.2 mg, 42.3—55.0%, retention time=16.4 min) as an oil. **1a**, **1b**: ^{1}H-NMR[10] δ: 0.88 (3H, t, J=6.8 Hz), 1.29 (8H, br m), 1.52 (4H, m), 2.39 (1H, dd, J=7.2, 17.8 Hz), 2.70 (1H, dd, J=5.2, 17.8 Hz), 2.97 (1H, m), 3.15 (1H, m), 4.92 (1H, m), 5.25 (1H, d, J=10.1 Hz), 5.47 (1H, d, J=16.9 Hz), 5.95 (1H, ddd, J=5.3, 10.1, 16.9 Hz), ^{13}C-NMR δ: 14.1, 19.4, 22.6, 26.4, 27.5, 29.1, 29.4, 31.7, 54.3, 57.0, 63.4, 66.3, 70.8, 74.9, 76.6, 117.1, 136.0, CI-MS: *m*/*z*: 261 $(M+1)^+$.

Oxidation of 1a or 1b with MnO_2 MnO_2 (100 mg) was added to the solution of **1a** or **1b** (13.3 mg) in $CHCl_3$ (2.0 ml) and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was filtered and evaporated *in vacuo*. The residue was purified by column chromatography and HPLC (hexane : AcOEt=7 : 1) to give **2a** or **2b** (7.0—6.4 mg, 53.4—48.8%, retention time=7.8 min) as an oil. **2a**, **2b**: ^{1}H-NMR δ: 0.89 (3H, t, J=6.8 Hz), 1.29 (8H, br m), 1.53 (4H, m), 2.51 (1H, dd, J=6.8, 18.0 Hz), 2.77 (1H, dd, J=5.7, 18.0 Hz), 3.00 (1H, m), 3.18 (1H, m), 6.23 (1H, d, J=9.9 Hz), 6.41 (1H, dd, J=9.9, 17.5 Hz), 6.56 (1H, d, J=17.5 Hz), ^{13}C-NMR δ: 14.1, 19.8, 22.6, 26.4, 27.5, 29.2, 29.4, 31.7, 53.9, 56.9, 60.4, 65.7, 71.0, 84.5, 134.4, 137.7, 177.6, CI-MS: *m*/*z*: 259 $(M+1)^+$.

Diastereomeric Mixture (3a, b) at C-3 of Panaxydiol *n*-Buli (1.60 mmol/ml) in hexane [880 μl (1.4 mmol)] was added dropwise to a stirred solution of **4a** or **4b** (94.0 mg, 0.46 mmol) in THF (2 ml) at −78 °C. After 30 min, acrolein (100 μl) was added and stirring was continued for 3 h at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution (2.0 ml) and then extracted with AcOEt (20 ml×2). The organic layer was washed with brine (10 ml×2), dried over $MgSO_4$ and concentrated under reduced pressure to leave an oil, which was purified on a HPLC (hexane : AcOEt=5 : 1) to give **3a** or **3b** (72.3—76.0 mg, 60.2—63.3%, retention time=20.6 min) as an oil. **3a**, **3b**: ^{1}H-NMR δ: 0.88 (3H, t, J=7.0 Hz), 1.29 (10H, br m), 1.52 (2H, t, J=6.8 Hz), 4.19 (1H, m), 4.98 (1H, m), 5.26 (1H, d, J=10.1 Hz), 5.48 (1H, d, J=16.9 Hz), 5.76 (1H, d, J=15.8 Hz), 5.96 (1H, ddd, J=5.3, 10.1, 16.9 Hz), 6.33 (1H, dd, J=5.3, 15.8 Hz), ^{13}C-NMR δ: 14.1, 22.6, 25.2, 29.2, 29.4, 31.4, 36.9, 63.6, 70.9, 72.0, 73.5, 77.2, 80.4, 108.0, 117.2, 135.9, 149.9, CI-MS: *m*/*z*: 259 $(M+1)^+$.

Acetylation of Diastereomeric Mixture (1a, b) at C-3 of Panaxydol with Lipase (CHIRAZYME L-2, C3) Lipase (CHIRAZYME L-2, C3, 80.0 mg) and vinyl acetate (40 μl, 0.44 mmol) was added to a stirred solution of **1a** or **1b** (37.5 mg, 0.35 mmol) in *t*-butyl methyl ether (5.0 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was filtered with celite and evaporated *in vacuo*. The residue was purified by HPLC (hexane : AcOEt=7 : 1) to give **1a′-Ac** or **1b′-Ac** (18.4—15.0 mg, 42.2—40.0%, retention time=6.0 min) and **1a″** or **1b″** (15.4—16.2 mg, 41.1—43.2%, retention time=12.4 min) as an oil. **1a′-Ac**, **1b′-Ac**: ^{1}H-NMR δ: 0.88 (3H, t, J=7.0 Hz), 1.29 (8H, br m), 1.53 (4H, m), 2.11 (3H, s), 2.38 (1H, dd, J=7.2, 17.6 Hz), 2.70 (1H, dd, J=5.2, 17.6 Hz), 2.96 (1H, m), 3.14 (1H, m), 5.34 (1H, d, J=9.7 Hz), 5.54 (1H, dd, J=16.4 Hz), 5.87 (1H, ddd, J=5.7, 9.7, 15.6 Hz), 5.90 (1H, m), Low-MS: *m*/*z*: 302 $(M)^+$. The ^{1}H- and ^{13}C-NMR spectra of acetylpanaxydol were identical with those of **1a′-Ac**.

Hydrolysis of 1a′-Ac or 1b′-Ac with Lipase (CHIRAZYME L-2, C2) Compound **1a′-Ac** or **1b′-Ac** (15 mg, 0.22 mmol) was dissolved in 0.5 ml of acetone and 4.5 ml of pH 7.4 phosphate buffer, and then lipase (CHIRAZYME L-2, C2, 50 mg) was added. The reaction mixture was stirred overnight at room temperature. The mixture was filtered by celite, and then extracted with AcOEt (30 ml). The organic layer was washed with brine (30 ml×2), dried over $MgSO_4$ and evaporated *in vacuo* to leave an oil. The residue was purified by HPLC (hexane : AcOEt=7 : 1) to give **1a′** or **1b′** (7.5—9.6 mg, 58.1—74.5%, retention time=12.4 min) as an oil.

Acetylation of Diastereomeric Mixture (3a or b) at C-3 of Panaxydiol with Lipase (CHIRAZYME L-2, C3) The reaction was carried out in a similar manner as described in acetylation of diastereomeric mixture at C-3 of panaxydol with lipase. **3a′-Ac** or **3b′-Ac** (20.5—20.1 mg, 40.3—39.5%, retention time=10.0 min) and **3a″** or **3b″** (18.0—19.8 mg, 40.0—44.0%, retention time=20.6 min). **3a′-Ac**, **3b′-Ac**: ^{1}H-NMR δ: 0.88 (3H, t, J=7.3 Hz), 1.29 (10H, br m), 1.52 (2H, t, J=7.3 Hz), 2.11 (3H, s), 4.20 (1H, m), 5.35 (1H, d, J=9.9 Hz), 5.55 (1H, d, J=16.7 Hz), 5.76 (1H, d, J=15.8 Hz), 5.90 (1H, ddd, J=5.7, 9.9, 16.9 Hz), 5.95 (1H, m), 6.35 (1H, dd, J=5.5, 15.8 Hz).

Hydrolysis of 3a′-Ac or 3b′-Ac with Lipase (CHIRAZYME L-2, C2) The reaction was carried out in a similar manner as described in hydrolysis of **1a′-Ac** or **3b′-Ac** with lipase.

MTPA Ester of Panaxydol Isomers Five drops (large excess) of (*S*)-(+)- or (*R*)-(−)-MTPA-Cl was added to a stirred solution of panaxydol isomers (5.0 mg, 0.05 mmol) in pyridine (1.0 ml) and the stirring was continued overnight at room temperature. The mixture was diluted with AcOEt (30 ml) and then washed successively with 1 N-HCl (20 ml) and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by HPLC to give (*R*)-(+)- or (*S*)-(−)-MTPA ester of panaxydol isomers.

(*R*)-(+)-MTPA-ester of (3*R*,9*R*,10*S*)-Panaxydol The ^{1}H-NMR spectrum was identical with that of (*R*)-(+)-MTPA-ester of natural panaxydol. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.2 Hz), 1.28 (8H, br m), 1.51 (4H, m), 2.41 (1H, dd, J=7.0, 17.8 Hz), 2.70 (1H, dd, J=5.5, 17.8 Hz), 2.97 (1H, m), 3.15 (1H, m), 3.59 (3H, s), 5.35 (1H, d, J=10.1 Hz), 5.52 (1H, d, J=16.9 Hz), 5.83 (1H, ddd, J=5.7, 10.1, 16.9 Hz), 6.10 (1H, d, J=5.7 Hz), 7.41 (3H, m), 7.50 (2H, m).

(*S*)-(−)-MTPA-ester of (3*R*,9*R*,10*S*)-Panaxydol The ^{1}H-NMR spectrum was identical with that of (*S*)-(−)-MTPA-ester of natural panaxydol. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.26 (8H, br m), 1.53 (4H, m), 2.40 (1H, dd, J=7.0, 17.6 Hz), 2.69 (1H, dd, J=5.7, 17.6 Hz), 2.97 (1H, m), 3.14 (1H, m), 3.55 (3H, s), 5.40 (1H, d, J=9.9 Hz), 5.60 (1H, d, J=16.9 Hz), 5.93 (1H, ddd, J=6.1, 9.9, 16.7 Hz), 6.08 (1H, d, J=6.1 Hz), 7.42 (3H, m), 7.52 (2H, m).

(*R*)-(+)-MTPA-ester of (3*R*,9*S*,10*R*)-Panaxydol ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J= 6.8 Hz), 1.26 (8H, br m), 1.52 (4H, m), 2.42 (1H, dd, J=7.0, 17.8 Hz), 2.70 (1H, dd, J=5.5, 17.8 Hz), 2.97 (1H, m), 3.16 (1H, m), 3.59 (3H, s), 5.35 (1H, d, J=10.1 Hz), 5.52 (1H, d, J=16.9 Hz), 5.83 (1H, ddd, J=5.7, 10.1, 16.9 Hz), 6.11 (1H, d, J=5.7 Hz), 7.40 (3H, m), 7.52 (2H, m).

(*S*)-(−)-MTPA-ester of (3*R*,9*S*,10*R*)-Panaxydol ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.2 Hz), 1.28 (8H, br m), 1.51 (4H, m), 2.40 (1H, dd, J=7.0, 17.8 Hz), 2.68 (1H, dd, J=5.7, 17.8 Hz), 2.97 (1H, m), 3.15 (1H, m), 3.55 (3H, s), 5.41 (1H, d, J=9.9 Hz), 5.60 (1H, d, J=16.9 Hz), 5.93 (1H, ddd, J=6.1, 9.9, 16.7 Hz) 6.08 (1H, d, J=6.3 Hz), 7.41 (3H, m), 7.51 (2H, m).

(*R*)-(+)-MTPA-ester of (3*S*,9*R*,10*S*)-Panaxydol ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.28 (8H, br m), 1.51 (4H, m), 2.40 (1H, dd, J=7.0, 17.6 Hz), 2.69 (1H, dd, J=5.5, 17.8 Hz), 2.97 (1H, m), 3.15 (1H, m), 3.55 (3H, s), 5.40 (1H, d, J=9.9 Hz), 5.60 (1H, d, J=16.9 Hz), 5.93 (1H, ddd, J=6.1, 9.9, 16.9 Hz), 6.08 (1H, d, J=6.1 Hz), 7.41 (3H, m), 7.51 (2H, m).

(*S*)-(−)-MTPA-ester of (3*S*,9*R*,10*S*)-Panaxydol ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.28 (8H, br m), 1.52 (4H, m), 2.42 (1H, dd, J=6.8, 17.8 Hz), 2.70 (1H, dd, J=5.5, 17.8 Hz), 2.97 (1H, m), 3.14 (1H, m), 3.59 (3H, s), 5.35 (1H, d, J=10.1 Hz), 5.52 (1H, d, J=16.9 Hz), 5.83 (1H, ddd, J=5.7, 10.1, 16.9 Hz,) 6.11 (1H, d, J=5.9 Hz), 7.42 (3H, m), 7.50 (2H, m).

(*R*)-(+)-MTPA-ester of (3*S*,9*S*,10*R*)-Panaxydol ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.26 (8H, br), 1.51 (4H, m), 2.40 (1H, dd, J=7.0, 17.8 Hz), 2.69 (1H, dd, J=5.5, 17.8 Hz), 2.97 (1H, m), 3.14 (1H, m), 3.55 (3H, s), 5.40 (1H, d, J=10.1 Hz), 5.60 (1H, d, J=16.9 Hz), 5.93 (1H, ddd, J=6.1, 10.1, 16.7 Hz), 6.08 (1H, d, J=6.1 Hz), 7.41 (3H, m), 7.51 (2H, m).

(*S*)-(−)-MTPA-ester of (3*S*,9*S*,10*R*)-Panaxydol ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.28 (8H, br m), 1.51 (4H, m), 2.41 (1H, dd, J=6.8, 17.6 Hz), 2.69 (1H, dd, J=5.7, 17.6 Hz), 2.97 (1H, m), 3.15 (1H, m), 3.59 (3H, s), 5.35 (1H, d, J=10.1 Hz), 5.52 (1H, d, J=16.7 Hz), 5.83 (1H, ddd, J=5.88, 10.1, 16.9 Hz), 6.11 (1H, d, J=5.9 Hz), 7.41 (3H, m), 7.52 (2H, m).

The MTPA Esters of Panaxydiol Isomers The MTPA esters were prepared according to the method described in the synthesis of MTPA esters of panaxydol isomers.

Di-(*R*)-MTPA Ester of (3*R*,10*R*)-Panaxydiol ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.2 Hz), 1.26 (10H, br m), 1.64 (2H, m), 3.53 (3H, s), 3.60 (3H, s), 5.37 (1H, d, J=10.1 Hz), 5.49 (1H, m), 5.53 (1H, d, J=16.4 Hz), 5.78 (1H, d, J=15.1 Hz), 5.84 (1H, ddd, J=5.7, 10.1, 16.7 Hz), 6.16 (1H, d, J=5.5 Hz), 6.26 (1H, dd, J=7.0, 16.0 Hz), 7.41 (6H, m), 7.50 (4H, m).

Di-(*S*)-MTPA Ester of (3*R*,10*R*)-Panaxydiol ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.0 Hz), 1.25 (10H, br m), 1.69 (2H, m), 3.55 (6H, s), 5.42 (1H, d, J=9.9 Hz), 5.47 (1H, m), 5.61 (1H, d, J=16.9 Hz), 5.65 (1H, d, J=16.0 Hz), 5.94 (1H, ddd, J=6.1, 10.1, 16.4 Hz), 6.12 (1H, d, J=4.2 Hz), 6.18 (1H, dd, J= 6.6, 16.0 Hz), 7.41 (6H, m), 7.50 (4H, m).

Di-(*R*)-MTPA Ester of (3*R*,10*S*)-Panaxydiol The ^{1}H-NMR spectrum was identical with that of di-(*R*)-MTPA-ester of natural panaxydiol. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.2 Hz), 1.26 (10H, br m), 1.69 (2H, m), 3.55 (3H, s), 3.59 (3H, s), 5.36 (1H, d, J=10.1 Hz), 5.47 (1H, m), 5.53 (1H, d, J=16.9 Hz), 5.65 (1H, d, J=16.0 Hz), 5.84 (1H, ddd, J=5.7, 10.1, 16.9 Hz), 6.16 (1H, d, J=5.70 Hz), 6.18 (1H, dd, J=6.62, 15.8 Hz), 7.41 (6H, m), 7.50 (4H, m).

Di-(*S*)-MTPA Ester of (3*R*,10*S*)-Panaxydiol The ^{1}H-NMR spectrum was identical with that of di-(*S*)-MTPA-ester of natural panaxydiol. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.0 Hz), 1.26 (10H, br m), 1.60 (2H, m), 3.53 (3H, s), 3.55 (3H, s), 5.42 (1H, d, J=10.1 Hz), 5.49 (1H, m), 5.61 (1H, d, J=16.9 Hz), 5.78 (1H, d, J=15.8 Hz), 5.94 (1H, ddd, J=6.1, 9.9, 16.9 Hz), 6.13 (1H, d, J=6.1 Hz), 6.25 (1H, dd, J=6.99, 16.0 Hz), 7.40 (6H, m), 7.51 (4H, m)

Di-(*R*)-MTPA Ester of (3*S*,10*R*)-Panaxydiol ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.0 Hz), 1.26 (10H, br m), 1.60 (2H, m), 3.53 (3H, s), 3.55 (3H, s), 5.43 (1H, d, J=10.1 Hz), 5.49 (1H, m), 5.61 (1H, d, J=16.7 Hz), 5.78 (1H, d, J=15.8 Hz), 5.94 (1H, ddd, J=6.1, 10.1, 16.7 Hz), 6.13 (1H, d, J=6.1 Hz), 6.25 (1H, dd, J=7.2, 15.8 Hz), 7.42 (6H, m), 7.51 (4H, m).

Di-(*S*)-MTPA Ester of (3*S*,10*R*)-Panaxydiol ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.6 Hz), 1.25 (10H, br m), 1.69 (2H, m), 3.55 (3H, s), 3.59 (3H, s), 5.36 (1H, d, J=10.1 Hz), 5.47 (1H, m), 5.53 (1H, d, J=16.9 Hz), 5.65 (1H, d, J=16.0 Hz), 5.84 (1H, ddd, J=5.9, 10.1, 16.9 Hz), 6.15 (1H, d, J=6.6 Hz), 6.18 (1H, dd, J=6.62, 15.8 Hz), 7.39 (6H, m), 7.50 (4H, m).

Di-(*R*)-MTPA Ester of (3*S*,10*S*)-Panaxydiol ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.26 (10H, br m), 1.68 (2H, m), 3.55 (6H, s), 5.42 (1H, d, J=10.1 Hz), 5.47 (1H, m), 5.61 (1H, d, J=16.9 Hz), 5.65 (1H, d, J= 16.0 Hz), 5.94 (1H, ddd, J=6.07, 10.1, 16.5 Hz), 6.13 (1H, d, J=4.23 Hz), 6.17 (1H, dd, J= 6.6, 16.0 Hz), 7.42 (6H, m) ,7.50 (4H, m).

Di-(*S*)-MTPA Ester of (3*S*,10*S*)-Panaxydiol ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.4 Hz), 1.25 (10H, br m), 1.65 (2H, m), 3.53 (3H, s), 3.59 (3H, s), 5.36 (1H, d, J=10.1 Hz), 5.49 (1H, m), 5.53 (1H, d, J=17.1 Hz), 5.78 (1H, d, J=15.1 Hz), 5.84 (1H, ddd, J=5.9, 10.1, 16.9 Hz), 6.15(1H, d, J=5.70 Hz), 6.26 (1H, dd, J=7.0, 16.0 Hz), 7.40 (6H, m), 7.50 (4H, m).

References and Notes

1) Fujimoto Y., Satoh M., Takeuchi N., Kirisawa M., *Chem. Pharm. Bull.*, **39**, 521—523 (1991).
2) Fujimoto Y., Wang H., Satoh M., Takeuchi N., *Phytochemistry*, **35**, 1255—1257 (1994).
3) Satoh M., Takeuchi N., Fujimoto Y., *Heterocycles*, **45**, 177—180 (1997).
4) Lu W., Zheng G., Aisa A., Cai J., *Tetrahedron Lett.*, **39**, 9521—9522 (1998).
5) Yadav J. S., Maiti A., *Tetrahedron*, **58**, 4955—4961 (2002).
6) Kobayashi M., Mahmud T., Umezome T., Wang, W., Murakami N., Kitagawa I., *Tetrahedron*, **53**, 15691—15700 (1997).
7) Naoshima Y., Kamezawa M., Kimura T., Okimoto F., Watanabe M., Tachibana H., Ohtani T., *Recent Res. Devel. Org. & Bioorg. Chem.*, **4**, 1—16 (2001).
8) CHIRAZYME catalyzed acetylation of the hydroxyl group at C-10 did not proceed with any relation to the stereochemistry.
9) Ohtani I., Kusumi T., Kachman Y., Kakisawa H., *J. Am. Chem. Soc.*, **113**, 4092—4096 (1991).
10) The compounds having the same plane chemical structure in the text showed the same ^{1}H- and ^{13}C-NMR spectra in spite of the differences in their absolute stereostructures.