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Heterocycles. X.¹⁾ Syntheses and Absolute Configurations of a Chiral Naphthoquinone Epoxide and Chiral Naphtho[1,2-*c*]isocoumarins

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The (+)-naphthoquinone epoxide (2) has been obtained by the phase-transfer chiral epoxidation of the naphthoquinone (1). Reduction of (+)-2 with sodium borohydride gives the (–)-*cis*-epoxyhydroxy ketone (3) and (–)-*trans*-epoxyhydroxy ketone (4). Further reduction of (–)-3 affords the (–)-*cis*-lactone (5), (–)-*trans*-lactone (6) and (+)-*cis*-epoxydiol (7). Alumina-induced lactonization of (+)-7 yields (–)-6. The 2*S*,3*R* configuration for (+)-2 is deduced from the circular dichroism spectrum. The configurations of the 4-hydroxyl groups in (–)-3 and (–)-4 are determined by the Horeau's method.

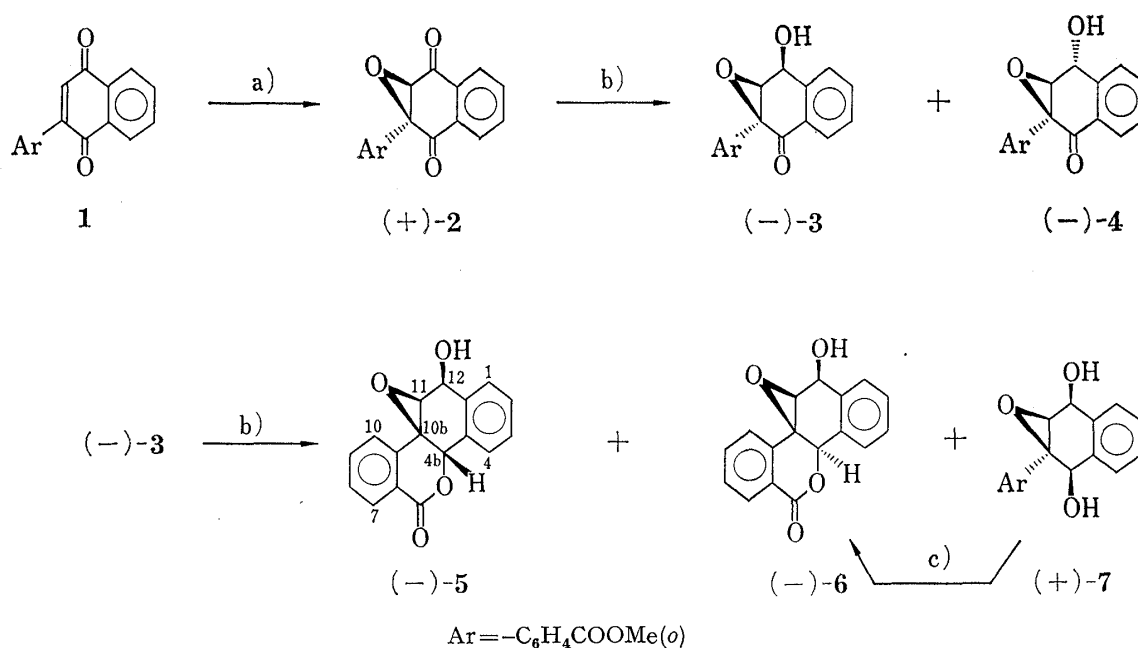
Keywords—naphtho[1,2-*c*]isocoumarin; naphthoquinone epoxide; phase-transfer chiral epoxidation; absolute configuration; circular dichroism; proton magnetic resonance

Although many synthetic methods for benzo[*c*]phenanthridines have been presented, no approach to chiral ones has been attempted. We have previously reported the stereoselective syntheses of benzo[*c*]phenanthridines from the (±)-naphthoquinone epoxide (2) *via* the (±)-*cis*-lactone (5).²⁾ Thus, if 2 can be obtained in a chiral form, the syntheses of chiral benzo[*c*]phenanthridines should be possible.

Asymmetric epoxidations of enones under phase-transfer conditions in the presence of chiral onium salts as catalysts have been reported.³⁾ In this connection, we have preliminarily reported the asymmetric epoxidation of the naphthoquinone (1) to chiral 2, and the syntheses of the chiral lactones (5) and (6) from chiral 2.¹⁾ We now wish to report in detail the results obtained by further investigation.

The naphthoquinone (1)⁴⁾ was treated with *tert*-butyl hydroperoxide in the presence of 1-benzylquininium chloride (BQC) and sodium hydroxide in toluene. Work-up of the reaction mixture and preparative thin-layer chromatography (prep. TLC) gave (±)-2 in 95% yield. Its enantiomeric excess (ee) (78%) was determined from the proton magnetic resonance (¹H NMR) spectrum using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) [Eu(hfc)₃] (Fig. 1). Recrystallization from ethanol furnished (+)-2 (100% ee) in 63% yield. On the other hand, the use of aqueous hydrogen peroxide as an oxygen source instead of *tert*-butyl hydroperoxide gave (+)-2 (50% ee) in 89% yield.

Reduction of (+)-2 with sodium borohydride at –50° for 1 hr afforded the (–)-*cis*-epoxyhydroxy ketone (3) (76%), [α]_D²⁵ –52.0°, and (–)-*trans*-epoxyhydroxy ketone (4) (23%), [α]_D²⁵ –136.3°. Since one-proton doublets were observed for the 3-protons in (–)-3 and (–)-4 in the ¹H NMR spectra, it is evident that the 4-oxo group in (+)-2 was reduced to yield two 4-epimeric alcohols. It is known that the intramolecular hydrogen-bondings between hydroxyl groups and adjacent oxirane oxygen atoms, and between hydroxyl groups and π -bonds in α -tetralols appear at 3580–3520 and 3620–3590 cm^{–1}, respectively, in the infrared (IR) spectra.⁵⁾ On the basis of these findings, absorptions at 3520 cm^{–1} observed for (–)-3 and 3587 cm^{–1} for (–)-4 may be assigned to the intramolecular hydrogen-bondings between the 4-hydroxyl group and oxirane oxygen atom, and between the 4-hydroxyl group and π -bond in the benzene moiety, respectively. Since the intramolecular hydrogen-bonding between the *trans*-hydroxyl group and oxirane oxygen atom in the compound in question is impossible, regardless of the conformation of the cyclohexene ring, the configurations of the 4-hydroxyl groups in (–)-3 and (–)-4 are established as *cis* and *trans* with respect to the oxirane rings,



a) *tert*-BuO₂H/BQC/NaOH/toluene. b) NaBH₄/MeOH. c) Al₂O₃/CHCl₃/MeOH.

Chart 1

respectively, on the basis of these IR data. Reduction of (+)-2 (50% ee) with sodium borohydride gave (-)-3 (51% ee)⁶⁾ in 70% yield, and its recrystallization from ethanol yielded (-)-3 (92% ee)⁶⁾ in 28% yield.

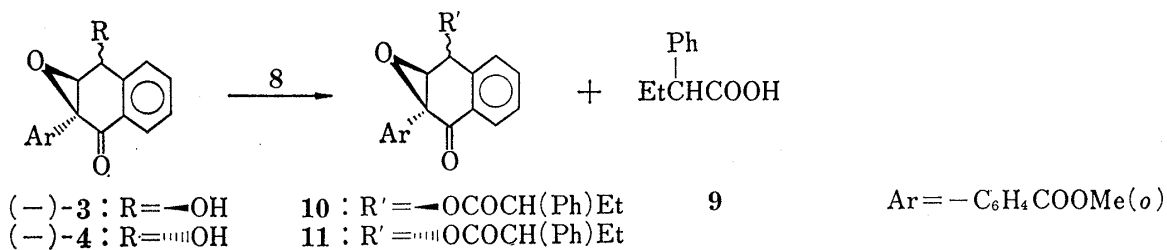
Further reduction of (-)-3 with sodium borohydride gave the (-)-*cis*-lactone (5) (44%), [α]_D²³ -217.8°, (-)-*trans*-lactone (6) (1%), [α]_D²⁰ -104.0°, and (+)-*cis*-epoxydiol (7) (38%), [α]_D²³ +161.4°. The *cis* steroidal conformation of the B/C ring fusion in (-)-5 was deduced on the basis of a W-path coupling ($J=1$ Hz) observed between the 4b- and 11-protons in the ¹H NMR spectrum.⁷⁾

Alumina-induced lactonization of (+)-7 afforded (-)-6 (74%), which showed a characteristic signal for the 4-proton at δ 7.93 (dd, $J=8$ and 2 Hz) (5: δ 7.43) shifted down-field by an interaction with the 4b-O(5) bond in the ¹H NMR spectrum. The optical purities (100%) of (-)-5 and (-)-6 were confirmed by measurement of the ¹H NMR spectra using Eu(hfc)₃.

Absolute Configuration

The (+)-Naphthoquinone Epoxide (2)—Wynberg *et al.* have reported that the circular dichroism (CD) spectra correlated with the absolute configurations of 2-alkyl- and 2-phenyl-naphthoquinone epoxides and that the compounds with negative Cotton effects between 400 and 340 nm had the 2*R*, 3*S* configurations.⁸⁾ The CD spectrum of (+)-2 showed positive Cotton effects between 400 and 340 nm, suggesting the 2*S*, 3*R* configuration for (+)-2 by comparison with the CD spectrum of one of the compounds examined by Wynberg *et al.* (Fig. 2).

The (-)-*cis*-Epoxyhydroxy Ketone (3) and (-)-*trans*-Epoxyhydroxy Ketone (4)—Horeau has found a novel method to determine the absolute configurations of secondary alcohols, *e.g.* (1) esterification of a chiral alcohol with ($\pm$)-2-phenylbutanoic anhydride (8), (2) hydrolysis of excess 8 at the end of the reaction, and (3) determination of the rotatory power of 2-phenylbutanoic acid (9) thus isolated. The relationship, in general, between the configuration of the alcohol and the sign of 9 is as shown in Chart 2.⁹⁾ On application of this method, *R*-(-)-9 and *S*-(+)-9 were obtained from (-)-3 and (-)-4, respectively. This result leads to the 4*S* and 4*R* configurations for (-)-3 and (-)-4, respectively. Talking into account the steric relationship of the 4-hydroxyl group and oxirane ring (*vide supra*), the 2*S*, 3*S*, 4*S* configuration for (-)-3 and the 2*S*, 3*S*, 4*R* configuration for (-)-4 can be deduced.



isolated 9

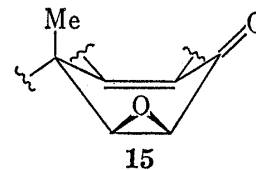
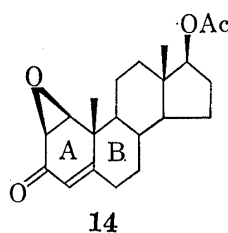
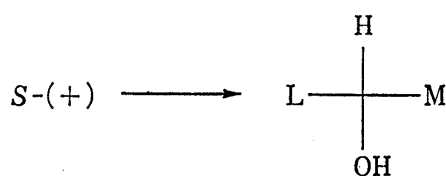
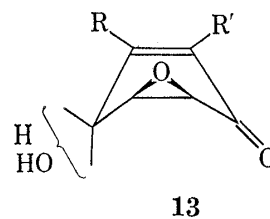
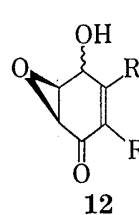
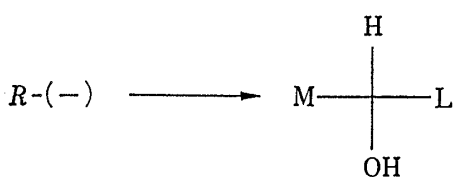
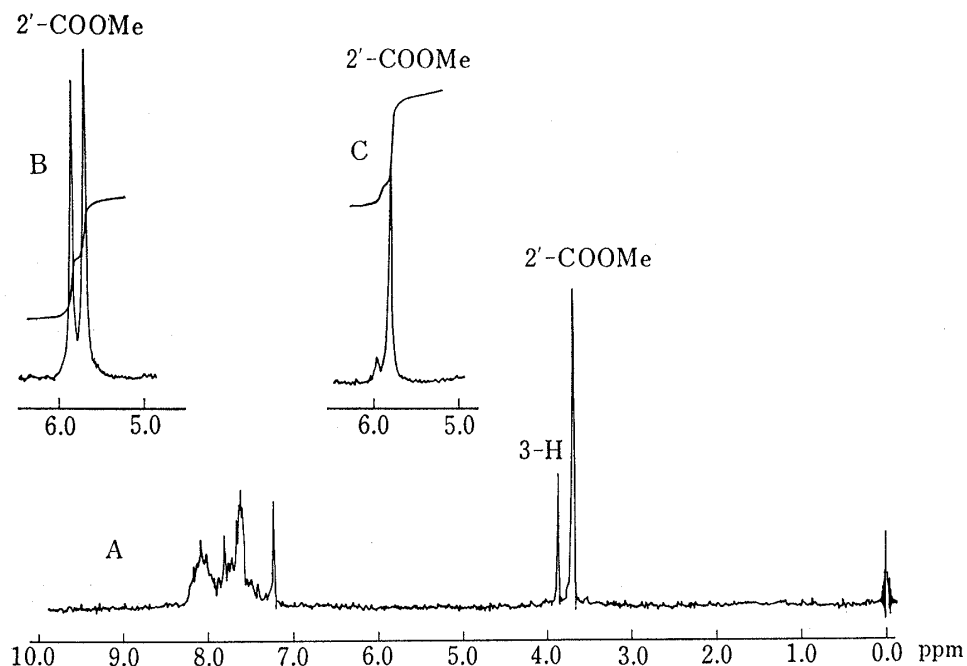
abs. configuration
of alcohol

Chart 2

Fig. 1. ¹H NMR Spectra of 2 taken on a Hitachi R-24B Spectrometer

A, normal spectrum of (±)-2 (18 mg, 5.8 × 10⁻⁵ mol) in CDCl₃ (0.4 ml) at 60 MHz; B, 60 MHz spectrum of (±)-2 (43 mg, 1.4 × 10⁻⁴ mol) in CDCl₃ (0.4 ml) containing Eu(hfc)₃ (136 mg); C, 60 MHz spectrum of (+)-2 (78% ee) (40 mg, 1.3 × 10⁻⁴ mol) in CDCl₃ (0.4 ml) containing Eu(hfc)₃ (156 mg).

This conclusion is supported by the correlation of the stereostructure of (+)-2 with the spatial orientation of the 4-hydroxyl groups in (–)-3 and (–)-4.

It is known that the 2,3-epoxy-4-hydroxycyclohex-5-en-1-one (12) has the conformation (13), because of the more favorable overlapping between the delocalized electrons of the oxirane ring and π -electrons of the carbonyl group, and that 13 shows a negative Cotton effect at 340–320 nm in the CD spectrum due to the $n\text{-}\pi^*$ carbonyl transition.¹⁰ From the coupling constant (2 Hz) observed between the 3- and 4-protons, it can be deduced that the 4-hydroxyl group in (–)-3 is equatorial in the 13-type conformation.¹¹ At present, we have no information on the ring conformation of (–)-4. However, although the A ring in the steroid (14) exists in the conformation (15), the negative Cotton effect, ascribed to the “epoxy ketone partial chromophore,” is also observed for 14.¹⁰ The CD spectra of (–)-3 and (–)-4 showed negative Cotton effects at *ca.* 330 nm (Fig. 3). If (–)-3 and (–)-4, which have the benzene moieties instead of the double bonds in 12 and 14, can be regarded as being similar to 12 and 14 in terms of the CD spectra,¹² both compounds have the same configurations (2*S*, 3*S*) at the 2- and 3-positions, as discussed above.

The (–)-*cis*-Lactone (5), (–)-*trans*-Lactone (6) and (+)-*cis*-Epoxydiol (7)—On the basis of the stereostructure of (–)-3, the following assignments can be made. 4*bS*, 10*bR*, 11*S*, 12*S* for (–)-5; 4*bR*, 10*bR*, 11*S*, 12*S* for (–)-6; 1*R*, 2*R*, 3*S*, 4*S* for (+)-7. Interestingly, the CD spectra of (–)-5 and (–)-6 appeared to be mirror images (see “Experimental”).

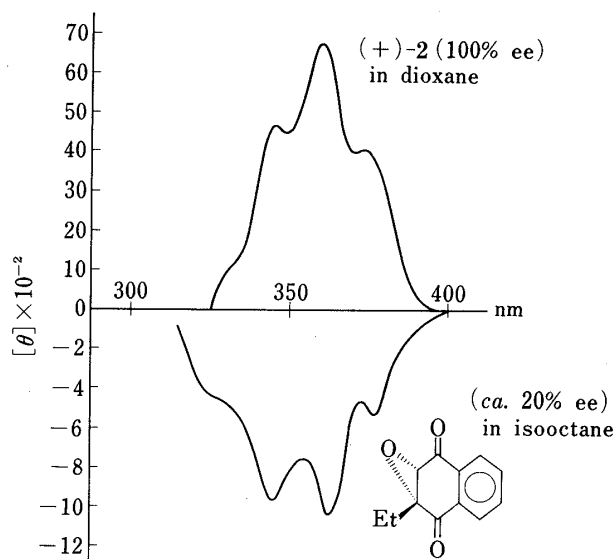


Fig. 2. CD Spectra of (+)-2 and a Related Compound⁸⁾

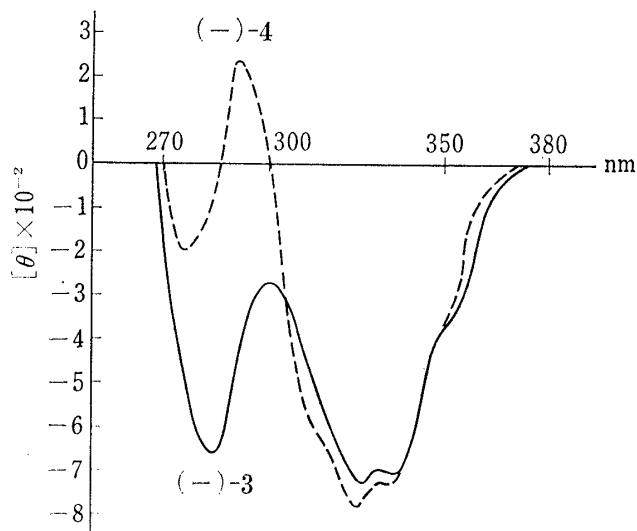


Fig. 3. CD Spectra of (–)-3 and (–)-4(dioxane)

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. The optical purities of the compounds (2–7) were estimated by ¹H NMR spectroscopy using Eu(hfc)₃ and were 100% unless otherwise noted. Optical rotations were taken on a JASCO DPI-181 polarimeter. Spectral data were recorded on the following spectrometers: UV–Hitachi EPS-2U (methanol); CD–JASCO J-20; IR–JASCO IR-G (chloroform) and JASCO DS-701G (hydrogen-bondings); ¹H NMR–JEOL JNM PS-100 (100 MHz) (deuteriochloroform); Mass (MS)–JEOL JMS-OIS.

1-Benzylquininium Chloride (BQC)¹³⁾—Quinine trihydrate was dried in a steel desiccator (CaCl₂) at 125° overnight, and then recrystallized from anhyd. benzene to afford colorless granules of mp 174–175° with $[\alpha]_{589}^{18.5} -121.9^\circ$ (*c* = 1.0, chloroform).

A solution of benzyl chloride (156 mg) in anhyd. acetone (1.8 ml) was added to a solution of the quinine (402 mg) in anhyd. acetone (20 ml), and the mixture was stirred at 60° for 36 hr. After concentration *in vacuo*, the residue was recrystallized from anhyd. ethanol/anhyd. ether to yield BQC (380 mg, 68%) as light yellow crystals of mp 176–180°, and further recrystallization from the same solvents gave BQC as colorless needles of mp 180–181° with $[\alpha]_{589}^{19} -235.5^\circ$ (*c* = 1.5, water).

(+)-2,3-Dihydro-2,3-epoxy-2'-methoxycarbonylphenyl-1,4-naphthoquinone (2)—a) *tert*-Butyl hydroperoxide (75%) (0.4 ml) was added to a stirred mixture of 1 (101 mg), BQC (2.6 mg) and NaOH (27 mg) in toluene (10 ml) with cooling. The mixture was vigorously stirred at 0° for 30 min and then at room temperature for 1 hr. The toluene phase was washed with aq. KI, aq. Na₂S₂O₃ and water, then dried over Na₂SO₄. Removal of the solvent *in vacuo*, followed by prep. TLC of the residue (silica gel; benzene/ethyl acetate=20/1, v/v; *R_f* 0.37) gave 2 (101 mg, 95%, 78% ee) as light yellow crystals of mp 135—137° with $[\alpha]_{589}^{25} +9.2^\circ$, $[\alpha]_{577}^{25} +12.5^\circ$, $[\alpha]_{446}^{25} +20.0^\circ$ and $[\alpha]_{435}^{25} +175.1^\circ$ (*c*=1.0, dioxane). Its recrystallization from ethanol yielded 2 (66 mg, 63%, 100% ee) as colorless prisms of mp 140—141.5° with $[\alpha]_{589}^{24} +10.5^\circ$, $[\alpha]_{577}^{24} +13.3^\circ$, $[\alpha]_{446}^{24} +22.0^\circ$ and $[\alpha]_{435}^{24} +200.3^\circ$ (*c*=1.3, dioxane). IR $\nu_{\max}$ cm⁻¹: 1705, 1700 (C=O and OC=O). UV $\lambda_{\max}$ nm (ϵ): 348 (shoulder) (141), 302 (1720), 260 (shoulder) (5800), 247 (33400). CD (*c*=3.7 × 10⁻³, dioxane) $[\theta]^{21}$ (nm): 0 (395), +4032 (374.5) (positive maximum), +3990 (371) (negative maximum), +6804 (359.5) (positive maximum), +4452 (349) (negative maximum), +4662 (345) (positive maximum), +1134 (332) (shoulder), 0 (325), -672 (320) (negative maximum), -630 (316.5) (positive maximum), -1008 (308) (negative maximum), -882 (298) (positive maximum), -15455 (264) (negative maximum). ¹H NMR δ : 8.19—7.99 (3H, m, aromatic H's), 7.86—7.43 (5H, m, aromatic H's), 3.88 (1H, s, 3-H), 3.71 (3H, s, 2'-COOMe). MS Calcd for C₁₈H₁₂O₅: M, 308.068. Found *m/e*: M⁺, 308.068.

b) A solution of 1 (200 mg) in toluene (10 ml) was added to a solution of BQC (5.1 mg) and NaOH (51.4 mg) in 30% aq. H₂O₂ (0.62 ml). The mixture was vigorously stirred at room temperature for 4.5 hr. Treatment of the reaction mixture as above afforded 2 (188 mg, 89%, 50% ee) as light yellow crystals of mp 126—137°. Its recrystallization from ethanol gave 2 (45 mg, 21%, 100% ee) as colorless prisms of mp 141—141.5°.

(-)-2,3-Epoxy-*cis*-4-hydroxy-*trans*-2'-methoxycarbonylphenyl- α -tetralone (3) and (-)-2,3-Epoxy-*trans*-4-hydroxy-*trans*-2'-methoxycarbonylphenyl- α -tetralone (4)—a) NaBH₄ (50 mg) was added to a solution of (+)-2 (150 mg) in methanol (50 ml). The mixture was stirred at -50° for 1 hr, and then acetic acid (1 ml) was added. After concentration *in vacuo*, the residue was extracted with ethyl acetate. Work-up gave an oil (160 mg), and prep. TLC (silica gel; benzene/ethyl acetate=10/1, v/v) afforded (-)-3 (115 mg, 76%) and (-)-4 (35 mg, 23%) from the zones with *R_f* 0.49 and 0.32, respectively.

The (-)-*cis*-Epoxyhydroxy Ketone (3): Colorless prisms of mp 128.5—130° (from ethanol). IR $\nu_{\max}$ cm⁻¹: 3520 (OH), 1702 (OC=O and C=O); hydrogen-bonding, 3520 cm⁻¹ (ϵ =117.5) (*c*=6.5 × 10⁻⁴ mol/l, tetrachloromethane). UV $\lambda_{\max}$ (ϵ): 336 (shoulder) (58), 280 (shoulder) (2780), 222 (12400), 201 (46500). Optical rotation $[\alpha]^{22}$ (nm): -52.0° (589), -72.0° (577), -94.0° (546), -314.0° (435), -2042.0° (365) (*c*=0.1, chloroform). CD (*c*=1.3 × 10⁻³, dioxane) $[\theta]^{24.5}$ (nm): 0 (373), -3580 (352) (shoulder), -7021.5 (337) (negative maximum), -6975 (332) (positive maximum), -7300.5 (327) (negative maximum), -2697 (300) (positive maximum), -6603 (284) (negative maximum), 0 (267.5), +7905 (257.5) (positive maximum), 0 (250), -17902.5 (240) (negative maximum), -5580 (228) (positive maximum), -15345 (220) (negative maximum), 0 (214). ¹H NMR δ : 8.15 (1H, dd, *J*=8 and 2 Hz, 8-H),¹⁴ 8.04 (1H, dd, *J*=8 and 2 Hz, 3'-H),¹⁴ 7.77—7.41 (6H, m, aromatic H's), 5.22 (1H, dd, *J*=12 and 2 Hz, 4-H),¹⁵ 3.85 (1H, d, *J*=2 Hz, 3-H), 3.80 (3H, s, 2'-COOMe), 3.68 (1H, d, *J*=12 Hz, 4-OH).¹⁶ MS Calcd for C₁₈H₁₄O₅: M, 310.084. Found *m/e*: M⁺, 310.084.

The (-)-*trans*-Epoxyhydroxy Ketone (4): A colorless oil. IR $\nu_{\max}$ cm⁻¹: 3590, 3370 (OH), 1712 (OC=O), 1695 (C=O); hydrogen-bonding, 3587 cm⁻¹ (ϵ =137.7) (*c*=1.3 × 10⁻³ mol/l, tetrachloromethane). UV $\lambda_{\max}$ (ϵ): 334 (shoulder) (92), 300 (shoulder) (1140), 284 (shoulder) (3180), 240 (14800), 207 (33300), 203 (34600). Optical rotation $[\alpha]^{25}$ (nm): -136.3° (589), -146.4° (577), -174.2° (546), -433.2° (435), -2024.4° (365) (*c*=0.3, chloroform). CD (*c*=1.7 × 10⁻³, dioxane) $[\theta]^{22}$ (nm): 0 (372), -3647 (351) (shoulder), -7294 (335) (negative maximum), -7257 (332) (positive maximum), -7841 (325) (negative maximum), -6491 (317) (shoulder), 0 (300), +2370 (291.5) (positive maximum), 0 (286), -1969 (277) (negative maximum), 0 (270.5), +15500 (254.5) (positive maximum), 0 (244), -24435 (228) (negative maximum). ¹H NMR δ : 8.12 (1H, dd, *J*=8 and 2 Hz, 8-H),¹⁴ 7.95 (1H, dd, *J*=8 and 2 Hz, 3'-H),¹⁴ 7.71 (1H, dt, *J*=2 and 8 Hz, aromatic H), 7.63—7.29 (5H, m, aromatic H's), 5.35 (1H, br s, W_H 11 Hz, 4-H),¹⁵ 3.81 (1H, d, *J*=3 Hz, 3-H), 3.69 (3H, s, 2'-COOMe), 3.28 (1H, br s, W_H 28 Hz, 4-OH).¹⁶ MS Calcd for C₁₈H₁₄O₅: M, 310.084. Found: *m/e*: M⁺, 310.083.

b) A solution of (+)-2 (50% ee) (200 mg) and NaBH₄ (30 mg) in methanol (100 ml) was stirred at -60° for 1 hr, and then acetic acid (1 ml) was added. Work-up of the reaction mixture and prep. TLC (silica gel; benzene/ethyl acetate=10/1, v/v) gave (-)-3 (141 mg, 70%, 51% ee) and (-)-4 (28 mg, 14%). The (-)-*cis*-epoxyhydroxy ketone (3) (100 mg) obtained above was recrystallized from ethanol (1.5 ml).

The First Crystals (50 mg): Colorless prisms of mp 138—139° and 23% ee. Optical rotation $[\alpha]^{24}$ (nm): -20.2° (589), -22.3° (577), -28.0° (546), -96.8° (435), -627.0° (365) (*c*=1.0, chloroform).

The Second Crystals (40 mg, 28%): Colorless prisms of mp 116—124° and 92% ee. Optical rotation $[\alpha]^{24}$ (nm): -57.3° (589), -62.9° (577), -80.4° (546), -274.7° (435) (*c*=1.0, chloroform), -1860.0° (365) (*c*=0.4, chloroform).

(-)-10b,11-Epoxy-*cis*-12-hydroxy-*cis*-4b,10b,11,12-tetrahydronaphtho[1,2-*c*]isocoumarin (5), (-)-10b,11-Epoxy-*cis*-12-hydroxy-*trans*-4b,10b,11,12-tetrahydronaphtho[1,2-*c*]isocoumarin (6) and (+)-1,2,3,4-tetrahydronaphthalene (7)—NaBH₄ (45 mg)

was added to a solution of (–)-3 (115 mg) in methanol (50 ml), and the mixture was stirred at –50° for 2 days. After addition of further NaBH₄ (20 mg), stirring was continued at –50° for 1 day, and then acetic acid (1 ml) was added. Work-up of the reaction mixture gave an oil (116 mg) which was purified by prep. TLC (silica gel; chloroform/ethyl acetate=10/1, v/v) to afford (–)-5 (46.1 mg, 44%), *R_f* 0.40, (–)-6 (0.9 mg, 1%), *R_f* 0.33, and (+)-7 (43.8 mg, 38%), *R_f* 0.54.

The (–)-*cis*-Lactone (5): Colorless leaflets of mp 177–178° (from ethanol). IR $\nu_{\max}$ cm^{–1}: 3580, 3340 (OH), 1729 (OC=O). UV $\lambda_{\max}$ (ε): 288 (shoulder) (1080), 281 (1140), 234 (7280), 202 (37800). Optical rotation [α]_D²³ (nm): –217.8° (589), –225.8° (577), –234.7° (546), –428.4° (435), –659.5° (365) (*c*=0.2, chloroform). CD (*c*=1.8 × 10^{–3}, dioxane) [θ]_D²⁴ (nm): 0 (303), +8720 (263) (positive maximum), 0 (247.5), –31830 (233.5) (negative maximum), 0 (219.5). ¹H NMR δ : 8.12 (1H, dd, *J*=8 and 2 Hz, 7-H), 7.69 (1H, dt, *J*=2 and 8 Hz, 9-H),¹⁴ 7.50 (1H, dt, *J*=2 and 8 Hz, 8-H),¹⁴ 7.43 (4H, s, aromatic H's), 7.39 (1H, dd, *J*=8 and 2 Hz, 10-H), 5.82 (1H, d, *J*=1 Hz, 4b-H), 5.14 (1H, br s, *W_H* 12 Hz, 12-H),¹⁵ 3.66 (1H, dd, *J*=2 and 1 Hz, 11-H), 2.46 (1H, d, *J*=8 Hz, 12-OH).¹⁶ MS Calcd for C₁₇H₁₂O₄: *M*, 280.074. Found *m/e*: *M*⁺, 280.074.

The (–)-*trans*-Lactone (6): Colorless prisms of mp over 300° (from ethanol). IR $\nu_{\max}$ cm^{–1}: 3610, 3400 (OH), 1728 (OC=O). UV $\lambda_{\max}$ (ε): 348 (shoulder) (23), 316 (shoulder) (30), 280 (1460), 234 (8630), 204 (37800). Optical rotation [α]_D²³ (nm): –104.0° (589), –120.0° (577), –136.0° (546), –264.0° (435), –526.0° (365) (*c*=0.1, chloroform). CD (*c*=1.0 × 10^{–3}, dioxane) [θ]_D¹⁸ (nm): 0 (305), –9744 (260) (negative maximum), 0 (242), +3360 (233) (positive maximum), 0 (220). ¹H NMR δ : 8.31 (1H, dd, *J*=8 and 2 Hz, 7-H), 7.93 (1H, dd, *J*=8 and 2 Hz, 4-H), 7.73 (1H, dt, *J*=2 and 8 Hz, 9- or 8-H), 7.65 (1H, dd, *J*=8 and 2 Hz, 10-H), 7.54–7.32 (4H, m, aromatic H's), 6.11 (1H, s, 4b-H), 5.37 (1H, br s, *W_H* 8 Hz, 12-H),¹⁵ 4.49 (1H, d, *J*=3 Hz, 11-H), 2.21 (1H, d, *J*=3 Hz, 12-OH).¹⁶ MS Calcd for C₁₇H₁₂O₄: *M*, 280.074. Found: *m/e*: *M*⁺, 280.077.

The (+)-*cis*-Epoxydiol (7): Colorless prisms of mp 150–151° (from ethanol). IR $\nu_{\max}$ cm^{–1}: 3580, 3520 (OH), 1709 (OC=O). UV $\lambda_{\max}$ (ε): 277 (1000), 229 (5360), 214 (8630). Optical rotation [α]_D²³ (nm): +161.4° (589), +167.0° (577), +195.0° (546), +343.6° (435), +557.9° (365) (*c*=0.3, chloroform). CD (*c*=1.0 × 10^{–3}, dioxane) [θ]_D²³ (nm): 0 (301), –3775 (281.5) (negative maximum), 0 (266) +3837 (252.5) (positive maximum), 0 (243), –4368 (234) (negative maximum), 0 (226). ¹H NMR δ : 8.09 (1H, dd, *J*=8 and 2 Hz, 3'-H), 7.76–7.28 (7H, m, aromatic H's), 5.20 (1H, d, *J*=11 Hz, 1-H),¹⁷ 5.03 (1H, dd, *J*=11 and 3 Hz, 4-H),¹⁵ 3.83 (3H, s, 2'-COOMe), 3.59 (1H, d, *J*=3 Hz, 3-H), 3.54, 2.34 (1H each, d, *J*=11 Hz, 1- and 4-OH's).¹⁶ MS Calcd for C₁₈H₁₆O₅·H₂O: *M*, 294.089. Found *m/e*: *M*⁺, 294.090.

Transformation of (+)-7 to (–)-6—A solution of (+)-7 (43 mg) in chloroform/methanol (1/1, v/v) (0.8 ml) was left on a column of neutral Al₂O₃ (grade III) (1 g) overnight. Elution with chloroform/methanol (100/1, v/v) afforded crystals (39 mg) which were purified by prep. TLC (silica gel; chloroform/ethyl acetate=5/1, v/v) to give (–)-6 (28.6 mg, 74%) from the zone with *R_f* 0.54.

Reaction of (–)-3 with the (±)-Anhydride (8)—A solution of 8 (225 mg) in anhyd. pyridine (2 ml) was added to a solution of (–)-3 (103 mg) in anhyd. pyridine (1 ml), and the mixture was stirred at room temperature for 22 hr. Water (0.5 ml) was added to hydrolyze excess 8, and the mixture was stirred at room temperature for 2 hr. Neutralization in the presence of benzene (5 ml) and a small amount of phenolphthalein required 0.1 *N* NaOH (factor=1.001) (11.3 ml): the esterification yield was therefore 100%. The reaction mixture was diluted with water, and the aqueous phase was extracted with benzene. On work-up, the combined benzene extracts gave an oil (167 mg), and prep. TLC (silica gel; benzene/ethyl acetate=10/1, v/v) afforded the ester (10) (147 mg, 97%) as a colorless oil. IR $\nu_{\max}$ cm^{–1}: 1722 (OC=O), 1698 (C=O). MS Calcd for C₂₈H₂₄O₆: *M*, 456.157. Found *m/e*: *M*⁺, 456.159. The aqueous phase was acidified with 10% HCl, and then extracted with benzene. Work-up gave 9 (182 mg) as a colorless oil with [α]_D³⁰ –0.002° (*c*=8.9, benzene) corresponding to the optical yield (0.15%). The spectral data for isolated 9 were in accord with those for an authentic sample.

Reaction of (–)-4 with the (±)-Anhydride (8)—A solution of 8 (216 mg) in anhyd. pyridine (2 ml) was added to a solution of (–)-4 (81 mg) in anhyd. pyridine (1 ml), and the mixture was stirred at room temperature for 18 hr. After hydrolysis of excess 8 with water (0.5 ml), it was found that 0.1 *N* NaOH (factor=1.001) (11.3 ml) was required for neutralization (the esterification yield, 100%). Work-up afforded the ester (11) (117 mg, 98%) as a colorless oil. IR $\nu_{\max}$ cm^{–1}: 1738, 1715 (OC=O), 1698 (C=O). MS Calcd for C₂₈H₂₄O₆: *M*, 456.157. Found: *m/e*: *M*⁺, 456.160. In addition 9 (185 mg) was obtained as a colorless oil with [α]_D³⁰ +0.217° (*c*=8.9, benzene) corresponding to the optical yield (21%). The spectral data for isolated 9 were in accord with those for an authentic sample.

References and Notes

- 1) Part IX: Y. Harigaya, H. Yamaguchi, and M. Onda, *Heterocycles*, **15**, 183 (1981).
- 2) Y. Harigaya, K. Yotsumoto, and M. Onda, Abstracts of Papers, 100th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1980, p. 63; *Chem. Pharm. Bull.*, accepted for publication.
- 3) R. Helder, J.C. Hummelen, R.W.P.M. Laane, J.S. Wiering, and H. Wynberg, *Tetrahedron Lett.*, **1976**, 1831; H. Wynberg and B. Greijdanus, *J. Chem. Soc., Chem. Comm.*, **1978**, 427; H. Wynberg and B. Marsman, *J. Org. Chem.*, **45**, 158 (1980).

- 4) Y. Harigaya, T. Suzuki, and M. Onda, *Chem. Pharm. Bull.*, **27**, 2636 (1979).
- 5) H.M. Fales and W.C. Wildman, *J. Am. Chem. Soc.*, **85**, 784 (1963); S. Watanabe, T. Suga, T. Shishibori, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **44**, 204 (1971); H. Iwamura and K. Hanaya, *ibid.*, **43**, 3901 (1970); K. Hanaya, S. Onodera, S. Awano, and H. Kudo, *ibid.*, **47**, 509 (1974); K. Hanaya, S. Onodera, and H. Kudo, *ibid.*, **47**, 2607 (1974); N. Mori, S. Kasuya, H. Miyazaki, and T. Takezawa, *ibid.*, **52**, 1423 (1979).
- 6) A distinct difference in the 3-proton signal was observed in the ^1H NMR spectrum using $\text{Eu}(\text{hfc})_3$.
- 7) A nuclear Overhauser effect (42%) was observed between the 4- and 4b-protons in the ^1H NMR spectrum of ($\pm$)-5.
- 8) H. Pluim and H. Wynberg, *J. Org. Chem.*, **45**, 2498 (1980).
- 9) A. Horeau, "Stereochemistry," Vol. 3, ed. by H. Kagan, Georg Thieme Publishers, Germany, 1977, pp. 51—94, and references cited therein.
- 10) M.W. Miller, *Tetrahedron*, **24**, 4839 (1968); Z. Kis, A. Closse, H.P. Sigg, L. Hruban, and G. Snatzke, *Helv. Chim. Acta*, **53**, 1577 (1970).
- 11) N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., London, 1964 pp. 99—101. If the 4-hydroxyl group is axial, the coupling constant between the 3- and 4-protons is expected to be *ca.* 5 Hz on the basis of the dihedral angle (0°) between them.
- 12) M. Legrand and M.J. Rougier, "Stereochemistry," Vol. 2, ed. by H. Kagan, Georg Thieme Publishers, Germany, 1977, p. 145.
- 13) W.A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.*, **41**, 2090 (1919); S. Colonna and R. Fornasier, *J. Chem. Soc., Perkin Trans. 1*, **1978**, 371.
- 14) These assignments may be reversed.
- 15) On addition of deuterium oxide, this signal changed to a doublet.
- 16) On addition of deuterium oxide, this signal disappeared.
- 17) On addition of deuterium oxide, this signal changed to a singlet.