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 9S and 10S, 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. In previous papers, we reported the isolation and structure elucidation of new C17- and C14-polyacetylenes, along with some known polyacetylenes including panaxytriol (1), from Panax species. Recently, Kobayashi et al. reported that the absolute stereostructure of panaxytriol is 3R, 9R, 10R based on the application of the modified Mosher's methodology 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 epoxyalcohol (2) via seven steps according to the method described in our previous paper. Compound 2 was treated with diacetylene in the presence of butyllithium–hexamethylphosphoronic triamide (HMPA) to give a diacetylene-glycol (3). After protection of the glycol moiety as an acetone, the diacetylene was coupled with acrolein to afford a diastereomeric mixture at C-3 of 9S,10S-panaxytriol acetone (4). Acid hydrolysis of the acetonide group gave a diastereomeric mixture of 9S,10S-panaxytriol (5) which showed negative optical rotation ([β]D -13.5°). Similarly, a diastereomeric mixture at C-3 of 9R,10R-panaxytriol ([β]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 9S and 10S, because panaxytriol was levorotatory ([β]D -16.3°). This presumption was proved to be true as follows. A diastereomeric mixture at C-3 of 9S,10S-panaxytriol acetone (4) was oxidized with dimethylsulfoxide (DMSO)-oxalyl chloride to give 3-oxo-9S,10S-panaxytriol acetone (6) ([β]D -15.3°). The natural panaxytriol was converted into an acetone which was oxidized under the same conditions. The compound obtained here was identical with 6 in all respects, including optical rotation ([β]D -16.0°). Thus, the absolute configurations at C-9 and C-10 of 1 were determined to be 9S and 10S, 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 9S,10S-panaxytriol acetone (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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A comparison of the ^1H-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 ^1H-NMR spectrum and retention time on HPLC. Thus, the absolute configuration of panaxytriol was confirmed to be 3R, 9S, 10S. The synthesis of some other polyacetylenic compounds isolated from *Panax* species are in progress.

**Experimental**

1H- and 13C-NMR spectra were measured on a JEOL JNM-e500 spectrometer in CDCl₃ 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.

(6S,7S,5)-6,7-Dihydroxytetradeca-1,3,5-triene (3) n-BuLi (1.57 mmol/l) in hexane [0.96 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 B (27.39 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 NH₄Cl (5 ml) and then extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, 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: [α]D = −14.1° (c = 0.87, CHCl₃). CI-MS: m/z = 223 (M + 1)°, 205 (M + 1—H₂O)°. 1H-NMR δ: 0.88 (3H, t, J = 7.3 Hz), 1.25—1.40 (10H, brm), 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). 13C-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.

(9S,10S)-Panaxytriol Acetone (4, a Diastereometric 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 NaHCO₃ solution (20 ml). The organic layer was washed with brine (20 ml × 2), dried over Na₂SO₄ and evaporated in vacuo. The residue was chromatographed on a silica gel column (hexane:AcOEt = 3:1) to give an acetone [6S,7S,5)-6,7-isopropylidenedierytreadeca-1,3,5-triene] as an oil (102 mg, 88%).

(6S,7S,6)-6,7-Isopropylidenedierytreadeca-1,3,5-triene: 1H-NMR δ: 0.89 (3H, t, J = 7.3 Hz), 1.25—1.40 (10H, brm), 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). [α]D = −11.3° (c = 0.64, CHCl₃). CI-MS: m/z = 263 (M + 1)°, 247 (M + 1—CH₃)°.

-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 acetone (47 mg, 0.18 mmol) in THF (0.5 ml) at −30 °C. After 2 h, saturated NH₄Cl 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 Na₂SO₄ 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: [α]D = 0.88 (3H, t, J = 6.8 Hz), 1.25—1.45 (10H, brm), 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).

**Chart 2**

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 Na₂SO₄ 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, 37.5%), R-(+)-MTPA Ester II (retention time; 14.4 min, 37.5%), and R-(-)-MTPA Ester II (retention time; 10.5 min, 37.5%).

R-(+)-MTPA Ester I: [α]D = 0.88 (3H, t, J = 6.8 Hz), 1.25—1.40 (10H, brm), 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). [α]D = 5.4, 10.5, 17.1 Hz), 6.08 (1H, m), 7.43 (3H, m), 7.52 (2H, m).

R-(+)-MTPA Ester II: [α]D = 0.88 (3H, t, J = 6.8 Hz), 1.25—1.40 (10H, brm), 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). [α]D = 5.4, 10.5, 17.1 Hz), 6.08 (1H, m), 7.43 (3H, m), 7.52 (2H, m).

**(9S,10S)-3-Oxopanaxytriol** (6) DMSO (30 ml, 0.46 mmol) and 4 (5 mg, 0.02 mmol) in CH₂Cl₂ (100 µl) were successively added dropwise to

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to a stirred solution of oxaly chloride (20 µl, 0.22 mmol) in CH₂Cl₂ (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 Na₂SO₄ and concentrated in vacuo to leave an oily material, which was purified by HPLC (Senshu Pack Silica 4251-N, 10 x 250 mm, solvent; hexane: AcOEt = 3:1, flow rate; 3 ml/min) to give 6 (2 mg, 40%, retention time; 7.5 min).

6 [α]₂₅ ≈ -15.3° (c = 0.13, MeOH), ³¹H-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 – CH₃)*.

Conversion of Panaxytritol into 3-Oxopanaxytritol. Panaxytritol was converted into an acetone, which was oxidized with DMSO(OCOCl)₂ to give 3-oxo-panaxytritol according to the procedures described above. The compound obtained here was identical with 6 in terms of ³¹H-NMR and the retention time on HPLC. [α]₀ = -16.0° (c = 0.05, MeOH).

References