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Heterocycles. XXII.[1] Stereoselective Synthesis of (+)-Aromadendrin Trimethyl Ether and Its Enantiomer, and Their Reduction

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Two enantiomeric chalcone epoxides **2a** and **2b** are synthesized under phase-transfer conditions using 1-benzylquinidinium chloride and 1-benzylquininium chloride as catalysts, respectively. Stereoselective cyclization of **2a** and **2b**, followed by methylation and preparative high performance liquid chromatography gives pure (+)-aromadendrin trimethyl ether (**4a**) and its enantiomer **4b**. Reduction of pure **4a** and **4b** with $NaBH_4$ affords four pure flavan-3,4-diol trimethyl ethers, **5a**, **6a**, **5b**, and **6b**.

Keywords——chalcone epoxide; flavanonol; flavan-3,4-diol; asymmetric epoxidation; enantioselective synthesis; preparative HPLC

Ganguly and Seshadri[2] isolated (−)-leucopelargonidin (3,4,5,7,4′-pentahydroxyflavan) from *Eucalyptus calophylla* KINO and established its 2*R*, 3*S* configuration as follows. Reduction of (2*R*, 3*R*)-(+)-aromadendrin trimethyl ether (**4a**) with sodium borohydride afforded two 4-epimeric flavan-3,4-diols, mp 150—153 °C and 197—200 °C. The one with mp 150—153 °C did not depress the melting point of natural (−)-leucopelargonidin trimethyl ether, mp 148—150 °C, $[\alpha]_D$ −122.8°, and its infrared (IR) spectrum had the same main bands. However the 4-configuration remained undecided. On the other hand, Janes and Morgan[3] reported that **4a** was reduced by the same reagent to give the flavan-3,4-diol (2*R*, 3*S*, 4*R*), mp 161—162 °C, $[\alpha]^{19}$ +3.6° ($CHCl_3$). This result is in conflict with that obtained by the former group. This paper is concerned with the stereoselective synthesis of **4a** and its enantiomer **4b**, and their reduction in order to approach the stereochemistry of (−)-leucopelargonidin.

Preparation of (+)-Aromadendrin Trimethyl Ether (4a) and Its Enantiomer 4b

We have already reported the asymmetric epoxidation of 2′-methoxymethoxychalcone[4] and also the stereoselective synthesis of (±)-**4**.[5] Combination of these procedures smoothly provided **4a** and **4b**.

Tetrakis(methoxymethoxy) isosalipurpol (**1**) was epoxidized with *tert*-butyl hydroperoxide in the presence of 1-benzylquinidinium chloride (BQdC) and sodium hydroxide in toluene. Work-up of the reaction mixture, followed by preparative thin-layer chromatography (TLC) of the product, gave the chalcone epoxide **2a** (70.4%), $[\alpha]_D^{25}$ −24.5°. Since **2a** is levorotatory, it must have the 2*R*, 3*S* configuration.[4,6] Its enantiomeric excess (ee) was determined to be 34.9% by high performance liquid chromatography (HPLC).[1,7]

Treatment of **2a** (34.9% ee) with hydrochloric acid/methanol stereoselectively furnished (+)-aromadendrin (**3a**) (81.0%), $[\alpha]_D^{25}$ +9.5°, as a sole product, which was converted into **4a** (35.7%) (34.6% ee), $[\alpha]_D^{29}$ −4.5°, on methylation with diazomethane. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum ($J_{2,3}$ = 12 Hz) of **4a** supported a 2,3-diequatorial configuration, and the 2*R*, 3*R*-configuration of **4a** was determined from the circular dichroism

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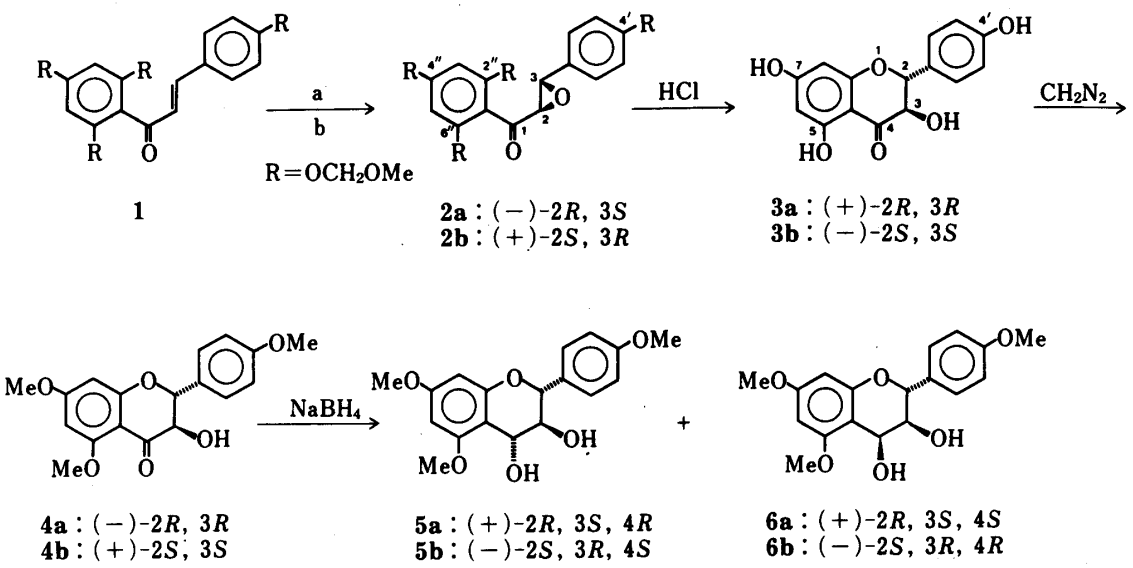

Chart 1. a) *tert*-BuO_2H/NaOH/BQdC/toluene for **2a**. *tert*-BuO_2H/NaOH/BQC/toluene for **2b**. b) The **b**-series compounds are the mirror images of those depicted (the **a**-series compounds).

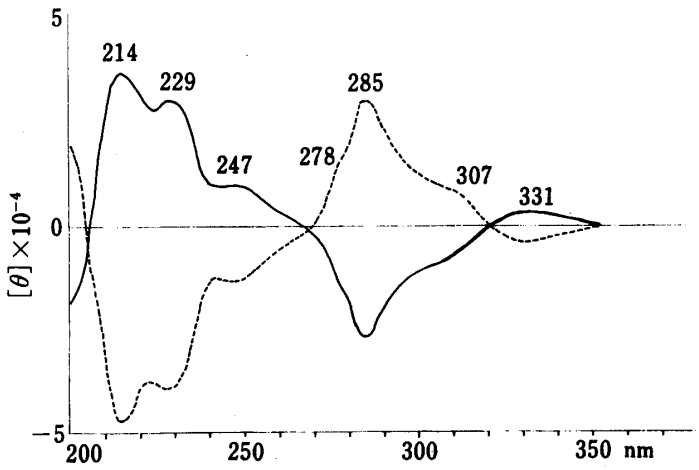

Fig. 1. CD Spectra of **4a** and **4b**
——, **4a**; ----, **4b**.

(CD) spectrum [a positive Cotton effect at 331 nm ($n\rightarrow\pi^*$) and a negative one at 285 nm ($\pi\rightarrow\pi^*$)][4,8] (Fig. 1).

The asymmetric epoxidation of **1** using 1-benzylquininium chloride (BQC) instead of BQdC gave the chalcone epoxide **2b** (48.5%) (32.0% ee), $[\alpha]_D^{25}$ +22.6°. The enantiomers **3b** (75.3%), $[\alpha]_D^{26}$ −9.6°, and **4b** (42.8%) (32.0% ee), $[\alpha]_D^{29}$ +4.4°, of **3a** and **4a**, respectively, were derived from **2b** by following the above procedures.

Preparative HPLC of **4a** and **4b** obtained above yielded optically pure **4a**, $[\alpha]_D^{28}$ −12.9° (lit.,[3] $[\alpha]_D^{18}$ −15.2°) and **4b**, $[\alpha]_D^{28}$ +13.7°, respectively, in a ratio approximately corresponding to the initial ee.[1]

Reduction of (+)-Aromadendrin Trimethyl Ether (4a) and Its Enantiomer 4b

Reduction of **4a** (100% ee) with sodium borohydride at −20 °C gave the flavan-3,4-diols **5a** (79.6%), mp 128—130 °C, $[\alpha]_D^{28}$ +12.0° ($CHCl_3$), and **6a** (12.8%), mp 143—145 °C, $[\alpha]_D^{28}$ +32.2° ($CHCl_3$). The ^{1}H-NMR spectra showed the 2*R*,3*S*,4*R* and the 2*R*,3*S*,4*S* configurations for **5a** ($J_{2,3}$=10.2 Hz, $J_{3,4}$=7.5 Hz) and **6a** ($J_{2,3}$=10.2 Hz, $J_{3,4}$=4.2 Hz), respectively. Their optical purities (100% ee) were confirmed by ^{1}H-NMR spectroscopy using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) [Eu(hfc)$_3$].[9]

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Optically pure **5b** (43.8%), mp 125—127 °C, $[\alpha]_D^{28}$ −12.4° ($CHCl_3$), and **6b** (34.6%), mp 140—142 °C, $[\alpha]_D^{28}$ −32.7° ($CHCl_3$), were prepared from **4b** (100% ee) by following the above procedures. The absolute configurations of the **b**-series compounds were deduced in the same way as employed for determining those of the **a**-series compounds (**2b**, 2*S*,3*R*; **4b**, 2*S*,3*S*; **5b**, 2*S*,3*R*,4*S*; **6b**, 2*S*,3*R*,4*R*).

Contrary to expectation, our results were not in accord with those obtained by the above two groups. Judging from the melting point and the specific rotation, it seems that the flavan-3,4-diol obtained by Janes and Morgan is considerably racemized **6a**.[10] The results obtained by Ganguly and Seshadri[2] appear extremely puzzling. The specific rotation, $[\alpha]_D$ −122.8° (*vide supra*), suggests that natural (−)-leucopelargonidin trimethyl ether cannot be the compound which can be derived from **4a**. It is our opinion that the stereochemistry and the optical properties of natural (−)-leucopelargonidin trimethyl ether should be reinvestigated.

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Specific rotations were taken on a JASCO DPI-181 polarimeter. Spectra were recorded on the following spectrometers: IR, Hitachi 260—30; ultraviolet (UV), Hitachi EPS-2U; CD, JASCO J-600; ^{1}H-NMR, Varian EM-390 (90 MHz) (reference, Me_4Si); mass spectra (MS), JEOL JMS DX-300. The IR and the ^{1}H-NMR spectra obtained were superimposable on those of the corresponding racemic compounds.[5] The **b**-series compounds were prepared by following the same procedures as employed for the preparations of the **a**-series compounds.

HPLC was performed on a Chiralpak OT(+) column under the same conditions as described in the literature.[1]

(2*R*,3*S*)-(−)-Tetrakis(methoxymethoxy)isosalipurpol Epoxide (2a) and Its (2*S*,3*R*)-(+)-Enantiomer 2b——a) A solution of tetrakis(methoxymethoxy)isosalipurpol[5] (503 mg) in toluene (4 ml) was added to a mixture of BQdC[4] (257 mg), 2 N aqueous NaOH (2.5 ml) and 72.9% *tert*-butyl hydroperoxide (1 ml) in toluene (6 ml), and the whole was stirred at 40 °C for 4 h. Work-up of the organic layer, followed by preparative TLC (silica gel, acetone : benzene = 1 : 20, v/v) of the product, gave **2a** (367 mg, 70.4%) (34.9% ee), *Rf* 0.31, as a colorless oil. Specific rotation $[\alpha]^{25}$ (nm): −24.5° (589), −26.2° (577), −31.7° (546), −82.6° (435) (c = 1.09, CH_2Cl_2), −297.7° (365) (c = 0.043, CH_2Cl_2). IR ($CHCl_3$): 1690 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.96 (1H, d, J = 1.8 Hz, 2-H), 3.87 (1H, d, J = 1.8 Hz, 3-H). MS Calcd for $C_{23}H_{28}O_{10}$: M, 464.168. Found m/z: M^+, 464.169.

b) A solution of the above chalcone (501 mg) in toluene (4 ml) was added to a mixture of BQC[4] (250 mg), 2 N aqueous NaOH (3 ml) and 72.9% *tert*-butyl hydroperoxide (1 ml) in toluene (6 ml), and the whole was stirred at 40 °C for 4 h. Work-up as above gave **2b** (251 mg, 48.5%) (32.0% ee). *Rf* 0.28, as a colorless oil. Specific rotation $[\alpha]^{25}$ (nm): +22.6° (589), +22.9° (577), +27.3° (546), +70.7° (435), (c = 1.01, CH_2Cl_2), +262.3° (365) (c = 0.050, CH_2Cl_2). MS Calcd for $C_{23}H_{28}O_{10}$: M, 464.168. Found m/z: M^+, 464.168.

(2*R*,3*R*)-(+)-Aromadendrin (3a) and the (2*S*,3*S*)-(−)-Enantiomer 3b——a) A 12% HCl–MeOH solution (1 ml) was added to a solution of (−)-**2a** (34.9% ee) (344 mg) in absolute MeOH (1 ml), and the mixture was stirred at 50 °C for 20 min. The reaction mixture was concentrated *in vacuo*, followed by preparative TLC (silica gel, $CHCl_3$: MeOH = 12 : 1, v/v) of the residue (210 mg), giving **3a** (173 mg, 81.0%), *Rf* 0.24, as colorless needles of mp 206—210 °C (MeOH). Specific rotation $[\alpha]^{25}$ (nm): +9.5° (589), +9.9° (577), +11.5° (546), +25.9° (435) (c = 0.98, MeOH), +105.2° (365) (c = 0.025, MeOH). IR (KBr): 3450, 3400 (OH), 1630 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 5.05 (1H, d, J = 11.5 Hz, 2-H), 4.60 (1H, d, J = 11.5 Hz, 3-H). *Anal.* Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20. Found: C, 62.77; H, 4.02. MS m/z: M^+, 288.063 (M, 288.063 for $C_{15}H_{12}O_6$).

b) A 12% HCl–MeOH solution (0.8 ml) was added to a solution of (+)-**2b** (32.0% ee) (250 mg) in absolute MeOH (0.8 ml), and the mixture was stirred at 50 °C for 20 min. Work-up of the residue (145.0 mg) as above, gave **3b** (116.7 mg, 75.3%), *Rf* 0.23, as colorless needles of mp 207—211 °C (MeOH). Specific rotation $[\alpha]^{26}$ (nm): −9.6° (589), −10.3° (577), −12.5° (546), −25.1° (435) (c = 0.57, MeOH), −102.1° (365) (c = 0.028, MeOH). *Anal.* Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20. Found: C, 62.34; H, 4.28. MS m/z: M^+, 288.063 (M, 288.063 for $C_{15}H_{12}O_6$).

(2*R*,3*R*)-(+)-Aromadendrin Trimethyl Ether (4a) and the (2*S*,3*S*)-(−)-Enantiomer 4b——a) A solution of **3a** ($[\alpha]^{25}$ +9.5°, 105 mg) in ether (10 ml) was methylated with CH_2N_2–ether (10 ml) in a sealed tube at room temperature for 70 h. Work-up of the reaction mixture, followed by preparative TLC (silica gel, acetone : benzene = 1 : 8, v/v) of the product (120 mg), gave **4a** (43.0 mg, 35.7%) (34.6% ee), *Rf* 0.32, as colorless needles of mp 132—134 °C (MeOH). Specific rotation $[\alpha]^{29}$ (nm): −4.5° (589), −5.0° (577), −6.4° (546), −19.6° (435) (c = 1.25, $CHCl_3$), −51.4° (365)(c = 0.062, $CHCl_3$). IR ($CHCl_3$): 3525, 3200 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 4.97 (1H, d, J = 12.3 Hz, 2-H), 4.41 (1H, dd, J = 12.3, 1.5 Hz, 3-H). *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.71; H, 5.30. MS m/z: M^+, 330.110. (M, 330.110 for $C_{18}H_{18}O_6$).

b) A solution of **3b** ($[\alpha]_D^{26}$ −9.6°) (99.0 mg) in ether (5 ml) was methylated with CH_2N_2–ether (15 ml) in a sealed

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tube at 0 °C for 30 h. Work-up as above gave **4b** (48.6 mg, 42.8%) (32.0% ee), *Rf* 0.35, as colorless needles of mp 137—139 °C (MeOH). Specific rotation $[\alpha]^{29}$ (nm): +4.4° (589), +4.8° (577), +6.3° (546), +20.5° (435) (c=1.33, $CHCl_3$), +48.5° (365) (c=0.066, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.38; H, 5.65. MS *m/z*: M^+, 330.110 (M, 330.110 for $C_{18}H_{18}O_6$).

Preparative HPLC of 4a and 4b——a) A solution of **4a** (34.6% ee) (20.0 mg) in methanol (0.2 ml) was chromatographed on a Chiralpak OT (+) column to yield **4a** (100% ee) (12.1 mg, 60.5%) as colorless needles of mp 148—149 °C (EtOH) and **4b** (100% ee) (5.6 mg, 28.0%) as colorless needles of mp 146.5—148 °C (EtOH).

Optical and Spectral Properties of **4a**: Specific rotation $[\alpha]^{28}$ (nm): −12.9° (589), −14.0° (577), −17.5° (546), −55.8° (435) (c=1.03, $CHCl_3$), −164.7° (365) (c=0.052, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 224.4 (4.59), 280.7 (4.33), 315.4 (sh) (380). CD (c=0.001, MeOH) $[\theta]^{25}$ (nm): +3200 (331), −8900 (307) (sh), −27100 (285), −15000 (278) (sh), +10100 (247), +30700 (229), +37700 (214), −17900 (200). *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.70; H, 5.79. MS *m/z*: M^+, 330.109 (M, 330.110 for $C_{18}H_{18}O_6$).

b) A solution of **4b** (32.0% ee) (25.1 mg) in methanol (0.2 ml) was chromatographed on a Chiralpak OT (+) column to give **4b** (100% ee) (16.2 mg, 64.5%) and **4a** (100% ee) (8.1 mg, 32.3%).

Optical and Spectral Properties of **4b**: Specific rotation $[\alpha]^{28}$ (nm): +13.7° (589), +15.1° (577), +18.8° (546), +58.4° (435) (c=0.90, $CHCl_3$), +172.3° (365) (c=0.045, $CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 224.8 (4.46), 280.0 (4.20), 315.4 (sh) (3.63). CD (c=0.001, MeOH) $[\theta]^{25}$ (nm): −4000 (331), +9600 (307) (sh), +31300 (285), +16300 (278) (sh), −12800 (247), −39300 (229), −47600 (214), +19600 (200). *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.69; H, 5.24. MS *m/z*: M^+, 330.109 (M, 330.110 for $C_{18}H_{18}O_6$).

(2*R*,3*S*,4*R*)-(+)-5,7,4′-Trimethoxyflavan-3,4-diol (5a), (2*R*,3*S*, 4*S*)-(+)-5,7,4′-Trimethoxyflavan-3,4-diol (6a), and Their (2*S*,3*R*, 4*S*)-(−)-Epimer (5b) and (2*S*,3*R*,4*R*)-(−)-Epimer (6b)——a) $NaBH_4$ (15.6 mg) was added to a solution of **4a** (100% ee) (39.7 mg) in methanol (8 ml), and the mixture was stirred at −20 °C for 3 h. Work-up of the reaction mixture and preparative TLC (silica gel, accetone : benzene = 1 : 6, v/v) of the product gave **5a** 31.8 mg, 79.6%), *Rf* 0.26, and **6a** (5.1 mg, 12.8%), *Rf* 0.31.

The Flavan-3,4-diol **5a**: Colorless needles of mp 128-130 °C (MeOH). IR ($CHCl_3$): 3600, 3550, 3400 cm^{-1} (OH). Specific rotation $[\alpha]^{28}$ (nm): +12.0° (589), +13.3° (577), +14.7° (546), +19.3° (435), +14.0 (365) (c=0.30, $CHCl_3$). ^{1}H-NMR ($CDCl_3$)δ: 7.41 (2H, d, J=9.0 Hz, 2′- and 6′-H), 6.94 (2H, d, J=9.0 Hz, 3′- and 5′-H), 6.12 (1H, d, J=1.8 Hz, 6- or 8-H), 6.07 (1H, d, J=1.8 Hz, 6- or 8-H), 5.00 (1H, d, J=7.5 Hz, 4-H), 4.69 (1H, d, J=10.2 Hz, 2-H), 4.06 (1H, dd, J=10.2, 7.5 Hz, 3-H), 3.84, 3.79, 3.70 (each 3H, s, Me×3), 2.30 (2H, brs, OH×2). *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.81; H, 6.14. MS *m/z*: M^+, 332.126 (M, 332.126 for $C_{18}H_{20}O_6$).

The Flavan-3,4-diol **6a**: Colorless needles of mp 143—145 °C (MeOH). IR ($CHCl_3$): 3580, 3400 cm^{-1} (OH). Specific rotation $[\alpha]^{27}$ (nm): +32.2° (589), +34.5° (577), +40.8° (546), 76.1° (435), +144.4° (365) (c=0.26, $CHCl_3$). ^{1}H-NMR ($CDCl_3$)δ: 7.41 (2H, d, J=9.0 Hz, 2′- and 6′-H), 6.96 (2H, d, J=9.0 Hz, 3′- and 5′-H), 6.09 (2H, s, 6- and 8-H), 4.99 (1H, d, J=4.2 Hz, 4-H), 4.89 (1H, d, J=10.2 Hz, 2-H), 3.93 (1H, dd, J=10.2, 4.2 Hz, 3-H), 3.82, 3.79, 3.72 (each 3H, s, Me×3), 2.55 (2H, brs, OH×2). *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.22; H, 5.82. MS *m/z*: M^+, 332.126 (M, 332.126 for $C_{18}H_{20}O_6$).

These flavan-3,4-diols were confirmed to be 100% ee by ^{1}H-NMR spectroscopy.[9]

b) The Flavanonol **4b** (100% ee) (52.0 mg) gave **5b** (22.9 mg, 43.8%) and **6b** (18.1 mg, 34.6%).

The Flavan-3,4-diol **5b**: Colorless needles of mp 125—127 °C (MeOH). Specific rotation $[\alpha]^{28}$ (nm): −12.4° (589), −13.2° (577), −14.5° (546), −19.7° (435), −16.3° (365) (c=1.05, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.27; H, 5.84. MS *m/z*: M^+, 332.126 (M, 332.126 for $C_{18}H_{20}O_6$).

The Flavan-3,4-diol **6b**: Colorless needles of mp 140—142 °C (MeOH). Specific rotation $[\alpha]^{28}$ (nm): −32.7° (589), −36.3° (577), −42.2° (546), −81.0° (435), −150.5° (365) (c=0.91, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.19; H, 6.22. MS *m/z*: M^+, 332.126. (M, 332.126 for $C_{18}H_{20}O_6$).

The IR and the ^{1}H-NMR spectra of **5b** and **6b** were superimposable on those of **5a** and **6a**, respectively. These flavan-3,4-diols were confirmed to be 100% ee by ^{1}H-NMR spectroscopy.[9]

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7) The ee's of all compounds were determined by HPLC.
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9) The ^{1}H-NMR spectra of (±)-**5** and (±)-**6** taken in the presence of Eu(hfc)$_3$ each showed double 2′- and 6′-proton signals, which were used for the estimation of ee.
10) The (±)-flavan-3,4-diol (**5**), mp 108—109 °C; (±)-**6**, mp 165—166 °C.[5]

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