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Heterocycles. XV.[1] Enantioselective Synthesis of Chiral Flavanonols and Flavan-3,4-diols

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Chiral flavanonols and flavan-3,4-diols have been enantioselectively synthesized from the chiral epoxychalcones (−)-**2a** and (+)-**2b**, which are obtained by the asymmetric epoxidation of the chalcone **1** under phase-transfer conditions. The absolute configurations of all the compounds obtained are deduced on the basis of the results obtained by circular dichroic spectroscopy on the dibenzoates (−)-**5a**, (+)-**5b**, (+)-**8a** and (−)-**8b**.

Keywords——flavonoid; phase-transfer asymmetric epoxidation; enantioselective synthesis; CD; absolute configuration

The majority of naturally occurring flavanonols exist in the 2*R*,3*R*-configuration, but a few compounds with the 2*S*,3*S*-configuration are known. On the other hand, a variety of configurations at the 2-, 3- and 4-positions are observed for flavan-3,4-diols. We have recently reported the efficient stereocontrolled synthesis of racemic flavonoids using 2′-hydroxychalcone as the starting materials.[1] This paper is concerned with the enantioselective synthesis of chiral flavanonols and flavan-3,4-diols by the application of this synthetic method.

The induction of chirality was accomplished at the α- and β-positions in the chalcone **1**[1] by asymmetric epoxidation.[2] The chalcone **1** was epoxidized with hydrogen peroxide in the presence of 1-benzylquininium chloride (BQC) and sodium hydroxide in toluene. Work-up of the reaction mixture, followed by preparative thin-layer chromatography (prep. TLC) of the product, gave the (−)-epoxychalcone **2a** in 38% yield. Its enantiomeric excess (ee) (26%) was determined by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III). Recrystallization from methanol raised the optical purity to 31% ee. The 2,3-*trans*-configuration of (−)-**2a** was deduced from the coupling (2 Hz) observed between the 2- and 3-protons in the ^{1}H-NMR spectrum.

Treatment of (−)-**2a** (31% ee) with hydrochloric acid (purification by recrystallization) afforded (−)-flavanonol **3a** with $[\alpha]_{589}^{22}$ −7.5° in 61% yield [2,3-*trans* (2,3-diequatorial substituents), $J_{2,3}=12.5$ Hz]. Reduction of (−)-**3a** ($[\alpha]_{589}^{20}$ −6.5°) with sodium borohydride (purification by prep. TLC) gave (+)-3,4-*trans*-flavan-3,4-diol **4a** with $[\alpha]_{589}^{18}$ +2.3° in 94% yield [2,3- and 3,4-*trans* (2,3,4-triequatorial substituents), $J_{2,3}=10$ and $J_{3,4}=8.5$ Hz]. The optical purity was raised to $[\alpha]_{589}^{25}$ +3.0° and 31% ee on recrystallization from ethanol. Benzoylation of (+)-**4a** (31% ee) with benzoyl chloride (purification by prep. TLC and recrystallization) provided the (−)-*trans*-dibenzoate **5a** with 43% ee in 80% yield.

Reduction of (−)-**2a** (30% ee) with sodium borohydride (purification by prep. TLC) gave the (+)-epoxypropanol **6a** with 30% ee in 62% yield. The 1,2-*erythro*-configuration of (+)-**6a** was deduced on the basis of the stereochemistry of the compound obtained in the next reaction. Treatment of (+)-**6a** (30% ee) with hydrochloric acid (purification by recrystalli-

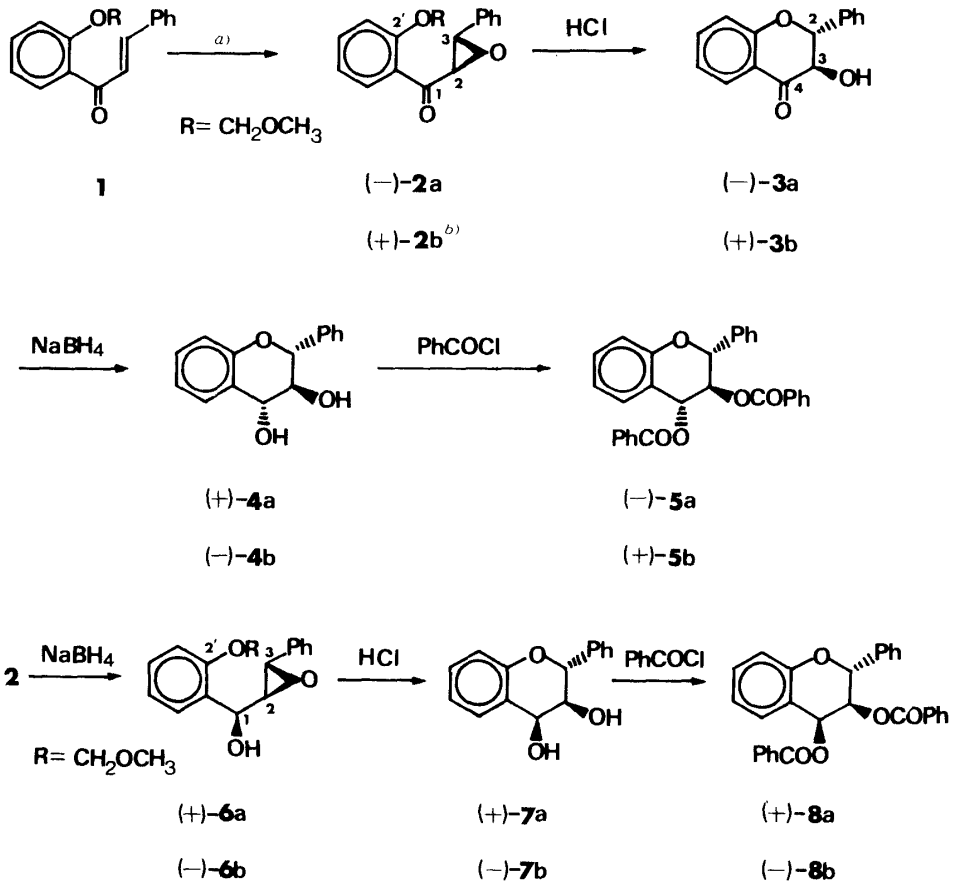
zation) afforded (+)-3,4-*cis*-flavan-3,4-diol **7a** with $[\alpha]_{589}^{19}$ +6.2° in 49% yield [2,3-*trans* and 3,4-*cis* (2,3-diequatorial and 4-axial substituents), $J_{2,3}=9$ and $J_{3,4}=3.5$ Hz]. Further recrystallization from chloroform raised the optical purity to $[\alpha]_{589}^{19}$ +7.8° and 31% ee. Benzoylation of (+)-**7a** (31% ee) with benzoyl chloride (purification by prep. TLC and recrystallization) gave the (+)-*cis*-dibenzoate **8a** with 34% ee in 77% yield.

The asymmetric epoxidation of **1** using 1-benzylquinidinium chloride (BQdC) instead of BQC yielded the (+)-epoxychalcone **2b** with 25% ee in 41% yield. The optical purity was raised to 52% ee on recrystallization from methanol. The enantiomers of the compounds **3a**—**8a** were derived from (+)-**2b** by following the procedures mentioned above.

Stereochemistry

The absolute configurations of the four flavan-3,4-diol dibenzoates were assigned by the application of the dibenzoate chirality rule.[3]

The (−)-*trans*-dibenzoate **5a** showed a negative Cotton effect at 234 nm and a positive Cotton effect at 219 nm in the circular dichroism (CD) spectrum (Fig. 1). These data correspond to the 3*S*,4*R*-configuration, and furthermore, the 2*R*-configuration is indicated by the coupling (7.5 Hz) observed between the 2- and 3-protons (diaxial) in the ^{1}H-NMR spectrum. Positive and negative Cotton effects were observed at 228 and 210 nm, respectively, in the CD spectrum of the (+)-*cis*-dibenzoate **8a**, corresponding to the 2*R*,3*S*,4*S*-configuration (Fig. 2).



a) H_2O_2/NaOH/BQC for **2a**. H_2O_2/NaOH/BQdC for **2b**.
b) The drawings of b-series compounds refer to the mirror images of those depicted for a-series compounds.

Chart 1

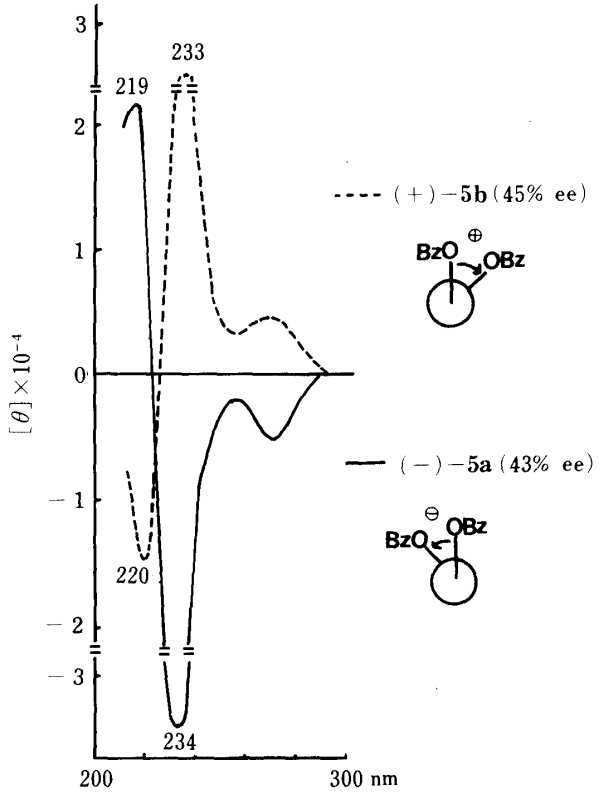


Fig. 1. The CD Spectra of (−)-**5a** and (+)-**5b**

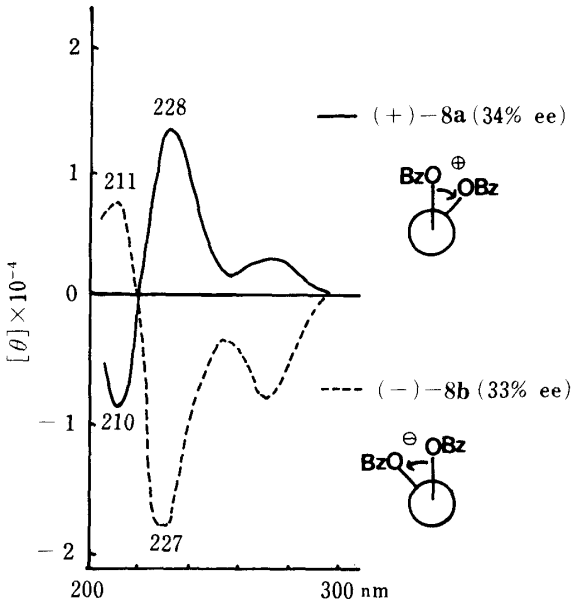


Fig. 2. The CD Spectra of (+)-**8a** and (−)-**8b**

The CD spectra of the (+)-*trans*-dibenzoate **5b** and the (−)-*cis*-dibenzoate **8b**, derived from (−)-**4b** and (−)-**7b**, were mirror images of those observed for (−)-**5a** and (+)-**8a**, respectively.

On the basis of these observations, the stereochemistry of the other compounds can be assigned as follows: (−)-**2a**, 2*R*,3*S*; (+)-**2b**, 2*S*,3*R*; (−)-**3a**, 2*R*,3*R*; (+)-**3b**, 2*S*,3*S*; (+)-**4a**, 2*R*,3*S*,4*R*; (−)-**4b**, 2*S*,3*R*,4*S*; (+)-**6a**, 1*S*,2*S*,3*S*; (−)-**6b**, 1*R*,2*R*,3*R*; (+)-**7a**, 2*R*,3*S*,4*S*; (−)-**7b**, 2*S*,3*R*,4*R*.

Wynberg *et al.* showed that (−)-epoxychalcone has the 2*R*,3*S*-configuration on the basis of chemical correlation.[4] This finding is in accord with the result obtained for (−)-**2a** in this work. The CD spectrum of (−)-**3a** exhibited a positive Cotton effect at 336 nm (n→π*) and a negative Cotton effect at 306 nm (π→π*), being in consistent with those of naturally occurring (2*R*,3*R*)-flavanonols reported by Gaffield.[5]

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Optical rotations were taken on a JASCO DPI-181 polarimeter. Enantiomeric excess (ee) was estimated by ^{1}H-NMR spectroscopy using Eu(hfc)$_3$. Spectra were recorded on the following spectrometers: infrared (IR), Hitachi 260-30; ultraviolet (UV), Hitachi EPS-2U; CD, JASCO J-20; ^{1}H-NMR, Varian EM-390 (90 MHz) (reference, Me_4Si); mass spectra (MS), JEOL JMS DX-300. The IR and ^{1}H-NMR spectra obtained were superimposable on those of the corresponding racemic compounds.[1] The b-series compounds were prepared by following the same procedures as employed for the preparations of the a-series compounds.

(2*R*,3*S*)-(−)-2,3-Epoxy-1-2′-methoxymethoxyphenyl-3-phenylpropanone 2a and the (2*S*,3*R*)-(+)-Enantiomer 2b——a) A solution of 2′-methoxymethoxychalcone **1** (301.7 mg) in toluene (15 ml) was added to a mixture of BQC[6] (103.3 mg), 2 N aqueous NaOH (1 ml) and 30% aqueous H_2O_2 (0.8 ml), and the whole was stirred at room temperature for 22 h. The organic phase was washed with 10% aqueous KI, 10% aqueous $Na_2S_2O_3$ and H_2O, then

dried over Na_2SO_4. Removal of the solvent *in vacuo*, followed by prep. TLC (Al_2O_3; acetone/C_6H_6 = 1/5, v/v) of the residue, gave (−)-**2a** (26% ee) (120.3 mg, 38%), *Rf* 0.28, as colorless needles of mp 74—77 °C. Optical rotation $[\alpha]^{20}$ (nm); −28.4° (589), −31.2° (577), −38.3° (546), −102.6° (435) (c = 0.51, CH_2Cl_2). Recrystallization from MeOH yielded (−)-**2a** (31% ee) as colorless needles of mp 72—73 °C. Optical rotation $[\alpha]^{17}$ (nm); −37.2° (589), −41.2° (577), −49.6° (546), −140.0° (435) (c = 0.50, CH_2Cl_2). UV λ_{max}^{MeOH} nm (log ε): 306.5 (3.74), 254 (4.12), 206 (4.44). CD (c = 0.001, MeOH) $[\theta]^{19}$ (nm): −4885 (300) (neg. max.),[7] −1988 (272) (pos. max.),[8] −3010 (258) (neg. max.), 0 (248), +9088 (230) (pos. max.), 0 (218). ^{1}H-NMR (C_6D_6) δ: 7.94 (1H, dd, J = 7.5 and 2 Hz, 6′-H),[9] 4.10, 3.96 (1H each, d, J = 2 Hz, 2- and 3-H's). MS Calcd for $C_{17}H_{16}O_4$: M, 284.105. Found m/z: M^+, 284.106. Unreacted **1** (134.3 mg, 45%) was recovered from the zone with *Rf* 0.79.

b) A solution of **1** (503.3 mg) in toluene (5 ml) was added to a mixture of BQdC[10] (100.1 mg), 2 N aqueous NaOH (1 ml) and 30% aqueous H_2O_2 (1 ml), and the whole was stirred at room temperature for 3 d. Work-up of the reaction mixture gave (+)-**2b** (25% ee) (219.4 mg, 41%) as colorless needles of mp 74—77 °C. Optical rotation $[\alpha]^{16}$ (nm): +35.0° (589), +39.4° (577), +45.2° (546), +125.4° (435) (c = 0.18, CH_2Cl_2). Recrystallization from MeOH yielded (+)-**2b** (52% ee) as colorless needles of mp 74—76 °C. Optical rotation $[\alpha]^{19}$ (nm): +50.0° (589), +53.0° (557), +63.9° (546), +172.2° (435) (c = 0.46, CH_2Cl_2). CD (c = 0.001, MeOH) $[\theta]^{20}$ (nm): +9811 (295) (pos. max.), +5422 (274) (neg. max.), +6713 (260) (pos. max.), 0 (248), −13942 (235) (neg. max.), 0 (221). MS Calcd for $C_{17}H_{16}O_4$: M, 284.105. Found m/z: M^+, 284.104. Unreacted **1** (146.1 mg, 29%) was recovered.

(2*R*,3*R*)-(−)-Flavanonol 3a and the (2*S*,3*S*)-(+)-Enantiomer 3b——a) 10% HCl/MeOH (0.3 ml) was added to a solution of (−)-**2a** (31% ee) (72.0 mg) in MeOH (1 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from EtOH to yield (−)-**3a** (36.5 mg, 61%) as colorless needles of mp 170—173 °C. Optical rotation $[\alpha]^{22}$ (nm): −7.5° (589), −11.3° (577), −12.2° (546), −24.4° (435) (c = 0.40, CH_2Cl_2). UV λ_{max}^{MeOH} nm (log ε): 317.5 (3.66), 252 (4.00), 212.5 (4.65). CD (c = 0.001, MeOH) $[\theta]^{20}$ (nm): +3032 (336) (pos. max.), 0 (324), −4446 (306) (neg. max.), −960 (269) (pos. max.), −2577 (252) (neg. max.), 0 (239), +3284 (228) (shoulder), +15663 (208) (pos. max.). ^{1}H-NMR ($CDCl_3$) δ: 5.13 (1H, d, J = 12.5 Hz, 2-H), 4.56 (1H, dd, J = 12.5 and 2 Hz, 3-H),[11] 3.64 (1H, d, J = 2 Hz, 3-OH).[12] MS Calcd for $C_{15}H_{12}O_3$: M, 240.079. Found m/z: M^+, 240.079.

Acetate: A colorless oil (30% ee) (from (−)-**3a**, $[\alpha]_{589}^{22}$ −7.5°). IR (KBr): 1745 (OC=O), 1705 cm^{-1} (C=O). Optical rotation $[\alpha]^{20}$ (nm): +5.1° (589), +6.0° (577), +6.8° (546), +22.6° (435) (c = 0.47, CH_2Cl_2). UV λ_{max}^{MeOH} nm (log ε): 318 (3.47), 252 (3.96), 211.5 (4.52). CD (c = 0.001, MeOH) $[\theta]^{19}$ (nm): +3384 (335) (pos. max.), 0 (324), −4512 (304) (neg. max.), −537 (270) (pos. max.), −2256 (250) (neg. max.), 0 (239), +11280 (208) (pos. max.). ^{1}H-NMR ($CDCl_3$) δ: 7.91 (1H, dd, J = 9 and 1.5 Hz, 5-H), 7.65—7.35 (5H, m, aromatic H's), 7.21—7.00 (3H, m, aromatic H's), 5.80 (1H, d, J = 12 Hz, 3-H), 5.40 (1H, d, J = 12 Hz, 2-H), 1.97 (3H, s, 3-OCOCH$_3$).[9] MS Calcd for $C_{17}H_{14}O_4$: M, 282.089. Found m/z: M^+, 282.089.

b) The (+)-epoxychalcone **2b** (52% ee) gave (+)-**3b** as colorless needles of mp 167—168 °C (from EtOH) in 51% yield. Optical rotation $[\alpha]^{19}$ (nm): +12.9° (589), +15.3° (577), +18.8° (546), +42.4° (435) (c = 0.17, CH_2Cl_2). CD (c = 0.001, MeOH) $[\theta]^{20}$ (nm): −9024 (338) (neg. max.), 0 (323), +12720 (304) (pos. max.), +600 (263) (neg. max.), +3480 (247) (pos. max.), 0 (238), −11280 (225) (shoulder), −19200 (208) (neg. max.). MS Calcd for $C_{15}H_{12}O_3$: M, 240.079. Found m/z: M^+, 240.079.

Acetate: A colorless oil (60% ee) (from (+)-**3b**, $[\alpha]_{589}^{19}$ +12.9°). Optical rotation $[\alpha]^{19}$ (nm): −12.5° (589), −12.4° (577), −14.1° (546), −40.9° (435) (c = 0.48, CH_2Cl_2). CD (c = 0.001, MeOH) $[\theta]^{20}$ (nm): −2051 (337) (neg. max.), 0 (324), +2871 (304) (pos. max.), +205 (262) (neg. max.), +1333 (246) (pos. max.), 0 (240), −5384 (208) (neg. max.). MS Calcd for $C_{17}H_{14}O_4$: M, 282.089. Found m/z: M^+, 282.090.

(2*R*,3*S*,4*R*)-(+)-Flavan-3,4-diol 4a and the (2*S*,3*R*,4*S*)-Enantiomer 4b——a) $NaBH_4$ (62 mg) was added to a solution of (−)-**3a** ($[\alpha]_{589}^{20}$ −6.5°) (92.4 mg) in MeOH (30 ml), and the mixture was stirred at −30 °C for 2 h. After addition of AcOH (5 drops), the reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. Removal of the solvent *in vacuo*, followed by prep. TLC (silica gel; acetone/C_6H_6 = 1/3, v/v) of the residue, gave (+)-**4a** (87.9 mg, 94%), *Rf* 0.40, as colorless needles of mp 136—138 °C. $[\alpha]_{589}^{18}$ +2.3° (c = 1.11, CH_2Cl_2). Recrystallization from EtOH gave (+)-**4a** (31% ee) as colorless needles of mp 134—136 °C. $[\alpha]_{589}^{25}$ +3.0° (c = 0.81, CH_2Cl_2). UV λ_{max}^{MeOH} nm (log ε): 283 (3.31), 275 (3.32), 200.5 (4.43). CD (c = 0.001, MeOH) $[\theta]^{20}$ (nm): −774 (270) (neg. max.), 0 (265), +1404 (243) (pos. max.), 0 (231), −4598 (225) (neg. max.). ^{1}H-NMR ($CDCl_3$) δ: 4.80 (1H, dd, J = 8.5 and 5.5 Hz, 4-H),[11] 4.76 (1H, d, J = 10 Hz, 2-H),[9] 3.80 (1H, ddd, J = 10, 8.5 and 3 Hz, 3-H),[11] 3.03 (1H, d, J = 5.5 Hz, 4-OH),[12] 2.45 (1H, d, J = 3 Hz, 3-OH).[12] MS Calcd for $C_{15}H_{14}O_3$: M, 242.094. Found m/z: M^+, 242.093.

b) (+)-Flavanonol **3b** ($[\alpha]_{589}^{19}$ +12.9°) gave (−)-**4b** as colorless needles of mp 129—131 °C in 97% yield. $[\alpha]_{589}^{18}$ −3.5° (c = 0.52, CH_2Cl_2). Recrystallization from EtOH gave (−)-**4b** as colorless needles of mp 130—131 °C. $[\alpha]_{589}^{22}$ −6.0° (c = 0.10, CH_2Cl_2). CD (c = 0.001, MeOH) $[\theta]^{19}$ (nm): +1681 (275) (pos. max.), +713 (245) (neg. max.), +2751 (228) (pos. max.), +1427 (218) (neg. max.). MS Calcd for $C_{15}H_{14}O_3$: M, 242.094. Found m/z: M^+, 242.094.

The (−)-*trans*-Dibenzoate 5a and the (+)-*trans*-Enantiomer 5b——a) A mixture of (+)-**4a** (31% ee) (12.9 mg) and benzoyl chloride (0.04 ml) in anhydrous pyridine (0.2 ml) was stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O and then extracted with C_6H_6. Removal of the solvent *in vacuo*, followed by prep. TLC (silica gel; AcOEt/C_6H_6 = 1/20, v/v) of the residue, gave (−)-**5a** (43% ee) (19.1 mg, 80%), *Rf* 0.70, as colorless needles

of mp 143—145 °C (from EtOH). $[\alpha]_{589}^{18}$ −57.3° (c=0.51, CH_2Cl_2). IR ($CHCl_3$): 1720 cm^{-1} (OC=O). UV λ_{max}^{MeOH} nm (log ε): 280 (3.43), 274 (3.48), 227 (4.39). CD (c=0.001, MeOH) $[\theta]^{19}$ (nm): −4800 (269) (neg. max.), −1700 (251) (pos. max.), −36500 (234) (neg. max.), 0 (223), +22000 (219) (pos. max.). ^{1}H-NMR ($CDCl_3$) δ: 7.90—6.85 (19H, m, aromatic H's), 6.63 (1H, d, J=6.5 Hz, 4-H), 5.96 (1H, dd, J=7.5 and 6.5 Hz, 3-H), 5.50 (1H, d, J=7.5 Hz, 2-H).[9] MS Calcd for $C_{29}H_{22}O_5$: M, 450.147. Found m/z: M^+, 450.149.

b) The (+)-*trans*-enantiomer **5b** (45% ee) was prepared from (−)-**4b** ($[\alpha]_{589}^{22}$ −6.0°) as colorless needles of mp 143—145 °C (from EtOH) in 66% yield. $[\alpha]_{589}^{15}$ +58.6° (c=0.43, CH_2Cl_2). CD (c=0.001, MeOH) $[\theta]^{17}$ (nm): +5040 (271) (pos. max.), +2520 (253) (neg. max.), +25920 (233) (pos. max.), 0 (226), −15218 (220) (neg. max.). MS Calcd for $C_{29}H_{22}O_5$: M, 450.147. Found m/z: M^+, 450.145.

(1*S*,2*S*,3*S*)-(+)-2,3-Epoxy-1-2′-methoxymethoxyphenyl-3-phenylpropanol 6a and the (1*R*,2*R*,3*R*)-(−)-Enantiomer 6b——a) $NaBH_4$ (50 mg) was added to a solution of (−)-**2a** (30% ee) (87.4 mg) in MeOH (7 ml), and the mixture was stirred at −20 °C for 2 h. After addition of AcOH (5 drops), the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. Work-up gave an oil, which was purified by prep. TLC (Al_2O_3; $CHCl_3$/hexane=4/1, v/v) to yield (+)-**6a** (30% ee) (54.6 mg, 62%), *Rf* 0.30, as a colorless oil. Optical rotation $[\alpha]^{19}$ (nm): +7.5° (589), +7.7° (577), +8.3° (546), +16.3° (435) (c=0.44, CH_2Cl_2). UV λ_{max}^{MeOH} nm (log ε): 300 (2.89), 267 (3.45), 214.5 (4.13). CD (c=0.001, MeOH) $[\theta]^{18}$ (nm): +686 (265) (pos. max.), 0 (248), +1258 (224) (pos. max.), 0 (220), −1298 (216) (neg. max.). ^{1}H-NMR (C_6D_6) δ: 3.06 (3H, s, 2′-OCH_2OCH_3).[9] MS Calcd for $C_{17}H_{18}O_4$: M, 286.121. Found m/z: M^+, 286.122.

b) The (+)-epoxychalcone **2b** (35% ee) gave (−)-**6b** (36% ee) as a colorless oil in 69% yield. Optical rotation $[\alpha]^{20}$ (nm): −8.4° (589), −8.2° (577), −10.6° (546), −21.2° (435) (c=0.47, CH_2Cl_2). CD (c=0.001, MeOH) $[\theta]^{18}$ (nm): −646 (264) (neg. max.), 0 (243), −2288 (224) (neg. max.), 0 (217), +1740 (214), (pos. max.). MS Calcd for $C_{17}H_{18}O_4$: M, 286.121. Found m/z: M^+, 286.123.

(2*R*,3*S*,4*S*)-(+)-Flavan-3,4-diol 7a and the (2*S*,3*R*,4*R*)-(−)-Enantiomer 7b——a) 10% HCl/MeOH (2 ml) was added to a solution of (+)-**6a** (30% ee) (50.0 mg) in MeOH (0.2 ml), and the mixture was stirred at room temperature for 40 min. Removal of the solvent *in vacuo* and recrystallization of the residue from $CHCl_3$ gave (+)-**7a** (20.6 mg, 49%) as colorless needles of mp 158.5—164 °C. $[\alpha]_{589}^{19}$ +6.2° (c=0.40, CH_2Cl_2). Recrystallization from $CHCl_3$ yielded (+)-**7a** (31% ee) as colorless needles of mp 160—163 °C. Optical rotation $[\alpha]^{19}$ (nm): +7.8° (589), +7.7° (577), +8.2° (546), +8.5° (435) (c=0.56, CH_2Cl_2). UV λ_{max}^{MeOH} nm (log ε): 282 (3.34), 274.5 (3.40), 213.5 (4.39). CD (c=0.001, MeOH) $[\theta]^{19}$ (nm): +229 (270) (pos. max.), 0 (255), −185 (242) (neg. max.), 0 (232), +13640 (222) (pos. max.). ^{1}H-NMR ($CDCl_3$) δ: 5.04 (1H, d, J=9 Hz, 2-H),[9] 4.72 (1H, d, J=3.5 Hz, 4-H), 4.04 (1H, dd, J=9 and 3.5 Hz, 3-H). MS Calcd for $C_{15}H_{14}O_3$: M, 242.094. Found m/z: M^+, 242.094.

b) The (−)-epoxypropanol **6b** (36% ee) gave (−)-**7b** (28% ee) as colorless needles of mp 159—162.5 °C (from $CHCl_3$) in 68% yield. Optical rotation $[\alpha]^{18}$ (nm): −6.2° (589), −6.5° (577), −8.0° (546), −8.7° (435) (c=0.80, CH_2Cl_2). CD (c=0.001, MeOH) $[\theta]^{20}$ (nm): −1211 (275) (neg. max.), −285 (245) (pos. max.), −1682 (220) (neg. max.). MS Calcd for $C_{15}H_{14}O_3$: M, 242.094. Found m/z: M^+, 242.093.

The (+)-*cis*-Dibenzoate 8a and the (−)-*cis*-Enantiomer 8b——a) A mixture of (+)-**7a** (31% ee) (10.0 mg) and benzoyl chloride (0.1 ml) in anhydrous pyridine (0.3 ml) was stirred at room temperature for 4 h. Work-up of the reaction mixture, followed by prep. TLC (Al_2O_3; C_6H_6) of the residue, gave (+)-**8a** (34% ee) (14.3 mg, 77%), *Rf* 0.60, as colorless needles of mp 118.5—120 °C (from EtOH). $[\alpha]_{589}^{20}$ +43.3° (c=0.47, CH_2Cl_2). IR ($CHCl_3$): 1720 cm^{-1} (OC=O). UV λ_{max}^{MeOH} nm (log ε): 280 (3.45), 274.5 (3.51), 217.5 (4.42). CD (c=0.001, MeOH) $[\theta]^{20}$ (nm): +2895 (273) (pos. max.), +1120 (252) (neg. max.), +13500 (228) (pos. max.), 0 (218), −9900 (210) (neg. max.). ^{1}H-NMR ($CDCl_3$) δ: 8.13—6.80 (19H, m, aromatic H's), 6.55 (1H, d, J=3.5 Hz, 4-H), 5.82 (1H, dd, J=9.5 and 3.5 Hz, 3-H), 5.58 (1H, d, J=9.5 Hz, 2-H).[9] MS Calcd for $C_{29}H_{22}O_5$: M, 450.147. Found m/z: M^+, 450.146.

b) The (−)-*cis*-enantiomer **8b** (33% ee) was prepared from (−)-**7b** (28% ee) as colorless needles of mp 117—119.5 °C (from EtOH) in 84% yield. $[\alpha]_{589}^{19}$ −40.3° (c=0.42, CH_2Cl_2). CD (c=0.001, MeOH) $[\theta]^{20}$ (nm): −8100 (268) (neg. max.), −3375 (250) (pos. max.), −19125 (227) (neg. max.), 0 (217), +7875 (211) (pos. max.). MS Calcd for $C_{29}H_{22}O_5$: M, 450.147. Found m/z: M^+, 450.145.

References and Notes

1) Part XIV: H. Takahashi, Y. Kubota, H. Miyazaki, and M. Onda, *Heterocycles*, **22**, 1147 (1984).
2) Y. Harigaya, H. Yamaguchi, and M. Onda, *Chem. Pharm. Bull.*, **29**, 1321 (1981); R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, and H. Wynberg, *Tetrahedron Lett.*, **1976**, 1831; J. C. Hummelen and H. Wynberg, *ibid.*, **1978**, 1089; H. Wynberg and B. Greijdanus, *J. Chem. Soc., Chem. Commun.*, **1978**, 427; S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, and H. Molinari, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1317; S. Colonna, H. Molinari, S. Banfi, S. Juliá, J. Masana, and A. Alvarez, *Tetrahedron*, **39**, 1635 (1983).
3) N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **91**, 3989 (1969); *idem*, "Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry (in Japanese)," Tokyo Kagaku Dōzin, Tokyo, 1982, and references cited therein.
4) B. Marsman and H. Wynberg, *J. Org. Chem.*, **44**, 2312 (1979).

5) W. Gaffield, *Tetrahedron*, **26**, 4093 (1970).
6) $[\alpha]_{589}^{26}$ −219.6° (c=0.99, H_2O), mp 183—185 °C (from EtOH).
7) Negative maximum.
8) Positive maximum.
9) These signals appeared at two positions in the ^{1}H-NMR spectra taken in the presence of Eu(hfc)$_3$ and were used for the estimation of ee.
10) $[\alpha]_{589}^{22}$ +198° (c=0.82, H_2O), mp 177—179 °C (from acetone).
11) On addition of D_2O, these splittings changed to those corresponding to disappearance of the hydroxyl protons.
12) On addition of D_2O, these signals disappeared.