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Synthesis and Absolute Configuration of Panaxytriol

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A diastereomeric mixture at C-3 of panaxytriol (1) was synthesized starting from L-(+)-diethyl tartrate, and the absolute configurations at C-9 and C-10 of 1 were confirmed to be 9*S* and 10*S*, respectively. The absolute configuration at C-3 of 1 was reconfirmed to be *R* by the application of Mosher's method.

Key words panaxytriol; chiral synthesis; diethyl tartrate; Mosher's method; absolute configuration; *Panax* species

The polyacetylene compounds isolated from *Panax* species exhibit interesting biological activities such as cytotoxicity, antifungal activity and neurotoxicity.[1] In previous papers,[2,3] we reported the isolation and structure elucidation of new C_{17}- and C_{14}-polyacetylenes, along with some known polyacetylenes including panaxytriol (**1**),[4] from *Panax* species. Recently, Kobayashi *et al.*[5] reported that the absolute stereostructure of panaxytriol is 3*R*, 9*R*, 10*R* based on the application of the modified Mosher's method and the dibenzoate CD exciton chirality method. However, we reached a different conclusion regarding the absolute configurations at C-9 and C-10, based on the synthesis of panaxytriol (**1**) starting from L-(+)-diethyl tartrate. In this paper, we would like to describe the synthesis of a diastereomeric mixture at C-3 of panaxytriol and the determination of the absolute configuration of **1**.

L-(+)-Diethyl tartrate was transformed into an epoxy-alcohol (**2**) *via* seven steps according to the method described in our previous paper.[6] Compound **2** was treated with diacetylene in the presence of butyllithium–hexamethylphosphoric triamide (HMPA) to give a diacetylene-glycol (**3**). After protection of the glycol moiety as an acetonide, the diacetylene was coupled with acrolein to afford a diastereomeric mixture at C-3 of 9*S*,10*S*-panaxytriol acetonide (**4**). Acid hydrolysis of the acetonide group gave a diastereomeric mixture of 9*S*,10*S*-panaxytriol (**5**) which showed negative optical rotation ($[\alpha]_D$ $-13.5°$). Similarly, a diastereomeric mixture at C-3 of 9*R*,10*R*-panaxytriol ($[\alpha]_D$ $+13.8°$) was synthesized from D-(−)-diethyl tartrate. If the effect of the chirality at C-3 in panaxytriol is not so large as to reverse the sign of the optical rotation, the absolute configurations at C-9 and C-10 in panaxytriol can be presumed to be 9*S* and 10*S*, because panaxytriol was levorotatory ($[\alpha]_D$ $-16.3°$). This presumption was proved to be true as follows. A diastereomeric mixture at C-3 of 9*S*,10*S*-panaxytriol acetonide (**4**) was oxidized with dimethylsulfoxide (DMSO)–oxalyl chloride to give 3-oxo-9*S*,10*S*-panaxytriol acetonide (**6**) ($[\alpha]_D$ $-15.3°$). The natural panaxytriol was converted into an acetonide which was oxidized under the same conditions. The compound obtained here was identical with **6** in all respects, including optical rotation ($[\alpha]_D$ $-16.0°$). Thus, the absolute configurations at C-9 and C-10 of **1** were determined to be 9*S* and 10*S*, respectively.

Finally, the absolute configuration at C-3 of panaxytriol determined by Kobayashi *et al.* was reconfirmed as follows. Treatment of the diastereomeric mixture of 9*S*,10*S*-panaxytriol acetonide (**4**) with *S*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) gave a mixture of *R*-(+)-MTPA ester which was separated into *R*-(+)-MTPA ester-I (retention time 13.2 min) and *R*-(+)-MTPA ester-II (retention time 14.4 min) by HPLC.

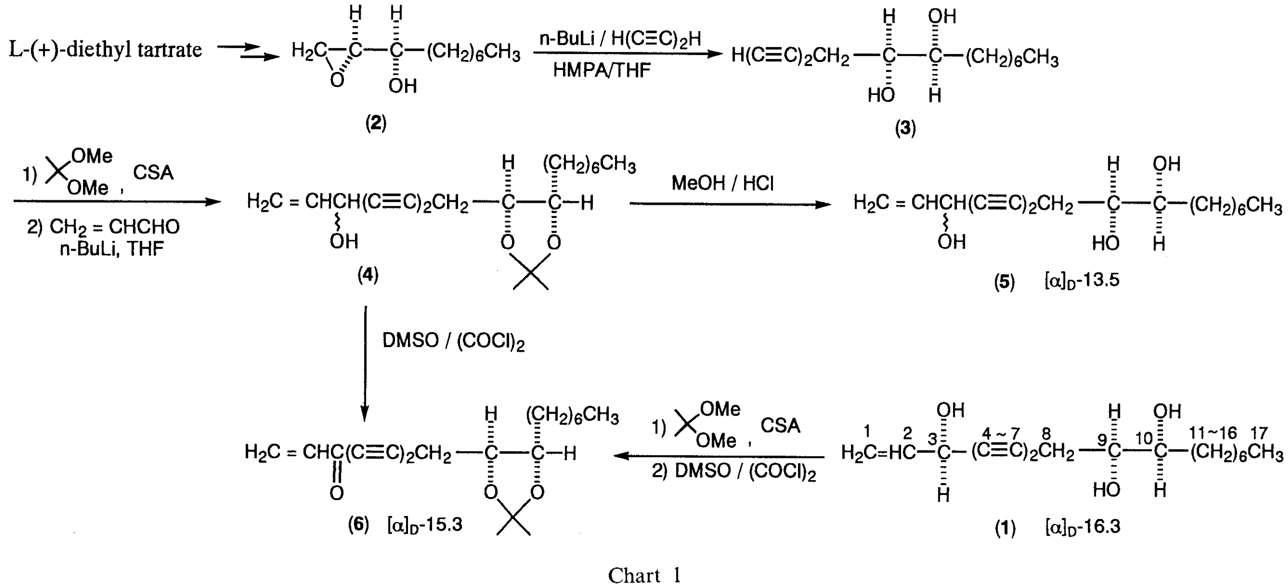

Chart 1

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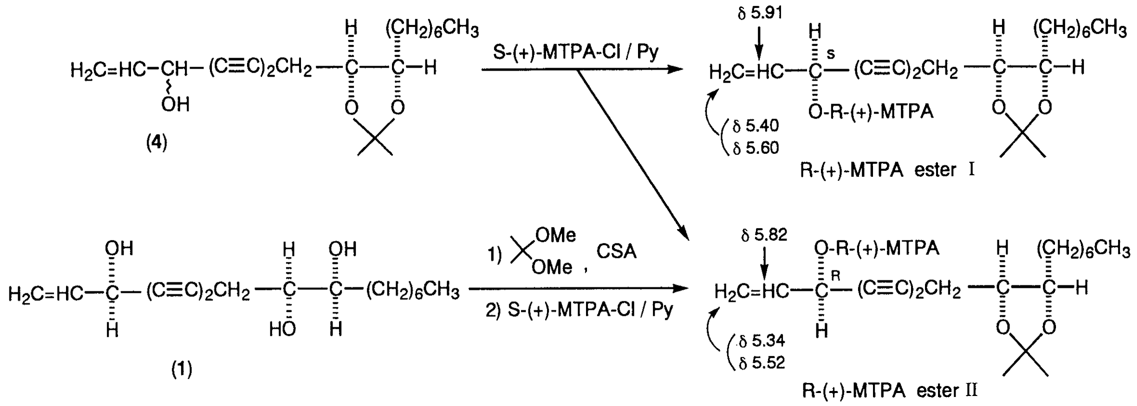

Chart 2

A comparison of the ^{1}H-NMR of ester-I with that of ester-II revealed that the vinyl proton signals [δ 5.34, 5.52 (H-1), δ 5.82 (H-2)] of the ester-II appeared at higher field than those [δ 5.40, 5.60 (H-1), δ 5.91 (H-2)] of ester-I. Thus, the absolute configurations at C-3 of the ester-I and the ester-II were assigned as *S* and *R*, respectively, based on the general rules of the MTPA method.

Similarly, natural panaxytriol was also transformed to the *R*-(+)-MTPA ester after protection of the glycol moiety. The ester obtained here was identical with the MTPA ester-II in terms of the ^{1}H-NMR spectrum and retention time on HPLC. Thus, the absolute configuration of panaxytriol was confirmed to be 3*R*, 9*S*, 10*S*. The syntheses of some other polyacetylene compounds isolated from *panax* species are in progress.

Experimental

^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-α500 spectrometer in $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. MS were recorded on a JEOL JMS-D300 instrument. Optical rotations were measured on a JASCO DIP-370 polarimeter.

(6*S*,7*S*)-6,7-Dihydroxytetradeca-1,3-diyne (3) *n*-BuLi (1.57 mmol/l) in hexane [0.98 ml (1.54 mmol)] and HMPA (0.25 ml) were added dropwise to a stirred solution of diacetylene in tetrahydrofuran (THF) [1.2 ml (1.0 mmol/ml)] at −30 °C. After 10 min, a solution of **2** (37.9 mg, 0.27 mmol) in THF (1.0 ml) was added and stirring was continued for 2 h at the same temperature. The reaction mixture was quenched with saturated NH_4Cl (5 ml) and then 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 **3** (46 mg, 94.1%) as an oil.

3: $[\alpha]_D$ −14.1° (c=0.87, $CHCl_3$). CI-MS: m/z=223 $(M+1)^+$, 205 $(M+1-H_2O)^+$. ^{1}H-NMR δ: 0.88 (3H, t, J=7.3 Hz), 1.25—1.40 (10H, br m), 1.50 (2H, m), 2.01 (1H, s), 2.55 (1H, dd, J=7.3, 17.6 Hz), 2.57 (1H, dd, J=5.8, 17.6 Hz), 3.60 (1H, m), 3.65 (1H, m). ^{13}C-NMR δ: 14.1, 22.7, 24.7, 25.6, 29.2, 29.5, 31.8, 33.6, 65.3, 66.8, 68.1, 72.1, 73.0, 74.4.

(9*S*,10*S*)-Panaxytriol Acetonide (4, a Diastereomeric Mixture at C-3) The compound (**3**, 138 mg) was dissolved in 3 ml of 2,2-dimethoxypropane and then camphorsulfonic acid (CSA) (2 mg) was added under stirring at room temperature. After 1 h, the reaction mixture was diluted with AcOEt (20 ml) and then washed with saturated $NaHCO_3$ solution (20 ml). The organic layer was washed with brine (20 ml × 2), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (hexane : AcOEt = 3 : 1) to give an acetonide [(6*S*,7*S*)-6,7-isopropylidenedioxytetradeca-1,3-diyne] as an oil (102 mg, 88.7%).

(6*S*,7*S*)-6,7-Isopropylidenedioxytetradeca-1,3-diyne: ^{1}H-NMR δ: 0.89 (3H, t, J=7.3 Hz), 1.25—1.40 (10H, br m), 1.41 (6H, s), 1.51 (2H, m), 2.00 (1H, s), 2.57 (1H, dd, J=7.3, 17.6 Hz), 2.61 (1H, J=5.8, 17.6 Hz), 3.71 (1H, m), 3.80 (1H, m). $[\alpha]_D$ −11.3° (c=0.64, $CHCl_3$). CI-MS: m/z=263 $(M+1)^+$, 247 $(M+1-CH_3)^+$.

n-BuLi in hexane (228 μl, 0.36 mmol) and acrolein (147 μl, 1.8 mmol) were successively added dropwise to a stirred solution of the acetonide (47 mg, 0.18 mmol) in THF (0.5 ml), at −30 °C. After 2 h, saturated NH_4Cl solution (5 ml) was added and then the reaction mixture was extracted with AcOEt (20 ml × 3). The combined organic layer was washed with brine (20 ml × 2), 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 = 5 : 1) to give **4** (10 mg, 17.5%) as an oil.

4: ^{1}H-NMR δ: 0.88 (3H, t, J=6.8 Hz), 1.25—1.45 (10H, br m), 1.40 (6H, s), 1.50 (2H, m), 2.58 (1H, dd, J=6.6, 17.3 Hz), 2.60 (1H, dd, J=5.6, 17.3 Hz), 3.59 (1H, m), 3.65 (1H, m), 4.92 (1H, d, J=5.4 Hz), 5.26 (1H, d, J=10.3 Hz), 5.47 (1H, d, J=17.1 Hz), 5.95 (1H, ddd, J=5.4, 10.3, 17.1 Hz).

(9*S*,10*S*)-Panaxytriol (5, a Diastereomeric Mixture at C-3) Compound **4** (5.0 mg, 0.02 mmol) was dissolved in 0.5 ml of MeOH–2 N HCl (1 : 1) under stirring at room temperature. After 1 h, brine (10 ml) was added and the mixture was extracted with AcOEt (10 ml × 2). The combined organic layer was washed with brine (15 ml × 2), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (hexane : AcOEt = 3 : 1) to give **5** as an oil (4.5 mg, 90.7%).

5: $[\alpha]_D$ −13.5° (c=0.42, MeOH), ^{1}H-NMR δ: 0.88 (3H, t, J=6.8 Hz), 1.25—1.45 (10H, br m), 1.50 (2H, m), 1.64 (1H, m), 2.14 (1H, m), 2.47 (1H, s), 2.58 (1H, dd, J=6.6, 17.3 Hz), 2.60 (1H, dd, J=5.6, 17.3 Hz), 3.59 (1H, m), 3.65 (1H, m), 4.92 (1H, d, J=5.4 Hz), 5.26 (1H, d, J=10.3 Hz), 5.47 (1H, d, J=17.1 Hz), 5.95 (1H, ddd, J=5.4, 10.3, 17.1 Hz).

(9*R*,10*R*)-Panaxytriol (a Diastereomeric Mixture at C-3) This compound was synthesized starting from D-(−)-diethyl tartrate according to the procedures described for the synthesis of (9*S*,10*S*)-panaxytriol (**5**). $[\alpha]_D$ +13.8° (c=0.40, MeOH). The ^{1}H-NMR spectrum was identical with that of **5**.

***R*-(+)-MTPA Ester I and II** A mixture of **4** (5 mg, 0.02 mmol) and five drops (large excess) of (*S*)-(+)-MTPA-Cl in pyridine (0.5 ml) was allowed to stand for 2 h at room temperature. It was diluted with AcOEt (20 ml), washed with brine (15 ml × 2), dried over Na_2SO_4 and concentrated *in vacuo* to leave an oil, which was separated by HPLC (Senshu Pack Silica 5251-N, 20 × 250 mm, solvent; hexane : AcOEt = 8 : 1, flow rate; 8 ml/min) to give *R*-(+)-MTPA ester I (retention time; 13.2 min, 3 mg, 37.5%) and *R*-(+)-MTPA ester II (retention time; 14.4 min, 3 mg, 37.5%).

R-(+)-MTPA Ester I: ^{1}H-NMR δ: 0.88 (3H, t, J=6.8 Hz), 1.25—1.40 (10H, br m), 1.40, 1.41 (3H each, s), 1.57 (2H, m), 2.59 (1H, dd, J=6.6, 17.3 Hz), 2.62 (1H, dd, J=5.6, 17.3 Hz), 3.59 (3H, s), 3.74 (1H, m), 3.80 (1H, m), 5.40 (1H, d, J=10.5 Hz), 5.60 (1H, d, J=17.1 Hz), 5.91 (1H, ddd, J=5.4, 10.5, 17.1 Hz), 6.08 (1H, m), 7.43 (3H, m), 7.52 (2H, m).

R-(+)-MTPA Ester II: ^{1}H-NMR δ: 0.88 (3H, t, J=6.8 Hz), 1.25—1.40 (10H, br m), 1.40, 1.41 (3H each, s), 1.57 (2H, m), 2.59 (1H, dd, J=6.6, 17.3 Hz), 2.62 (1H, dd, J=5.6, 17.3 Hz), 3.59 (3H, s), 3.74 (1H, m), 3.80 (1H, m), 5.34 (1H, d, J=10.5 Hz), 5.52 (1H, d, J=17.1 Hz), 5.82 (1H, ddd, J=5.4, 10.5, 17.1 Hz), 6.11 (1H, m), 7.43 (3H, m), 7.52 (2H, m).

(9*S*,10*S*)-3-Oxopanaxytriol (6) DMSO (30 ml, 0.46 mmol) and **4** (5 mg, 0.02 mmol) in CH_2Cl_2 (100 μl) were successively added dropwise to a stirred solution of oxalyl chloride (20 μl, 0.22 mmol) in CH_2Cl_2 (200 μl), at -40 °C. After 2 h, triethylamine (200 μl, 1.43 mmol) was added and stirring was continued for 20 min. The reaction mixture was diluted with AcOEt (10 ml), then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to leave an oily material, which was purified by HPLC (Senshu Pack Silica 4251-N, 10 × 250 mm, solvent; hexane : AcOEt = 3 : 1, flow rate; 3 ml/min) to give **6** (2 mg, 40%, retention time; 7.5 min).

6: $[\alpha]_D$ $-15.3°$ ($c=0.13$, MeOH), ^{1}H-NMR δ: 0.88 (3H, t, $J=6.8$ Hz), 1.25—1.40 (10H, br m), 1.40, 1.41 (3H each, s), 1.58 (2H, m), 2.58 (1H, dd, $J=6.7$, 17.3 Hz), 2.60 (1H, dd, $J=5.6$, 17.3 Hz), 3.59 (1H, m), 3.66 (1H, m), 6.24 (1H, d, $J=10.5$ Hz), 6.40 (1H, dd, $J=10.5$, 16.6 Hz), 6.57 (1H, d, $J=16.6$ Hz). CI-MS: $m/z=316$ $(M+1)^+$, 301 $(M+1-CH_3)^+$.

Conversion of Panaxytriol into 3-Oxopanaxytriol Panaxytriol was converted into an acetonide, which was oxidized with DMSO–$(COCl)_2$ to give 3-oxo-panaxytriol according to the procedures described above. The compound obtained here was identical with **6** in terms of ^{1}H-NMR and the retention time on HPLC. $[\alpha]_D$ $-16.0°$ ($c=0.05$, MeOH).

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