Synthesis and Absolute Configurations of the Cytotoxic Polyacetylenes Isolated from the Callus of *Panax ginseng*

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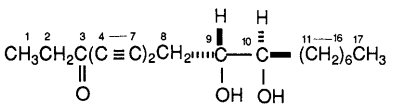
Panaxacol (1) and dihydropanaxacol (2), cytotoxic polyacetylenes isolated from the callus of *Panax ginseng*, were synthesized starting from D-(−)-diethyl tartrate. The absolute configuration of 1 was determined to be 9*R*, 10*R* and the absolute configuration at C-3 of 2 was tentatively assigned as 3*S* by the application of the *R*(+)-α-methoxy-α-(trifluoro methyl)phenylacetyl (MTPA) method.

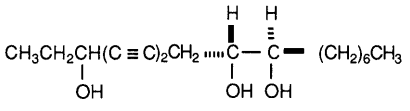
Keywords *Panax ginseng*; panaxacol; callus; dihydropanaxacol; absolute configuration; polyacetylene; chiral synthesis

In the previous papers,[1,2] we have reported the isolation and structural elucidation of three new cytotoxic polyacetylenes (**1**, **2** and **3**) and panaxydol (**4**)[3] isolated from the callus of *Panax ginseng* C. A. MEYER. Although we have established the relative configuration at C-9 and C-10 in panaxacol to be *threo* from the results of nuclear Overhauser effect (NOE) experiments on the acetonide of **1**, the absolute configurations of **1** and **2** have not been determined yet. Thus, we planned to establish the absolute configurations of these polyacetylenes by synthesizing them, using L-(+)- or D-(−)-diethyl tartrate as a chiral template.

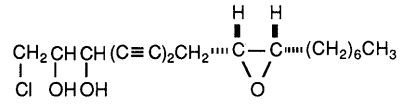
D-(−)-Diethyl tartrate was treated with 2,2-dimethoxypropane and camphorsulfonic acid (CSA) to give an acetonide (**5**, 68.5%, 15% recovery of starting material), which was then converted into a diol (**6**, 77.3%)[4a,b] by the action of $LiAlH_4$. Tosylation of **6** with *p*-toluenesulfonyl chloride (TsCl, 1.0 eq)–pyridine gave a mixture of the monotosylate (**7**, 54.5%) and ditosylate (**8**, 14.8%)[4a,b] which was separated by silica gel column chromatography. After protection of the hydroxyl group with tetrahydropyranyl (THP) ether, **7** was treated with dihexyl copper lithium[5] and then 2 N HCl–MeOH (1:4) to afford



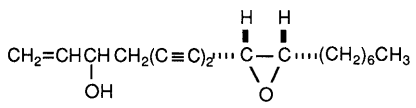
panaxacol (**1**)



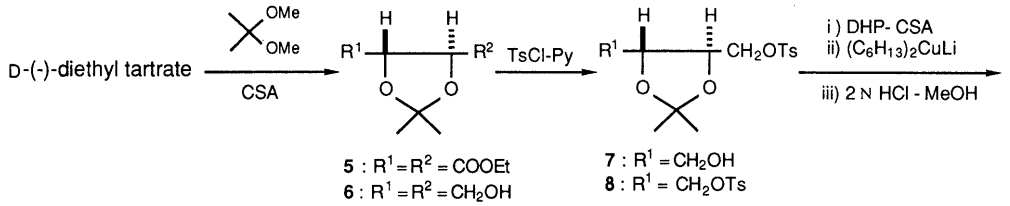
dihydropanaxacol (**2**)

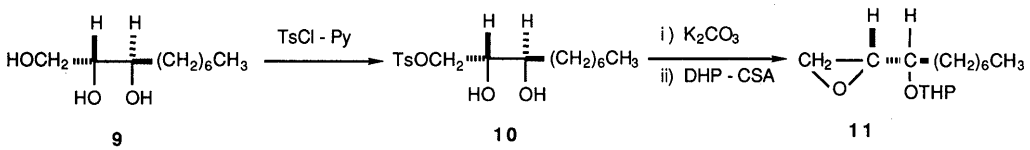


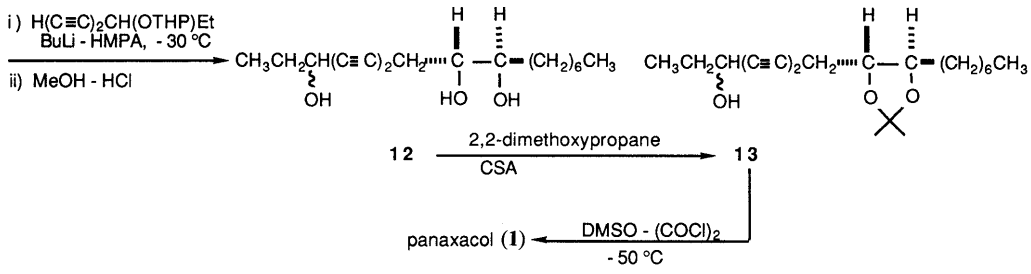
chloropanaxydiol (**3**)



panaxydol (**4**)







a triol (**9**, 66.4%). Tosylation of **9** gave a diol-monotosylate (**10**, 43.6%) which was transformed to an acetonide. Coupling reaction of the actonide with 1,3-heptadiyne-5-ol THP ether in the presence of BuLi–hexamethylphosphoric triamide (HMPA) failed to give the desired compounds. Therefore, the compound (**10**) was converted into an epoxide (**11**, 75.7%) by usual means and **11** was allowed to react with 1,3-heptadiyne-5-ol THP ether to give the coupling products, which, without purification, were deprotected to afford a diastereomeric mixture of 9*R*,-10*R*-dihydropanaxacol {**12**, 40%, $[\alpha]_D$ +12.3° (*c*=0.79, MeOH)}. Similarly, a diastereomeric mixture of 9*S*,10*S*-dihydropanaxacol {$[\alpha]_D$ −17.0° (*c*=0.36, MeOH)} was synthesized from L-(+)-diethyl tartrate. The diastereomeric mixture of dihydropanaxacol (**12**) prepared from natural panaxacol (**1**) by $NaBH_4$ reduction exhibited positive optical rotation {$[\alpha]_D$ +13.5° (*c*=1.0, MeOH)}. Thus, the absolute configuration of panaxacol can be presumed to be the same as that of D-(−)-diethyl tartrate. In order to cofirm this presumption, **12** was converted into panaxacol as follows.

The glycol moiety of **12** was protected as the acetonide and then the hydroxyl group at C-3 was oxidized by Swern's method. Deprotection of the oxidation product, followed by purification using high-performance liquid chromatography (HPLC) gave a solid which was identical including optical rotation with natural panaxacol. Thus, the absolute configurations at C-9 and C-10 in panaxacol were confirmed as 9*R* and 10*R*.

Finally, the absolute configuration at C-3 in dihydropanaxacol was tentatively assigned[6] by the application of Mosher's method. The acetonide (**13**) was treated with *R*-(+)-α-methoxy-α-(trifluoro methyl)phenylacetyl chloride (MTPA-Cl)[7] to give a diastereomeric mixture of *R*-(+)-MTPA esters which was separated into *R*-(+)-MTPA ester (A) (retention time: 9.2 min) and (B) (retention time: 10.6 min) by HPLC. A comparison of the proton nuclear magnetic resonance spectrum (^{1}H-NMR) of ester (A) with that of ester (B) revealed that the methyl (δ 0.93) and the methylene (δ 1.83) signals of the ester (A) appeared in higher field than those (δ 1.03 for the methyl and δ 1.98 for the methylene) of the ester (B). Therefore, the absolute configurations at C-3 of the ester (A) and the ester (B) were deduced to be *R* and *S*, respectively, based on the general rule of the MTPA method[8] (Chart 1).

Similarly, natural dihydropanaxacol was also transformed to the *R*-(+)-MTPA ester after protection of the glycol moiety. The ester obtained here was identical with the MTPA ester (B) in terms of the ^{1}H-NMR and retention time on HPLC. Thus, the absolute configuration of dihydropanaxacol was deduced to be 3*S*, 9*R*, 10*R*. The biological activities of these polyacetylenes and related compounds will be reported elsewhere.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Spectral data were obtained on the following instruments: Infrared spectrum (IR) on a Shimadzu IR-430; ^{1}H-NMR on a JEOL GX-400, GX-270 or FX-100 instrument in $CDCl_3$ containing tetramethylsilane as an internal standard; mass spectra (MS) on a Hitachi RMU-6M or a JEOL JMS-D 300.

(2*S*,3*S*)-2,3-Isopropyridenedioxy-4-tosyloxybutan-1-ol (7) TsCl (3.0 g) was added to a stirred solution of **6** (3.2 g) in pyridine (30 ml), and the mixture was allowed to stand overnight at room temperature. Brine (50 ml) was then added, and the reaction mixture was extracted with AcOEt. The organic layer was concentrated under reduced pressure to leave an oil, which was chromatographed on a silica gel column (hexane : AcOEt = 2 : 1) to give **7** (3.4 g, 54.5%) as an oil, the ditosylate (**8**, 14.8%) and **6** (10% recovery). **7**: Oil, EI-MS *m/z* (relative intensity): 301 $(M-Me)^+$ (100), 285 $(M-CH_2OH)^+$ (9); ^{1}H-NMR δ: 1.33, 1.39 (3H each, s), 2.45 (3H, s), 3.63 (1H, dd, *J*=4.2, 12.0 Hz), 3.80 (1H, dd, *J*=3.7, 12.0 Hz), 3.81 (1H, m), 3.99 (1H, m), 4.04 (1H, m), 4.11 (1H, m), 7.36 (2H, d, *J*=8.3 Hz), 7.80 (2H, d, *J*=8.3 Hz).

(2*R*,3*R*)-1,2,3-Trihydroxydecane (9) A mixture of **7** (1.7 g), 3,4-dihydro-2*H*-pyran (DHP) (670 mg) and CSA (50 mg) in CH_2Cl_2 (10 ml) was stirred for 30 min at room temperature. The mixture was diluted with AcOEt (50 ml) and then washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure to leave an oil, which was chromatographed on a silica gel column (hexane : AcOEt = 3 : 1) to afford the THP ether of **7** [2.0 g, 93.0%; EI-MS *m/z* (relative intensity): 400 $(M)^+$ (2), 385 $(M-Me)^+$ (100); ^{1}H-NMR δ: 1.35 (3H, s), 1.38 (3H, s), 1.40—1.60 (8H, br m, $W_{1/2}$=20 Hz), 2.45 (3H, s), 3.52 (1H, m), 3.57 (1H, m), 4.0—4.2 (4H, m), 4.61 (1H, m), 7.34 (2H, d, *J*=8.3 Hz), 7.81 (2H, d, *J*=8.3 Hz)]. This compound was submitted to

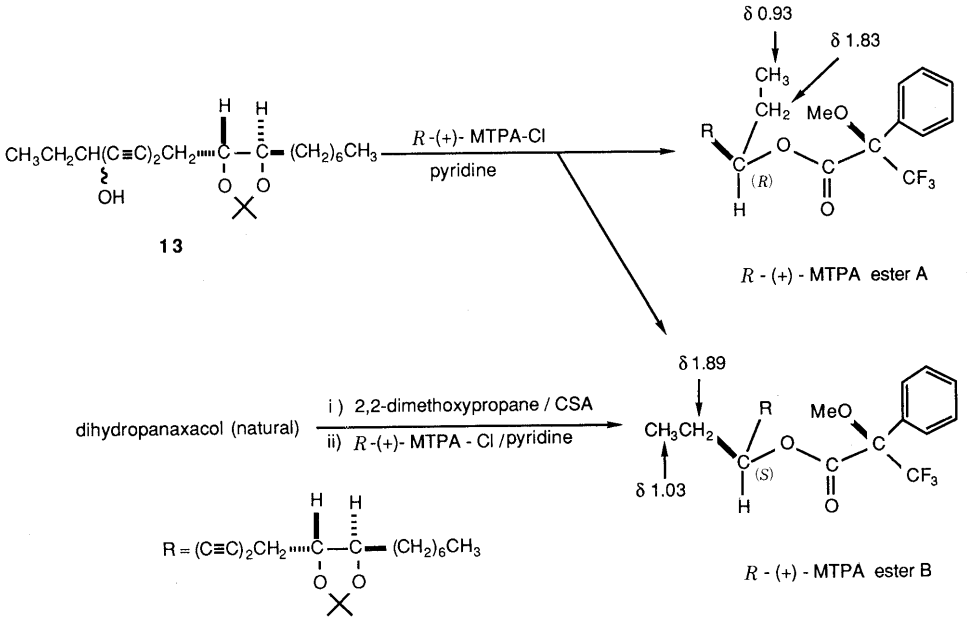


Chart 1

the following reaction. An Et_2O solution (9.0 ml) of hexyl lithium (1.56 mmol/ml) was added dropwise to a stirred suspension of cuprous iodide (1.34 g) in Et_2O (25 ml) at −40 °C. After 15 min, a solution of the above THP ether (930 mg) in Et_2O (8 ml) was added at −30 °C and then the mixture was further stirred for 1 h at the same temperature. Saturated NH_4Cl (10 ml) was added to the reaction mixture and the whole was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (hexane : AcOEt = 7 : 1), followed by HPLC (Senshu Pack Silica-3301-N, 8 × 300 mm, hexane : AcOEt = 20 : 1) to give a diastereomeric mixture of coupling products (500 mg, 66.4%). The mixture of coupling products (400 mg) was dissolved in 5 ml of MeOH–2N HCl (4 : 1) under stirring at room temperature. After 1 h, brine (40 ml) was added and the mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to leave **9** (206 mg, 88.0%) as colorless crystals. **9**: mp 52—54°C, CI-MS *m/z*: 191 $(M+1)^+$, EI-MS *m/z* (relative intensity): 159 $(M-CH_2OH)^+$ (17), 129 $(M-C_2H_5O_2)^+$ (41), 111 $(M-C_2H_7O_3)^+$ (100); IR ($CHCl_3$): 3400, 2930, 2850 cm^{-1}; ^{1}H-NMR δ: 0.95 (3H, t, J=7.1 Hz), 1.20—1.40 (10H, br m, $W_{1/2}$=25 Hz), 1.50 (2H, br m), 3.62 (2H, m), 3.75 (2H, m); ^{13}C-NMR δ: 14.1, 22.7, 25.8, 29.4, 29.8, 31.9, 33.6, 64.5, 72.3, 74.4.

(2*R*,3*R*)-1-Tosyloxy-2,3-dihydroxydecane (10) A mixture of **9** (190 mg) and TsCl (185 mg) in pyridine (2 ml) was allowed to stand overnight at room temperature. The mixture was diluted with AcOEt (50 ml) and then washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (hexane : AcOEt = 3 : 1) to give **10** as a colorless solid (150 mg, 43.6%), mp 63 °C, CI-MS *m/z*: 345 $(M+1)^+$; EI-MS *m/z* (relative intensity): 301 $(M-C_3H_7)^+$ (3), 215 $(M-C_8H_{17}O)^+$ (2), 173 $(M-OTs)^+$ (100); IR ($CHCl_3$): 3550, 2930, 2850, 1730, 1600, 1460 cm^{-1}; ^{1}H-NMR δ: 0.88 (3H, t, J=7.1 Hz), 1.20—1.40 (10H, br m, $W_{1/2}$= 25 Hz), 1.42 (2H, m), 2.46 (3H, s), 3.72 (2H, br m), 4.05 (1H, dd, J=5.6, 12.8 Hz), 4.12 (1H, dd, J=5.4, 12.8 Hz), 7.35 (2H, d, J=8.3 Hz), 7.80 (2H, d, J=8.3 Hz); ^{13}C-NMR δ: 14.2, 21.8, 22.8, 25.7, 29.4, 29.6, 31.9, 33.5, 70.9, 71.6, 78.5, 128.0 (two carbons), 130.0 (two carbons), 132.6, 145.2.

(2*R*,3*R*)-1,2-Epoxydecan-3-ol THP Ether (11) A mixture of **10** (114 mg) and K_2CO_3 (457 mg) in MeOH (3.5 ml) was stirred for 1 h at room temperature. The mixture was diluted with AcOEt (40 ml), washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (hexane : AcOEt = 2 : 1) to give an epoxide (55 mg, 75.7%). ^{1}H-NMR δ: 0.88 (3H, t, J=7.3 Hz), 1.20—1.40 (10H, br m, $W_{1/2}$=25 Hz), 1.60 (2H, m), 1.78 (1H, d, J=5.9 Hz, OH), 2.72 (1H, dd, J=2.7, 4.9 Hz). 2.83 (1H, dd, J=3.9, 4.9 Hz), 2.98 (1H, m), 3.44 (1H, m). A mixture of the above epoxide (50 mg), DHP (40 μl) and CSA (trace amount) in CH_2Cl_2 (1.5 ml) was stirred for 30 min at room temperature. The mixture was diluted with AcOEt (20 ml) and washed successively with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (hexane : AcOEt = 3 : 1) to afford **11** (67 mg, 90.0%). **11**: A mixture of diasteromers, two spots (*Rf* 0.40 and 0.47) on a silica gel thin-layer chromatography (TLC) plate (hexane : AcOEt = 5 : 1), MS *m/z* (relative intensity): 256 $(M)^+$ (5), 213 $(M-C_2H_3O)^+$ (27), 157 $(M-C_7H_{15})^+$ (56), 155 $(M-OTHP)^+$ (100), ^{1}H-NMR δ: 0.88 (t, J=7.1 Hz), 1.20—1.40 (br m, $W_{1/2}$=25 Hz), 1.58 (m), 1.76 (m), 1.84 (m), 2.49 (dd, J=2.7, 4.9 Hz), 2.67 (dd, J=2.7, 4.9 Hz), 2.76 (t, J=4.9 Hz), 2.80 (t, J=4.9 Hz), 2.95 (m), 3.09 (m), 3.38 (m), 3.50 (m), 3.88 (m), 4.00 (m), 4.70 (t, J=4.4 Hz), 4.98 (t, J=4.4 Hz).

1,3-Heptadiyn-5-ol THP Ether BuLi in hexane [10 ml (1.5 mmol/ml)] was added dropwise to a stirred solution of diacetylene[9] in tetrahydrofuran (THF) [15 ml (1 mmol/ml)] at −50 °C and then propionaldehyde (840 mg) was added at the same temperature. After 30 min, saturated NH_4Cl (50 ml) was added to the reaction mixture and then the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave an oil, which was chromatographed on a silica gel column (hexane : AcOEt = 5 : 1) to give 1,3-heptadiyn-5-ol [^{1}H-NMR δ: 1.03 (3H, t, J=7.1 Hz), 1.76 (2H, m), 1.95 (1H, br s, OH), 2.20 (1H, d, J=1.0 Hz), 4.38 (1H, m); ^{13}C-NMR δ: 9.2, 30.4, 63.6, 67.3, 68.2, 68.9, 77.1]. A mixture of 1,3-heptadiyn-5-ol, DHP (1 ml) and CSA (20 mg) in CH_2Cl_2 (10 ml) was stirred for 1 h at room temperature. The mixture was diluted with AcOEt (20 ml) and then washed successively with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and evaporated *in vacuo*. The residual material was chromatographed on a silica gel column (hexane : AcOEt = 7:1) to afford 1,3-heptadiyn-5-ol THP ether (1.4 g, 50% from diacetylene). [A mixture of diastereomers; two spots on a silica gel TLC plate (*Rf* 0.60 and 0.68, hexane : AcOEt = 5 : 1), CI-MS *m/z*: 193 $(M+1)^+$, ^{1}H-NMR δ: 1.00 (t, J=7.3 Hz), 1.04 (t, J=7.3 Hz), 1.56 (m), 1.78 (m), 2.14 (d, J=0.9 Hz), 2.15 (d, J=0.9 Hz), 3.54 (m), 3.57 (m), 3.80 (ddd, J=3.1, 8.6, 11.6 Hz), 4.00 (ddd, J=3.1, 9.8, 12.8 Hz), 4.25 (t, J=6.4 Hz), 4.41 (t, J=6.4 Hz), 4.74 (t, J=3.4 Hz), 4.93 (t, J=4.0 Hz)].

(9*R*,10*R*)-Dihydropanaxacol (12, a Diastereomeric Mixture at C-3) BuLi (0.3 mmol) in hexane (230 μl) and the epoxide (**11**, 25 mg) in THF (100 μl) were successively added dropwise to a stirred solution of 1,3-heptadiyn-5-ol THP ether (77 mg, 0.4 mmol) and HMPA (50 μl) in THF (130 μl) at −30°C. After 2 h, the reaction was quenched with saturated NH_4Cl (10 ml), and then the mixture was extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (hexane : AcOEt = 5 : 1) to give a diastereomeric mixture of the coupling products (two spots on a silica gel TLC plate, hexane : AcOEt = 5 : 1). A mixture of the coupling products (10 mg) and CSA (trace amount) in MeOH (500 μl) was stirred at room temperature. After 1 h, the mixture was diluted with AcOEt (10 ml), then washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by HPLC (Senshu Pack Silica-3251-N, 8 × 250 mm, hexane : AcOEt = 2 : 1) to give **12** (4 mg, 64.5%). $[\alpha]_D$ +12.3° (c=0.79, MeOH), CI-MS *m/z*: 281 $(M+1)^+$, IR ($CHCl_3$): 3500—3300, 2930 (s), 2850 (m), 2260 (w) cm^{-1}, ^{1}H-NMR δ: 0.89 (3H, t, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz), 1.20—1.40 (10H, br m, $W_{1/2}$=25 Hz), 1.50 (2H, m), 1.74 (2H, m), 1.88 (1H, d, J=5.8 Hz, OH), 2.01 (1H, d, J=5.5 Hz, OH), 2.37 (1H, d, J=5.8 Hz, OH), 2.56 (1H, dd, J=6.4, 16.5 Hz), 2.59 (1H, dd, J=6.4, 16.5 Hz). 3.59 (1H, m), 3.64 (1H, m), 4.36 (1H, q, J=6.1 Hz); ^{13}C-NMR δ: 9.36 (q), 14.09 (q), 22.66 (t), 24.91 (t), 25.62 (t), 29.24 (t), 29.59 (t), 30.74 (t), 31.84 (t), 33.59 (t), 64.04 (d), 66.67 (s), 69.61 (s), 72.24 (d), 73.17 (d), 77.31 (s), 77.51 (s).

(9*R*,10*R*)-Dihydropanaxacol Acetonide (13) A mixture of **12** (72 mg), CSA (10 mg) and 2,2-dimethoxypropane (3 ml) was stirred for 30 min at room temperature. The mixture was diluted with AcOEt (30 ml) and washed with saturated $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to leave an oily material, which was chromatographed on a silica gel column (hexane : AcOEt = 5 : 1) to give **13** (80 mg, 97.3%). EI-MS *m/z* (relative intensity): 305 $(M-CH_3)^+$ (17.7), 245 $(M-C_3H_7O_2)^+$ (12.2), 199 $(M-C_8H_9O)^+$ (100); ^{1}H-NMR δ: 0.89 (3H, t, J=6.8 Hz), 1.01 (3H, t, J=7.33 Hz), 1.20—1.40 (10H, br m, $W_{1/2}$=25 Hz), 1.40 (6H, s), 1.60 (2H, m), 1.74 (2H, m), 1.85 (1H, br s, OH), 2.58 (1H, dd, J=5.4, 17.6 Hz), 2.63 (1H, dd, J=5.4, 17.6 Hz), 3.74 (1H, m), 3.79 (1H, m), 4.36 (1H, t, J=6.6 Hz); ^{13}C-NMR: 9.32 (q), 14.09 (q), 22.66 (t), 23.55 (t), 25.97 (t), 26.98 (q), 27.37 (q), 29.16 (t), 29.66 (t), 30.75 (t), 31.82 (t), 32.90 (t), 64.06 (d), 66.66 (s), 69.65 (s), 76.58 (s), 77.18 (s), 78.21 (d), 80.56 (d), 108.76 (s).

Panaxacol Dimethylsulfoxide (20 μl) and **13** (20 mg) in CH_2Cl_2 (100 μl) were successively added dropwise to a stirred solution of oxalyl chloride (12 μl) in CH_2Cl_2 (250 μl) at −50°C. After 1 h, triethylamine (170 μl) was added to the mixture and then stirring was continued for 10 min. The reaction mixture was diluted with AcOEt (40 ml), then washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residual oily material was dissolved in MeOH (2 ml) and then CSA (trace amount) was added at room temperature under stirring. After 2 h, the reaction mixture was diluted with AcOEt (30 ml), washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by HPLC (Senshu Pack Silica-3251-N, 8 × 250 mm, hexane : AcOEt = 2 : 1) to give panaxacol (retention time: 13.2 min) (10 mg, 60.0%). $[\alpha]_D$ +18.3° (c=1.0, MeOH); CI-MS *m/z*: 279 $(M+1)^+$; IR ($CHCl_3$): 3560 (w), 3400 (s), 2930 (s), 2850 (m), 2240 (s), 2150 (w), 1665 (s) cm^{-1}; ^{1}H-NMR δ: 0.89 (3H, t, J=7.1 Hz), 1.15 (3H, t, J=7.3 Hz), 1.20—1.40 (10H, br m, $W_{1/2}$=25 Hz), 1.51 (2H, m), 1.91 (1H, d, J=5.6 Hz, OH), 2.36 (1H, d, J=5.9 Hz, OH), 2.60 (2H, q, J=7.3 Hz), 2.64 (1H, dd, J=6.3, 17.6 Hz), 2.68 (1H, dd, J=5.9, 17.6 Hz), 3.59 (1H, m), 3.70 (1H, m).

***R*-(+)-MTPA Ester (A) and (B)** A mixture of **13** (8 mg) and five drops (large excess) of *R*-MTPA-Cl in pyridine (500 μl) was allowed to stand overnight at room temperature. The mixture was diluted with AcOEt (30 ml), washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was separated by HPLC (Senshu Pack Silica-3251-N, 8 × 250 mm, hexane : AcOEt = 20 : 1) to give the *R*-(+)-MTPA ester (A) (retention time: 9.2 min) and *R*-(+)-MTPA ester (B) (retention time: 10.6 min).

R-(+)-MTPA Ester (A): ^{1}H-NMR δ: 0.88 (3H, t, J=7.1 Hz), 0.93 (3H, t, J=7.3 Hz). 1.20—1.40 (10H, br m, $W_{1/2}$=25 Hz), 1.40 and 1.41 (3H each, s), 1.58 (2H, m), 1.83 (2H, m), 2.58 (1H, dd, J=5.1, 17.8 Hz), 2.64 (1H, dd, J=5.1, 17.8 Hz), 3.59 (3H, br s), 3.73 (1H, m), 3.84 (1H, m), 5.54

(1H, t, J=6.6 Hz). 7.42 (3H, m), 7.53 (2H, m).

R-(+)-MTPA Ester (B): ^{1}H-NMR δ: 0.88 (3H, t, J=7.1 Hz), 1.03 (3H, t, J=7.3 Hz), 1.20—1.40 (10H, br m, $W_{1/2}$=25 Hz), 1.40 and 1.41 (3H each, s), 1.58 (1H, m), 1.89 (2H, m), 2.58 (1H, dd, J=5.1, 18.3 Hz), 2.64 (1H, dd, J=5.1, 18.3 Hz), 3.55 (3H, br s), 3.73 (1H, m), 3.80 (1H, m), 5.51 (1H, t, J=6.6 Hz), 7.43 (3H, m), 7.52 (2H, m).

References and Notes

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