SYNTHESIS AND THE ABSOLUTE CONFIGURATION OF PQ-8, A C_{14} -POLYACETYLENE COMPOUND ISOLATED FROM *PANAX QUINQUEFOLIUM*

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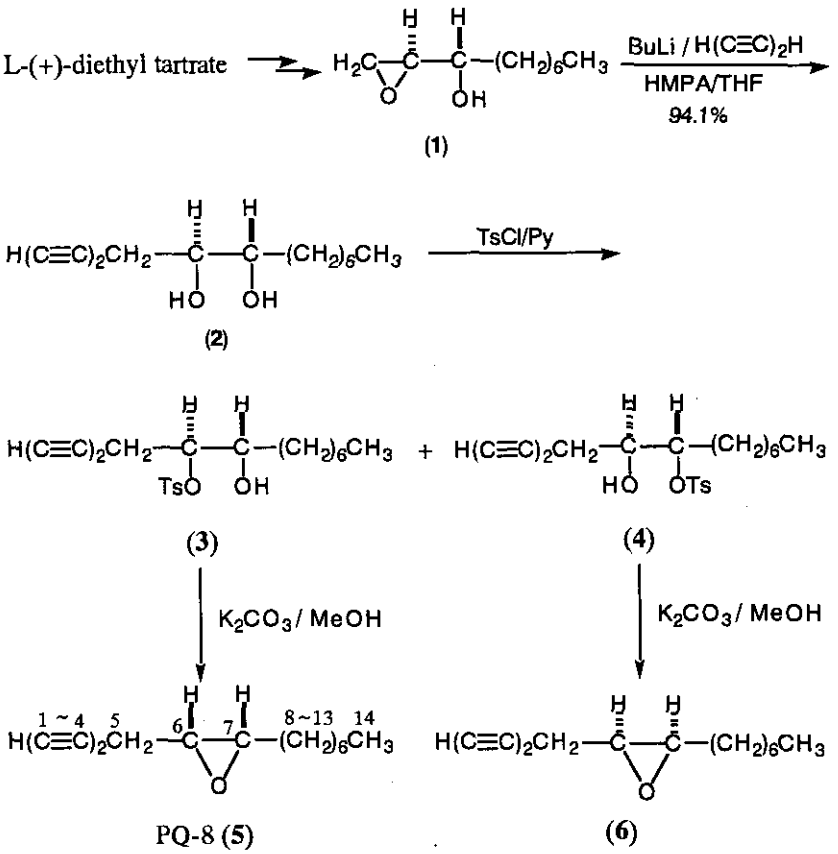
Abstract — PQ-8 (**5**), a C_{14}-polyacetylene compound isolated from *Panax quinquefolium*, was synthesized starting from L-(+)-diethyl tartrate. The absolute stereostructure of PQ-8 was confirmed as (6R,7S)-6,7-epoxytetradeca-1,3-diyne.

In the previous papers,[1a-c] we have reported the isolation and structural elucidation of cytotoxic C_{14}- and C_{17}-polyacetylene compounds from *Panax quinquefolium*. Although we have confirmed the relative configuration of the epoxide ring of PQ-8 (**5**) to be *cis*, the absolute configuration have not been elucidated yet. Therefore, we planned to determine the absolute configuration of PQ-8 (**5**) by synthesizing it using L-(+)-diethyl tartrate as a chiral template.

L-(+)-Diethyl tartrate was transformed into an epoxy alcohol (**1**) *via* seven steps according to the method described in our previous paper.[2] Compound (**1**) was treated with diacetylene[3] in the presence of n-butyl-lithium-hexamethylphosphoric triamide (HMPA) to give a diacetylene-glycol (**2**). Tosylation of **2** with *p*-TsCl-pyridine afforded a mixture of monotosylates which was separated by high performance liquid chromatography to give 6-tosyloxy (**3**) and 7-tosyloxy (**4**) compounds in a ratio of 1 : 1.6. The structures of **3** and **4** were confirmed by the analyses of their ^{1}H NMR spectra. In the ^{1}H-^{1}H COSY spectrum of **3**, the signal (δ 4.49) assignable to tosyloxy-methine proton (H-6) showed the cross peaks due to the couplings with the nonequivalent methylene proton signals [δ 2.62 (dd, J = 4.3, 16.5 Hz), δ 2.85 (dd, J = 6.8, 16.5 Hz)] and the oxymethine proton signal [δ 3.80 (m), H-7]. On the other hand, the proton signal (δ 4.60) due to tosyloxy-methine proton in the ^{1}H-^{1}H COSY spectrum of **4** exhibited the cross peaks with oxymethine proton signal [δ 3.86 (m)] and the multiplet signals [δ 1.61 (m) and δ 1.75 (m)] due to nonequivalent methylene protons (H-8). Thus, **3** and **4** were assigned as 6-tosyloxy and 7-tosyloxy derivatives, respectively. Finally, these tosylates were treated with K_2CO_3 - MeOH to give the epoxides (**5**) ([α]$_D$-30.0°, $CHCl_3$, c = 0.14) and (**6**) ([α]$_D$ +32.5°, $CHCl_3$, c = 0.12), respectively. The epoxide (**5**) obtained here was identical with PQ-8 ([α]$_D$-30.2°, $CHCl_3$, c = 0.60) in all respects including optical rotation. Thus, the absolute stereostructure of PQ-8 was determined to be (6R,7S)-6,7-epoxytetradeca-1,3-diyne.



EXPERIMENTAL

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

(6S, 7S)-6,7-Dihydroxytetradeca-1,3-diyne (**2**)

n-BuLi in hexane [0.98 ml (1.5 mmol / mL)] and HMPA (0.25 mL) was added dropwise to a stirred solution of diacetylene in THF [1.2 mL (1.0 mmol / mL)] at -30°C. After 10 min, a solution of **1** (37.9 mg, 0.27 mmol) in THF (1.0 mL) was added and the 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 **2** (46 mg, 94.1%) as an oil.

$[\alpha]_D$ - 14.1° (c = 0.87, $CHCl_3$). MS (CI): *m/z* = 223 (M + 1, 91.6)$^+$, 205 (M + 1 - H_2O, 100)$^+$.

^{1}H NMR: δ = 0.88 (3 H, t, *J* = 7.3 Hz), 1.25 ~ 1.40 (10 H, 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 Hz, 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.

(6S, 7S)-7-Hydroxy-6-tosyloxy-tetradeca-1,3-diyne (**3**) and (6S, 7S)-6-hydroxy-7-tosyloxy-tetradeca-1,3-diyne (**4**)

A mixture of **2** (53.6 mg, 0.24 mmol), TsCl (66.6 mg, 0.35 mmol) in pyridine (0.5 mL) and $CHCl_3$ (0.5 mL) was allowed to stand overnight at room temperature. The mixture was diluted with AcOEt and then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chormatographed on a silica gel column (hexane : AcOEt = 5 : 1) to afford a mixture of **3** and **4** which was separated by HPLC [Sensyu Pack, Silica 5251-N, 20 x 250 mm, hexane : AcOEt = 3 : 1, flow rate; 8 mL/min] to give **3** (22.0 mg, 30.3%, retention time = 15.0 min) and **4** (35.0 mg, 40.0%, retention time = 16.0 min).

3: $[\alpha]_D$ - 9.1° (c = 0.80, $CHCl_3$),
MS (CI): m/z = 377 $(M + 1,27.7)^+$, 205 $(M + 1 - TsOH, 100)^+$,
^{1}H NMR: δ = 0.88 (3H, t, *J* = 7.0 Hz), 1.25 ~ 1.35 (10H, m), 1.37 (1H, m), 1.64 (1H, m), 2.01 (1H, s), 2.46 (3H, s), 2.62 (1H, dd, *J* = 4.3, 16.5 Hz), 2.85 (1H, dd, *J* = 6.8, 16.5 Hz), 3.80 (1H, m), 4.49 (1H, m), 7.36 (2H, d, *J* = 8.0 Hz), 7.82 (2H, d, *J* = 8.0 Hz),
^{13}C NMR: δ = 14.1, 21.7, 22.0, 22.6, 25.4, 29.1, 29.3, 31.8, 33.0, 65.7, 67.3, 67.9, 71.2, 72.1, 81.5, 128.0 (two carbons), 130.0 (two carbons), 133.3, 145.3.

4: $[\alpha]_D$ + 11.1° (c = 1.1, $CHCl_3$), MS (CI): *m/z* = 377 $(M + 1, 30.7)^+$, 205 $(M + 1 - TsOH, 100)^+$,
^{1}H NMR: δ = 0.89 (3H, t, *J* = 7.0 Hz), 1.25 ~ 1.35 (10H, m), 1.61 (1H, m), 1.75 (1H, m), 2.02 (1H, s), 2.21 (1H, s), 2.46 (3H, s), 2.47 (1H, dd, *J* = 4.3, 16.5 Hz), 3.86 (1H, m), 4.60 (1H, m), 7.36 (2H, d, *J* = 8.0 Hz), 7.82 (2H, d, *J* = 8.0 Hz),
^{13}C NMR: δ = 14.1, 21.7, 22.6, 24.2, 24.9, 29.0, 29.1, 30.5, 31.6, 65.5, 67.1, 68.0, 70.1, 73.3, 84.2, 127.9 (two carbons), 129.9 (two carbons), 133.6, 145.1.

(6R, 7S)-6,7-Epoxytetradeca-1,3-diyne (**5**)

A mixture of **3** (6.9 mg, 0.02 mmol) and K_2CO_3 (13.2 mg, 0.1 mmol) in MeOH (0.5 mL) was stirred for 1 h at room temperature. The mixture was diluted with AcOEt (20 mL), washed with brine (20 mL x 2), dried (Na_2SO_4), and concentrated *in vacuo* to leave an oil which was purified by HPLC [Sensyu Pack Silica 4201-N, 10 x 200 mm, hexane : AcOEt = 8 : 1] to give **5** (3. 7 mg, 95.0%).
$[\alpha]_D$ -30.9° (c = 0.14, $CHCl_3$). PQ-8 (natural): $[\alpha]_D$ -30.2° (c = 0.6, $CHCl_3$).
MS (CI): *m/z* = 205 $(M + 1)^+$,
^{1}H NMR: δ = 0.89 (3 H, t, *J* = 6.6 Hz), 1.26 ~ 1.47 (10 H, m), 1.53 (2H, m), 2.02 (1H, s), 2.37 (1H, dd, *J* = 7.3, 17.6 Hz), 2.67 (1H, dd, *J* = 5.8 Hz, 17.6 Hz), 2.97 (1H, m), 3.16 (1H, ddd, *J* = 4.0, 5.8, 7.3 Hz).
^{13}C NMR: δ = 14.1, 19.2, 22.6, 26.5, 27.5, 29.2, 29.4, 31.7, 54.2, 56.9, 65.5, 66.7, 68.0, 73.0.

(6S, 7R)-6,7-Epoxytetradeca-1,3-diyne (**6**)

Compound (**4**) was treated with K_2CO_3-MeOH as described above to give **6** (80.0%). The ^{1}H and ^{13}C NMR data of **6** were identical with those of **5**.
$[\alpha]_D$ +32.5° (c = 0.12, $CHCl_3$).

REFERENCES

1. (a) Y. Fujimoto, M. Satoh, N. Takeuchi, and M. Kirisawa, *Chem. Pharm. Bull.*, 1991, ***39***, 521.
(b) Y. Fujimoto, H. Wang, M. Kirisawa, M. Satoh, and N. Takeuchi, *Phytochemistry*, 1992, ***31***, 3499.
(c) Y. Fujimoto, H. Wang, M. Kirisawa, M. Satoh, and N. Takeuchi, *Phytochemistry*, 1994, ***35***, 1255.
2. Y. Fujimoto, M. Satoh, N. Takeuchi, and M. Kirisawa, *Chem. Pharm. Bull.*, 1990, ***38***, 1447.
3. L. Brandsma and H. D. Verkruijsse, *Studies in Organic Chemistry, Vol. 8, Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier Scientific Publishing Co.: Amsterdam, 1981, 146.

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