Synthesis of *cis*- and *trans*-5,8-Dihydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone

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***Cis*- and *trans*-5,8-dihydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (1a, 1b) were for the first time synthesized from 5,8-dihydroxy-1,4-naphthoquinone (naphthazazine) (6) as a starting material and racemic triol (3) was first synthesized from 7. The configuration of 1a was determined by X-ray analysis.**

Key words naphthoquinone; spiroacetal-bridged compound; antitumor activity

Sch 49210 (**2**) is a novel metabolite having antitumor and inhibitory phospholipase D activities and was isolated from a fungal culture broth by Chu *et al.* in 1994.[1)] Compound **2** contains a unique structure, ketobisepoxydecalone with a spiroacetal linkage through a naphthalene moiety. CJ-12, 372 (**4**) isolated by Sakemi *et al.*[2)] was shown to possess DNA gyrase inhibition activity and is a spiroacetal compound with 1,8-naphtalenediol (**5**) as compound **2**. Recently, investigations of analogous compounds of **2** and **4** have been reported and the syntheses of a series of these naturally occurring spiroacetal-bridged compouds were published.[3—11)] The synthesis of bisepoxide **2** and naphthalene dimer **4** has not yet been published, however, we initially began to synthesize key compounds **1a** and **3** for **2** and **4** (Chart 1). In this paper, we describe the first synthesis of *cis*- and *trans*-5,8-dihydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (**1a**, **1b**) by two routes, and also the first synthesis of racemic triol **3**.

Results and Discussion

2,3-Dihydro-5,8-dihydroxy-1,4-naphthoquinone (**7**) was synthesized from naphthazazine (**6**) as the starting material by applying the procedure[12)] developed by Pearson *et al.* Reduction of **6** by 20 eq of stannous chloride under acidic conditions gave dihydro compound **7** in 90% yield (Chart 2). Diol **7** was used in the following procedure without purification because **7** is unstable to air-oxidation and returns to starting material **6** easily. Diol **7** was then reduced by treatment with large excess (24 eq) of $NaBH_4$ in the presence of a catalytic amount of $CeCl_3$[13—15)] in tetrahydrofuran (THF) at room temperature to afford a mixture of **8a** and **8b**. Oxidation of a mixture of **8a** and **8b** using ceric ammonium nitrate (CAN)[16—18)] as an oxidant in acetonitrile gave a mixture of **1a** (*cis*) and **1b** (*trans*).[19)] The mixture was separated by column chromatography to give crystals **1a** and oil **1b** in 34 and 50% yields, respectively (Chart 2). The stereostructures of **1a** and **1b** were decided as follows. The determination whether **1a** and **1b** are the *cis* or *trans* isomer by ^{1}H-NMR spectra presented great difficulty because each spectrum exhibits a complicated coupling pattern. Therefore, X-ray analysis of **1a** was performed. The ORTEP view of **1a** showed a *cis* diol structure and exhibited interesting stereochemical features as shown in Fig. 1. The cyclohexane ring adopts a half-chair conformation and two carbonyl groups in quinone are above so that they are apart from each *cis* hydroxyl group. From these results, it was proved that **1a** and **1b** are correspondent to a *cis* and *trans* diol, respectively.

In the procedure shown in Chart 2, separation of **1a** and **1b** by column chromatography was difficult because their *Rf* values are very close in spite of the short process. We therefore developed another method for **1a** and **1b** as shown in Chart 3. Methylation of **6** by treatment with Ag_2O and CH_3I afforded **9** in 76% yield according to the procedure developed by Pearson and co-workers.[12)] At first $LiAlH_4$ was used as a reducing agent, but 1,4-dihydroxy-5,8-dimetoxynaphthalene was obtained as a main compound by enolization. To avoid enolization, the selective 1,2-reduction was next performed with $NaBH_4$ in the presence of a catalytic amount of $CeCl_3$.[13—15)] Thus, methyl ether **9** was converted to a mixture of diols **10a** and **10b** by treatment with $NaBH_4$ in the presence of $CeCl_3$ in MeOH.[13—15)] A mixture of **10a** and **10b** was used in the next reaction without separation because of their

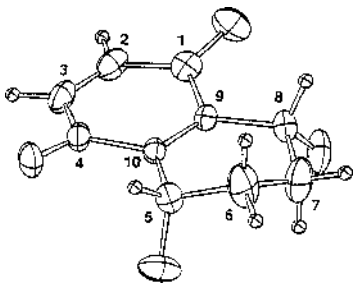

Fig. 1. ORTEP Views of **1a**

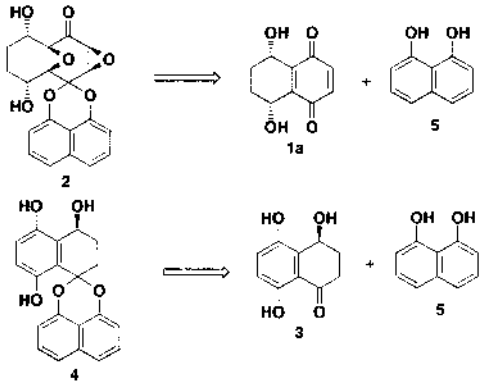

Chart 1

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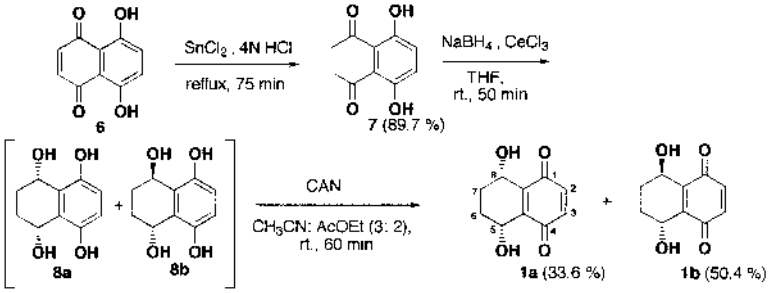

Chart 2

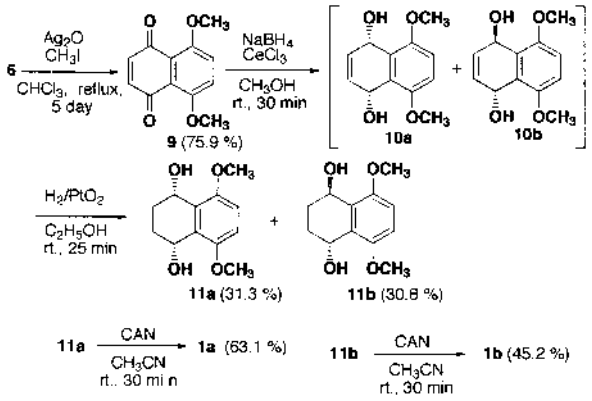

Chart 3

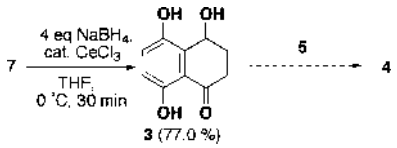

Chart 4

instability. Catalytic hydrogenation of a mixture of **10a** and **10b** with PtO_2 under hydrogen, followed by purification by column chromatography afforded **11a** (*cis*) and **11b** (*trans*) in 31 and 31% yield, respectively.[20] Oxidation of **11a** and **11b** by treatment with CAN[16—18] afforded **1a** and **1b** in 63 and 45% yield, respectively.

The stereostructures of **11a** and **11b** were determined by comparison of ^{1}H-NMR spectra of **1a** and **1b** with the spectra of these obtained by another procedure shown in Chart 2. Reduction of **7** using 4 eq of $NaBH_4$ in THF at 0 °C in the presence of a catalytic amount of $CeCl_3$ afforded stable racemic triol **3** in 77% yield. We are now going to synthesize **4** by acetalization of protected ketone derived from **3** and then coupling reaction with **5**.

In conclusion, **1a** and racemic **3** which are important synthetic intermediates for bioactive spiro ketal **2** and **4** were for the first time synthesized. The stereostructures of **1a** were precisely determined by X-ray analysis.

Experimental

Melting points were taken on a Yanagimoto hot-stage and are uncorrected. ^{1}H- and ^{13}C-NMR were recorded on Varian VXR-300 and XL-400 spectrometers. The signals were assigned on the basis of ^{1}H–^{1}H correlation spectroscopy (COSY), distortionless enhancement by polarization transfer (DEPT), heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond connectivity (HMBC) experiments. Mass spectra were obtained on a JEOL JMS-DX 300 mass spectrometer (low-resolution mass spectrometry) and a JEOL JMS-AX505 HA mass spectrometer (high-resolution (HR) mass spectrometry). Flash column chromatography was performed on Silica gel 60 H (Merck). Thin-layer chromatography (TLC) was done on Silica gel 60 PF_{254} (Merck).

5,8-Dihydroxy-1,2,3,4-tetrahydronaphthalene-1,4-dione (7) The synthetic method of **7** was modified for that of Pearson *et al.*[12] The suspension of 5,8-dihydroxy-1,4-naphthoquinone (**6**) (50.3 mg, 0.3 mmol) and stannous chloride (1.0 g, 5.3 mmol) in 4 N HCl (10 ml) was refluxed for 75 min. The hot reaction mixture was immediately filtered through a Celite pad, and the precipitate was washed with hot water (2 ml). The filtrate and the washings were combined and extracted with $CHCl_3$ (30 ml×3). The $CHCl_3$ layer was washed with brine (2 ml), dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product **7** as yellow crystals (40.5 mg, 89.7%). **7**: mp 152—157 °C (lit.[14] 154 °C). *Rf*=0.8 ($CHCl_3$: CH_3OH=50 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 11.92 (2H, s, 5, 8-OH), 7.25 (2H, s, 6,7-H), 3.05 (4H, s, 2,3-H_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 201.4 (s, C-1, 4), 155.2 (s, C-5, 8), 128.5 (d, C-6, 7), 114.4 (s, C-9, 10), 36.4 (t, C-2, 3). IR ($CHCl_3$) cm^{-1}: 3150, 1640, 1600. HR-electron impact (EI)-MS *m/z*: 192.0429 $[M]^+$ (Calcd for $C_{10}H_8O_4$: 192.0423).

***Cis*- and *trans*-5,8-Dihydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (1a, 1b) from 7** To a solution of **7** (20.0 mg, 0.11 mmol) in THF (5 ml) were added $CeCl_3 \cdot 7H_2O$ (31.3 mg, 0.08 mmol) and $NaBH_4$ (23.8 mg, 0.63 mmol) at room temperature. After stirring for 50 min, excess $NaBH_4$ was quenched with H_2O (0.5 ml). The mixture was evaporated *in vacuo* and the residue was acidified to pH 4 with 5% aqueous HCl and extracted with AcOEt (20 ml×3). The AcOEt layer was dried over Na_2SO_4, and concentrated to half *in vacuo*. A solution of CAN (115.1 mg, 0.21 mmol) in CH_3CN (20 ml) was added dropwise to the solution mentioned above at 0 °C. The mixture was stirred at room temperature for 60 min, and evaporated *in vacuo*. The residue was extracted with $CHCl_3$ (20 ml×4), and washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: CH_3OH=10 : 1) to give the mixture of **1a** and **1b** (20.0 mg, 93.7% from **7**, **1a** : **1b**=1 : 1.5), which was further purified by flash column chromatography ($CHCl_3$) to give **1a** as yellow crystals (6.8 mg, 33.6%) and **1b** as yellow oil (10.2 mg, 50.4%). **1a**: mp. 120 °C; *Rf*=0.50 ($CHCl_3$: CH_3OH=10 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.77 (2H, s, 2,3-H), 4.74 (2H, t, *J*=5.0 Hz, 5, 8-H), 3.19 (2H, br, 5,8-OH), 1.82—1.93, 1.97—2.08 (2H, m, each 6,7-H_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 189.0 (s, C-1, 4), 141.8 (s, C-9, 10), 136.8 (d, C-2, 3), 63.3 (d, C-5, 8), 25.5 (t, C-6, 7). IR ($CHCl_3$) cm^{-1}: 3550, 2950, 1640, 1600. HR-FAB-MS *m/z*: 194.0579 $[M]^+$ (Calcd for $C_{10}H_{10}O_4$: 194.0579). **1b**: *Rf*=0.51 ($CHCl_3$: CH_3OH=10 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.78 (2H, s, 2,3-H), 4.79 (2H, br, 5,8-H), 2.98 (2H, br, 5,8-OH), 2.13, 1.80 (2H, m, each 6,7-H_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 189.0 (s, C-1, 4), 141.4 (s, C-9, 10), 136.7 (d, C-2, 3), 62.3 (d, C-5, 8), 25.3 (t, C-6, 7). IR ($CHCl_3$) cm^{-1}: 3550, 2950, 1640, 1600. HR-FAB-MS *m/z*: 217.0421 $[M+Na]^+$ (Calcd for $C_{10}H_{10}O_4Na$: 217.0476).

5,8-Dimethoxy-1,4-naphthoquinone (9) The synthetic method of **9** was modified for that of Pearson *et al.*[12] Silver oxide (500.0 mg, 2.2 mmol) and methyl iodide (2.0 ml, 32.1 mmol) were added to a solution of 5,8-dihydroxy-1,4-naphthoquinone (**6**) (545.6 mg, 2.9 mmol) in $CHCl_3$ (40.0 ml), and the mixture was refluxed at 60—65 °C for 5 d. Silver oxide (500.0 mg, 2.2 mmol×4) and methyl iodide (2.0 ml, 32.1 mmol×9) were added repeatedly until the reaction was completed during 5 d. Then the mixture was filtered through a Celite pad, and the solid was washed with $CHCl_3$ (20.0 ml). The filtrate and the washings were combined and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: CH_3OH=50 : 1) to give **9**

as orange crystals (475.1 mg, 75.9%). **9**: mp. 151—155 °C (lit.[12] 155 °C); *Rf* =0.34 ($CHCl_3$: CH_3OH=50 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32 (2H, s, 6,7-H), 6.77 (2H, s, 2,3-H), 3.95 (6H, s, 5,8-OCH_3). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 184.8 (s, C-1, 4), 153.7 (s, C-5, 8), 138.3 (d, C-2, 3), 120.4 (d, C-6, 7), 119.7 (s, C-9, 10), 56.9 (q, 5,8-OCH_3). IR ($CHCl_3$) cm^{-1}: 1640. HR-FAB-MS *m/z*: 220.0737 $[M+2H]^+$ (Calcd for $C_{12}H_{12}O_4$: 220.0735).

***Cis*- and *trans*-5,8-Dimethooxy-1,2,3,4-tetrahydronaphthalene-1,4-diol (11a, 11b)** To a solution of **9** (50.0 mg, 0.23 mmol) in CH_3OH (8 ml) were added $CeCl_3 \cdot 7H_2O$ (68.6 mg, 0.18 mmol) and $NaBH_4$ (34.8 mg, 0.92 mmol) at room temperature. After stirring for 30 min, excess $NaBH_4$ was quenched by H_2O (5 ml). The mixture was evaporated *in vacuo* and was further added H_2O (5 ml) and extracted with $CHCl_3$ (30 ml×3). The $CHCl_3$ layer was washed with brine (5 ml×2), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude products (the mixture of **10a** and **10b**) (55.0 mg).

A solution of the crude products (the mixture of **10a** and **10b**) in EtOH (3 ml) was added to a suspension of PtO_2 (10 mg) in EtOH (1 ml) and hydrogenated for 25 min. After the reaction was completed, PtO_2 was removed by filtration. The filtrate was evaporated *in vacuo* to give the crude compounds of **11a** and **11b** (60.9 mg). These compounds were purified by column chromatography (hexane : AcOEt=2 : 1) to give **11a** as orange oil (16.1 mg, 31.3%) and **11b** as orange crystals (15.8 mg, 30.8%). **11a**: *Rf*=0.21 (benzene : AcOEt=1 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.78 (2H, s, 6,7-H), 4.97 (2H, t, *J*=5.5 Hz, 1,4-H), 3.85 (6H, s, 5,8-OCH_3), 3.46 (2H, br, 1,4-OH), 2.03—2.13, 1.86—1.96 (2H, m, each 2,3-H_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 151.9 (s, C-5, 8), 128.9 (s, C-9, 10), 109.5 (d, C-6, 7), 64.5 (d, C-1, 4), 55.8 (q, 5, 8-OCH_3), 26.3 (t, C-2, 3). IR ($CHCl_3$) cm^{-1}: 3550, 2900, 1600. HR-FAB-MS *m/z*: 224.1042 $[M]^+$ (Calcd for $C_{12}H_{16}O_4$: 224.1049). **11b**: mp. 113—114 °C; *Rf*=0.33 (benzene : AcOEt=1 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.79 (2H, s, 6, 7-H), 5.02 (2H, t, *J*=2.0 Hz, 1, 4-H), 3.85 (6H, s, 5,8-OCH_3), 2.83 (2H, br, 1,4-OH), 2.12—2.18, 1.86—1.94 (2H, m, each 2,3-H_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 151.7 (s, C-5, 8), 128.1 (s, C-9, 10), 109.6 (d, C-6, 7), 62.6 (d, C-1, 4), 55.8 (q, 5,8-OCH_3), 24.9 (t, C-2, 3). IR ($CHCl_3$) cm^{-1}: 3550, 2900, 1600. HR-FAB-MS *m/z*: 224.1042 $[M]^+$ (Calcd for $C_{12}H_{16}O_4$: 224.1049).

1a from 11a A solution of CAN (97.6 mg, 0.18 mmol) in CH_3CN (2.4 ml) was added dropwise to a solution of **11a** (20.3 mg, 0.09mmol) in CH_3CN (1.4 ml) at 0 °C. The mixture was stirred at room temperature for 30 min, and was evaporated *in vacuo*. Brine (3 ml) was added to the residue, and was extracted with $CHCl_3$ (20 ml×4). The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: CH_3OH=50 : 1) to give **1a** as yellow crystals (11.1 mg, 63.1%). **1a** was identical with **1a** obtained from **7** described above by comparison of the ^{1}H-NMR spectra.

1b from 11b A solution of CAN (142.5 mg, 0.26 mmol) in CH_3CN (3.5 ml) was added dropwise to a solution of **11b** (29.2 mg, 0.13mmol) in CH_3CN (2.0 ml) at 0 °C. The mixture was stirred at room temperature for 30 min, and was evaporated *in vacuo*. Brine (3 ml) was added to the residue, and was extracted with $CHCl_3$ (30 ml×3). The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: CH_3OH=50 : 1) to give **1b** as yellow oil (11.4 mg, 45.2%). **1b** was identical with **1b** obtained from **7** described above by comparison of the ^{1}H-NMR spectra.

4,5,8-Trihydroxy-1,2,3,4-tetrahydronaphthalene-1-one (3) To a solution of **7** (200.0 mg, 1.04 mmol) in THF (12 ml) were added $CeCl_3 \cdot 7H_2O$ (155.0 mg, 0.42 mmol) and $NaBH_4$ (39.3 mg, 1.04 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched by H_2O (5.0 ml). The mixture was evaporated *in vacuo* and the residue was acidified to pH3 with 10% aqueous HCl and extracted with AcOEt (50 ml×2). The AcOEt layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: CH_3OH=10 : 1) to give **3** as yellow oil (155.4 mg, 77.0%). **3**: *Rf*=0.41 ($CHCl_3$: CH_3OH=10 : 1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.02 (1H, s, 8-OH), 7.77 (1H, br, 5-OH), 7.07 (1H, d, *J*=9.0 Hz, 6-H), 6.85 (1H, d, *J*=9.0 Hz, 7-H), 5.27 (1H, dd, *J*=5.5, 10.0 Hz, 4-H), 2.78—2.90, 2.56—2.70 (1H, m, each 2-H), 2.37—2.48, 2.11—2.26 (1H, m, each 3-H), 1.70 (1H, br, 4-OH). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 203.4 (s, C-1), 156.5 (s, C-8), 147.3 (s, C-5), 126.6 (d, C-6), (s, C-10), 118.4 (d, C-7), 114.8 (s, C-9), 67.2 (d, C-4), 35.4 (t, C-2), 31.4 (t, C-3). IR ($CHCl_3$) cm^{-1}: 1640, 1600. HR-EI-MS *m/z*: 194.0576 $[M]^+$ (Calcd for $C_{10}H_{10}O_4$: 194.0579).

X-Ray Crystallographic Analysis of 1a Compound **1a** was crystallized from AcOEt to give a red prismatic crystal of $C_{10}H_{10}O_4$ having approximate dimensions of 0.400×0.400×0.300 mm, which was mounted on a glass fiber.

Crystal Data for **1a**: Formula $C_{10}H_{10}O_4$, fw=194.19; triclinic, space group *P*1(#2), *a*=9.826(3) Å, *b*=12.380(2) Å, *c*=8.648(2)Å, α=106.43(2)°, β=111.54(2)°, γ=68.10(2)°, *V*=894.9(4)Å^3; *Z*=4, D_{calc}=1.441 g/cm^3. *R*=0.088, R_w=0.096 for 1984 observed reflections with $I>5.00\sigma(I)$. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Cu$K\alpha$ radiation (λ=1.54178Å) and a 12 KW rotating anode generator. Cell constants and an orientation matrix for date collection were obtained from a least-squares. The data were collected at a temperature of 23±1 °C using the ω–2θ scan technique to a maximum 2θ value of 135.1°, and were corrected for Lorentz and polarization effects. The structure was solved by direct methods using MITHRIL.[21] The non-hydrogen atoms were refined anisotropically. All calculations were performed using the TEXSAN[22] crystallographic software package of the Molecular Structure Corporation.

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20) The $NaBH_4$–$CeCl_3$ reduction of **9** was examined at several temperatures and the yields of **11a** and **11b** from **9** at 75 °C and −50 °C exhibited 26 and 33%, and 27 and 42%, respectively.
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