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HETEROCYCLES, XXIII. AN APPROACH TO (+)-LEUCOCYANIDIN FROM *BUTEA FRONDOSA*[1]

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ABSTRACT.—Two enantiomeric chalcone epoxides **2a** and **2b** were synthesized under phase-transfer conditions using 1-benzylquinidinium chloride (BQdC) and 1-benzylquininium chloride (BQC) as catalyst, respectively. Stereoselective cyclization of **2a** and **2b**, followed by methylation and preparative hplc, gave optically pure (+)-taxifolin tetramethyl ether [**4a**] and its enantiomer **4b**. Reduction of **4a** and **4b** with $NaBH_4$ afforded four optically pure flavan-3,4-diol tetramethyl ethers **5a**, **6a**, **5b**, and **6b**.

From the comparison of the melting point and the specific rotation, it is deduced that (+)-leucocyanidin tetramethyl ether is **6a** with the 2*R*,3*S*,4*S* configuration.

Several descriptions of the isolation of leucocyanidins from natural sources have been reported (1). Among them, the existence of a leucocyanidin in the gum of *Butea frondosa* was first reported by Robinson (2). Later, Ganguly and Seshadri (3) isolated (+)-leucocyanidin from the same source, for which a 5,7,3′,4′-tetrahydroxyflavan-3,4-diol structure with the 2*R*,3*S* configuration was proposed as follows. Reduction of (+)-taxifolin (2*R*,3*R*) tetramethyl ether [**4a**] with $NaBH_4$ afforded two 4-epimeric flavan-3,4-diols, mp 171–172° and 198°. The one with mp 198° did not depress the melting point of (+)-leucocyanidin tetramethyl ether, mp 198–200°, $[\alpha]^{32}D$ +125.2° (EtOH), which was derived from the natural product on methylation with CH_2N_2. However, the configuration at C-4 remained undecided. On the other hand, Porter and Foo (4) reported that **4a** was reduced with $NaBH_4$ to yield two 4-epimeric flavan-3,4-diols, mp 167–168°, $[\alpha]^{25}D$ +1.2° ($CHCl_3$), and mp 187–189°, $[\alpha]^{25}D$ +35.0° ($CHCl_3$). This paper is concerned with the stereoselective synthesis of **4a** and its enantiomer **4b**, and their reduction to the flavan-3,4-diol tetramethyl ethers **5a**,**5b** and **6a**,**6b** in order to examine the discrepancy in the results obtained by both groups and the stereochemistry of (+)-leucocyanidin.

RESULTS AND DISCUSSION

The synthetic route to **5a**,**5b** and **6a**,**6b** is shown in Scheme 1. 3,4,2′,4′,6′-Pentakis(methoxymethoxy)chalcone [**1**] (5) was epoxidized with *tert*-butyl hydroperoxide in the presence of 1-benzylquinidinium chloride (BQdC) and NaOH in toluene. Workup of the reaction mixture, followed by preparative tlc of the product, gave the chalcone epoxide **2a** (42.0%), $[\alpha]^{25}D$ −24.4°. Since **2a** is levorotatory, it must have the 2*R*,3*S* configuration (6–8). Its enantiomeric excess (ee) was determined to be 39.6% by hplc (9). (The ee's of all compounds were determined by hplc unless otherwise noted.)

Treatment of **2a** (39.6% ee) with HCl/MeOH stereoselectively furnished (+)-taxifolin [**3a**] (60.2%), $[\alpha]^{25}D$ +4.6°, as the sole product, which was converted into **4a** (43.2%) (38.9% ee), $[\alpha]^{28}D$ −8.6°, on methylation with CH_2N_2 in Et_2O. The ^1H nmr ($J_{2,3}$ = 12.0 Hz) of **4a** supported a 2,3-diequatorial conformation. The 2*R*,3*R* configuration of **4a** was determined by its cd spectrum [a positive Cotton effect at 330 nm ($n \mapsto \pi^*$) and a negative one at 288 nm ($\pi \mapsto \pi^*$)] (7,8,10) (Figure 1).

The asymmetric epoxidation of **1** using 1-benzylquininium chloride (BQC) instead

[1]For part XXII, see Takahashi *et al.* (8).

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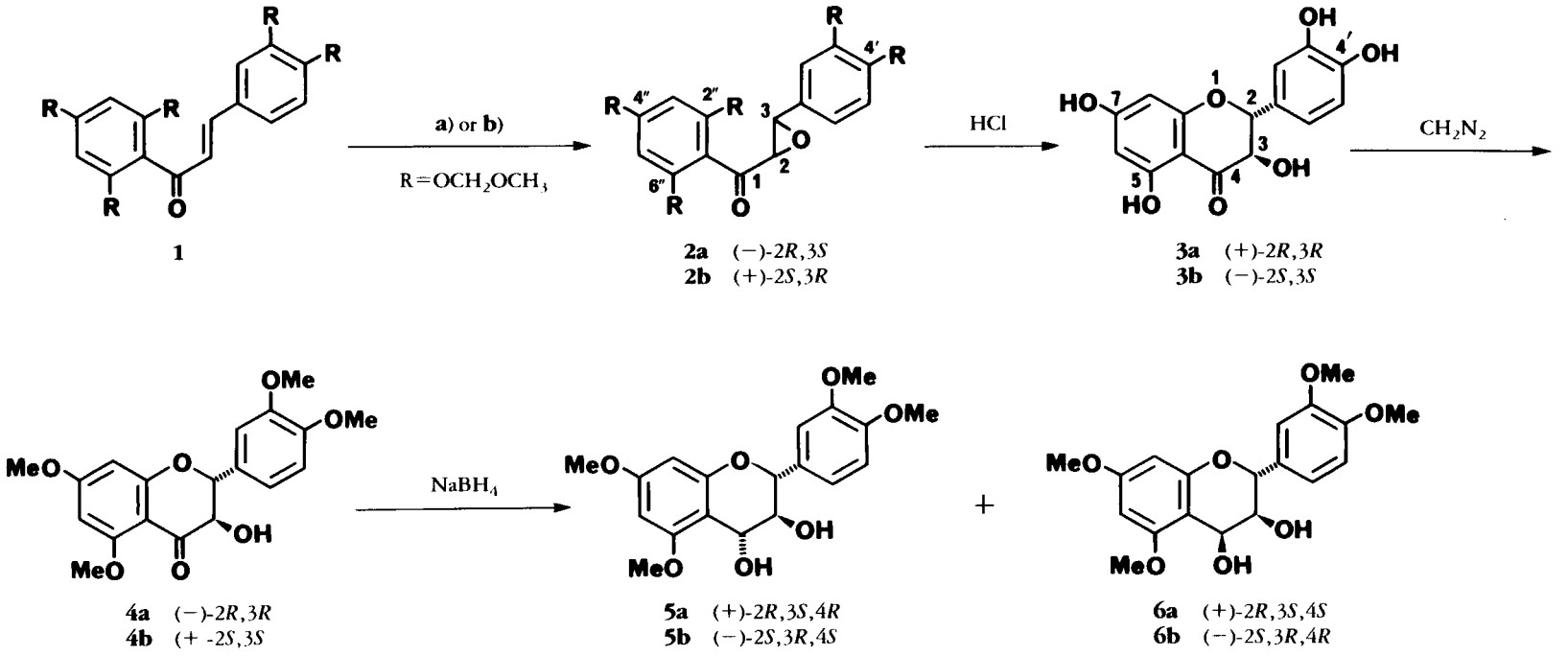

1

2a (−)-2*R*,3*S*
2b (+)-2*S*,3*R*

3a (+)-2*R*,3*R*
3b (−)-2*S*,3*S*

4a (−)-2*R*,3*R*
4b (+ -2*S*,3*S*

5a (+)-2*R*,3*S*,4*R*
5b (−)-2*S*,3*R*,4*S*

6a (+)-2*R*,3*S*,4*S*
6b (−)-2*S*,3*R*,4*R*

SCHEME 1. a) *tert*-BuO_2H/NaOH/BQdC/toluene for **2a**. b) *tert*-BuO_2H/NaOH/BQC/toluene for **2b**. The drawings of the **b** series compounds refer to the mirror images of those depicted for the **a** series compounds.

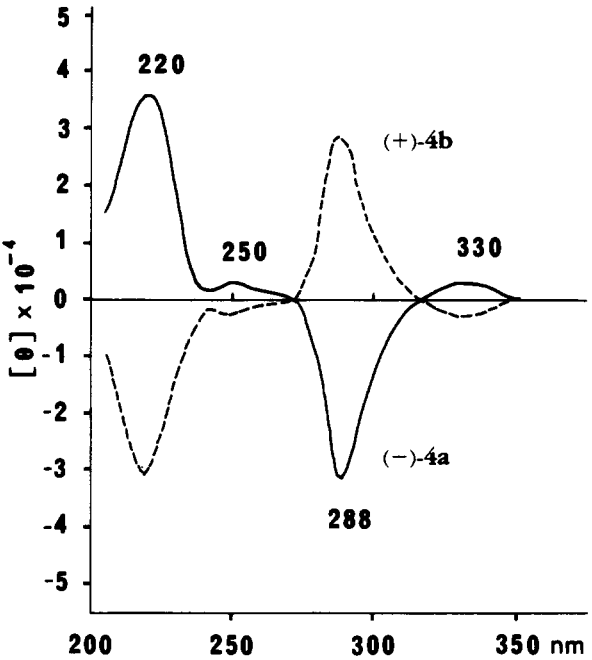

FIGURE 1. Cd spectra of (−)-**4a** and (+)-**4b** (each 100% enantiomeric excess).

of BQdC gave the chalcone epoxide **2b** (46.0%) (36.8% ee), $[\alpha]^{24}D$ +21.8°. The enantiomers **3b** (54.0%), $[\alpha]^{24}D$ −5.6°, and **4b** (62.7%) (36.1% ee), $[\alpha]^{26}D$ +9.0°, 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**, $[\alpha]^{28}D$ −25.5° {lit. (11) $[\alpha]^{16}D$ −23.4°} and **4b**, $[\alpha]^{28}D$ +26.7°, respectively, in the approximate ratio corresponding to the initial ee (9).

Reduction of **4a** (100% ee) with $NaBH_4$ at −20° gave the flavan-3,4-diols **5a** (57.0%), mp 172–174°, $[\alpha]^{28}D$ −4.9° (EtOH), and **6a** (36.0%), mp 192–194°, $[\alpha]^{29}D$ +32.0° (EtOH). 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 and $J_{3,4}$ = 7.2 Hz) and **6a** ($J_{2,3}$ = 10.2 Hz and $J_{3,4}$ = 3.6 Hz), respectively. Their optical purities (100%) were confirmed by ^{1}H-nmr spectroscopy using $Eu(hfc)_3$. The ^{1}H nmr spectra of (±)-**5** and (±)-**6** taken in the presence of $Eu(hfc)_3$ showed the 5′-H signals at two positions that were used for the estimation of ee.

Optically pure **5b** (63.0%), mp 170–172°, $[\alpha]^{28}D$ +4.2° (EtOH), and **6b** (33.0%), mp 191–193°, $[\alpha]^{28}D$ −33.4° (EtOH), 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 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*).

The results obtained by us were very similar to those of Porter and Foo (4). The discrepancy observed in the melting points and the specific rotations may be attributed to the optical purities (ours, 100% ee) and the solvents used for the measurements. None of the flavan-3,4-diol tetramethyl ethers obtained possessed a similar specific rotation to that ($[\alpha]^{32}D$ +125.2°) of (+)-leucocyanidin tetramethyl ether (see above). Accordingly, its chiral property must be reinvestigated. On the other hand, Fletcher *et al.* (12) and Porter and Foo (4) claimed that the structure of (+)-leucocyanidin was incorrect because of its sparing solubility in EtOH. However, Ganguly and Seshadri (3) stated that

(+)-leucocyanidin tetramethyl ether was the same as the synthetic one derived from (+)-taxifolin tetramethyl ether by the mixed melting point experiment. In our opinion, judging from the melting point and the specific dextro rotation, a possibility that (+)-leucocyanidin tetramethyl ether is **6a** with the 2*R*,3*S*,3*S* configuration cannot be completely ruled out.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—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; uv, Hitachi EPS-2U; cd, JASCO J-600; ^{1}H nmr, Varian EM-390 (90 MHz) (reference, TMS); hrms, 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 by Takahashi *et al.* (9).

(2*R*,3*S*)-(−)-1-2″,4″,6″-TRIS(METHOXYMETHOXY)PHENYL-2,3-EPOXY-3-3′,4′-BIS(METHOXYMETHOXY)PHENYLPROPANONE [**2a**] AND ITS (2*S*,3*R*)-(+)-ENANTIOMER **2b**.—*tert*-Butyl hydroperoxide (72.9%, 0.5 ml), BQdC (7) (20.4 mg), and 2 N aqueous NaOH (1 ml) were added to a solution of pentakis(methoxymethoxy)chalcone [**1**] (5) (184.1 mg) in toluene (5 ml), and the whole was stirred at 40° for 4 h. Workup of the organic layer, followed by preparative tlc (Al_2O_3; Me_2CO-C_6H_6, 1:20) of the product (180.4 mg), gave unreacted chalcone [**1**] (94.7 mg, 51.4%) and **2a** (78.9 mg, 42.0%) (39.6% ee), R_f 0.28, as a colorless oil; specific rotation $[\alpha]^{25}$ (nm) −24.4° (589), −25.9° (577), −34.0° (546), −112.5° (435) (*c* = 1.00, CH_2Cl_2), −402.7° (365) (*c* = 0.05, CH_2Cl_2); ir ν max ($CHCl_3$) cm^{-1} 1700 (C=O); ^{1}H nmr ($CDCl_3$) δ 3.93 (1H, d, *J* = 1.8 Hz, 2-H), 3.84 (1H, d, *J* = 1.8 Hz, 3-H). *Anal.* calcd for $C_{25}H_{32}O_{12}$: C 57.25, H 6.15, found C 57.53, H 6.39; hrms *m/z* $[M]^+$ 524.1892 ($[M]^+$ 524.1893 for $C_{25}H_{32}O_{12}$).

tert-Butyl hydroperoxide (72.9%, 0.5 ml), BQC (7) (20.4 mg), and 2N aqueous NaOH (1 ml) were added to a solution of the above chalcone (180.5 mg) in toluene (5 ml), and the whole was stirred at 40° for 4 h. Workup as above gave unreacted **1** (82.4 mg, 45.7%) and **2b** (85.7 mg, 46.0%) (36.8% ee), R_f 0.28, as a colorless oil; specific rotation $[\alpha]^{24}$ (nm) +21.2° (589), +25.8° (577), +32.6° (546), +89.1° (435) (*c* = 1.00, CH_2Cl_2), +370.6° (365) (*c* = 0.05, CH_2Cl_2); hrms *m/z* calcd for $C_{25}H_{32}O_{12}$: $[M]^+$ 524.1893, found $[M]^+$ 524.1889.

(2*R*,3*R*)-(+)-TAXIFOLIN [**3a**] AND THE (2*S*,3*S*)-(−)-ENANTIOMER **3b**.—HCl/MeOH (12%, 1 ml) was added to a solution of (−)-**2a** (39.6% ee) (78.0 mg) in absolute MeOH (1 ml), and the mixture was stirred at 50° for 20 min. Concentration of the reaction mixture in vacuo, followed by preparative tlc (Si gel; $CHCl_3$-MeOH, 10:1) of the residue (40.0 mg), gave **3a** (27.2 mg, 60.2%), R_f 0.35, as colorless plates of mp 232–235° (H_2O); specific rotation $[\alpha]^{25}$ (nm) +4.6° (589), +5.2° (577), +18.6° (546), +36.4° (435) (*c* = 0.82, EtOH), +94.1° (365) (*c* = 0.041, EtOH); ir ν max (KBr) cm^{-1} 3300 (OH), 1640 (C=O); ^{1}H nmr (Me_2CO-d_6) δ 5.98 (1H, d, *J* = 12.0 Hz, H-2), 4.55 (1H, d, *J* = 12.0 Hz, H-3); hrms *m/z* calcd for $C_{15}H_{12}O_7$: $[M]^+$ 304.0583, found $[M]^+$ 304.0582.

HCl/MeOH (12%, 1 ml) was added to a solution of (+)-**2b** (36.8% ee) (83.1 mg) in absolute MeOH (1 ml), and the mixture was stirred at 50° for 20 min. Workup of the residue (45.6 mg) as above gave **3b** (26.1 mg, 54.0%), R_f 0.37, as colorless plates, mp 232–234° (EtOH); specific rotation $[\alpha]^{26}$ (nm) −5.6° (589), −7.2° (577), −27.8° (546), −37.3° (435) (*c* = 1.00, EtOH), −98.9° (365) (*c* = 0.05, EtOH); hrms *m/z* calcd for $C_{15}H_{12}O_7$: $[M]^+$ 304.0583, found $[M]^+$ 304.0583.

(2*R*,3*R*)-(+)-TAXIFOLIN TETRAMETHYL ETHER [**4a**] AND THE (2*S*,3*S*)-(−)-ENANTIOMER **4b**.—A solution of **3a** ($[\alpha]^{24}$D +4.6°) (26.5 mg) in Et_2O (10 ml) was methylated with CH_2N_2/Et_2O (15 ml) in a sealed tube at 0° for 30 h. Workup of the reaction mixture, followed by preparative tlc (Si gel; Me_2CO-C_6H_6, 1:5) of the product (29.2 mg), gave **4a** (13.1 mg, 43.2%) (38.9% ee), R_f 0.54, as colorless needles of mp 166–168° (EtOH); specific rotation $[\alpha]^{27}$ (nm) −9.2° (589), −13.7° (577), −18.1° (546), −42.6° (435) (*c* = 0.92, $CHCl_3$), −105.3° (365) (*c* = 0.046, $CHCl_3$); ir ν max ($CHCl_3$) cm^{-1} 3450 (OH), 1670 (C=O); ^{1}H nmr ($CDCl_3$) δ 4.94 (1H, d, *J* = 12.0 Hz, H-2), 4.41 (1H, dd, *J* = 12.0, 1.8 Hz, H-3); *anal.* calcd for $C_{19}H_{20}O_7$: C 63.33, H 5.59, found C 63.61, H 5.74; hrms *m/z* $[M]^+$ 360.1206 ($[M]^+$ 360.1209 for $C_{19}H_{20}O_7$).

A solution of **3b** ($[\alpha]^{26}$D −5.6°) (25.6 mg) in Et_2O (10 ml) was methylated with CH_2N_2/Et_2O (20 ml) in a sealed tube at 0° for 30 h. Workup as above gave **4b** (18.7 mg, 62.7%) (36.1% ee), R_f 0.54, as colorless needles of mp 166–168° (EtOH); specific rotation $[\alpha]^{26}$ (nm) +9.0° (589), +12.4° (577), +18.7°

(546), +41.0° (435) (*c* = 1.00, $CHCl_3$), +101.8° (365) (*c* = 0.05, $CHCl_3$); *anal.* calcd for $C_{19}H_{20}O_7$: C 63.33, H 5.59, found C 63.28, H 5.59; hrms *m/z* $[M]^+$ 360.1209 ($[M]^+$ 360.1209 for $C_{19}H_{20}O_7$).

PREPARATIVE HPLC OF **4a** AND **4b** (5).—A solution of **4a** (38.9% ee) (13.1 mg) in MeOH (0.1 ml) was chromatographed on a Chiralpak OT(+) column to yield **4a** (100% ee) (8.4 mg, 64.1%), Rt 14.0, as colorless needles of mp 155–157° (EtOH) and **4b** (100% ee) (3.8 mg, 29.0%), Rt 12.0, as colorless needles of mp 158–160° (EtOH).

Optical and spectral properties of **4a**.—Specific rotation $[\alpha]^{28}$ (nm) −25.5° (589), −27.4° (577), −33.3° (546), −87.1° (435) (*c* = 1.13, $CHCl_3$), −256.1° (365) (*c* = 0.057, $CHCl_3$); uv λ max (MeOH) nm (log ε) 226 (4.04), 283 (3.90), 320 (3.31); cd (*c* = 2.6×10^{-5}, MeOH) $[\theta]^{25}$ (nm) +6090 (330), 0 (318), −31600 (288), 0 (217), +6650 (250), +2770 (240), +36600 (220); hrms *m/z* calcd for $C_{19}H_{20}O_7$: $[M]^+$ 360.1209, found $[M]^+$ 360.1209.

A solution of **4b** (36.1% ee) (18.7 mg) in MeOH (0.1 ml) was chromatographed on a Chiralpak OT(+) column to give **4b** (100% ee) (11.6 mg, 62.0%) and **4a** (100% ee) (5.5 mg, 29.4%).

Optical and spectral properties of **4b**.—Specific rotation $[\alpha]^{28}$ (nm) +26.7° (589), +29.0° (577), +35.1° (546), +92.4° (435) (*c* = 1.26, $CHCl_3$), +266.7° (365) (*c* = 0.063, $CHCl_3$); uv λ max (MeOH) nm (log ε) 226 (4.11), 283 (3.97), 320 (3.32); cd (*c* = 2.6×10^{-5}, MeOH) $[\theta]^{25}$ (nm) −6650 (330), 0 (318), +25800 (288), 0 (271), −7200 (250), −2770 (240), −31000 (220); hrms *m/z* calcd for $C_{19}H_{20}O_7$: $[M]^+$ 360.1209, found $[M]^+$ 360.1209.

(2*R*,3*S*,4*R*)-(+)-5,7,3′,4′-TETRAMETHOXYFLAVAN-3,4-DIOL [**5a**], (2*R*,3*S*,4*S*)-(+)-5,7,3′,4′-TETRAMETHOXYFLAVAN-3,4-DIOL [**6a**], AND THEIR (2*S*,3*R*,4*S*)-(−)-EPIMER **5b** AND (2*S*,3*R*,4*R*)-(−)-EPIMER **6b**.—$NaBH_4$ (10.4 mg) was added to a solution of **4a** (100% ee) (35.2 mg) in MeOH (15 ml), and the mixture was stirred at −20° for 3 h. Workup of the reaction mixture and preparative tlc (Si gel; Me_2CO-C_6H_6, 1:5) of the product gave **5a** (20.1 mg, 57.0%) and **6a** (12.8 mg, 36.0%).

The flavan-3,4-diol **5a**.—Colorless fine needles of mp 172–174° (EtOH); R_f 0.16; ir ν max ($CHCl_3$) cm^{-1} 3540, 3450, (OH); specific rotation $[\alpha]^{28}$ (nm) +4.9° (589), +8.2° (577), +14.3° (546), +32.2° (435), +56.4° (365) (*c* = 0.10, EtOH); ^1H nmr ($CDCl_3$) δ 7.08 (1H, dd, *J* = 9.0, 1.8 Hz, H-6′), 7.02 (1H, d, *J* = 1.8 Hz, H-2′), 6.89 (1H, d, *J* = 9.0 Hz, H-5′), 6.16, 6.07 (each 1H, d, *J* = 2.4 Hz, H-6, H-8), 4.99 (1H, d, *J* = 7.2 Hz, H-4), 4.68 (1H, d, *J* = 10.2 Hz, H-2), 4.07 (1H, dd, *J* = 10.2, 7.2 Hz, H-3); 3.87 (6H, s, Me × 2), 3.86 (3H, s, Me), 3.76 (3H, s, Me), 3- and 4-OH signals were not obtained; hrms *m/z* calcd for $C_{19}H_{22}O_7$: $[M]^+$ 362.1366, found $[M]^+$ 362.1367.

The flavan-3,4-diol **6a**.—Colorless prisms of mp 192–194° (EtOH); R_f 0.25; ir ν max ($CHCl_3$) cm^{-1} 3590, 3420, 3300 (OH); specific rotation $[\alpha]^{29}$ (nm) +32.0° (589), +34.0° (577), +38.0° (546), +70.0° (435), +136.0° (365) (*c* = 0.10, EtOH); ^1H nmr ($CDCl_3$) δ 7.06 (1H, dd, *J* = 9.0, 1.8 Hz, H-6′), 6.99 (1H, d, *J* = 1.8 Hz, H-2′), 6.89 (1H, d, *J* = 9.0 Hz, H-5′), 6.09 (2H, s, H-6, H-8), 5.02 (1H, d, *J* = 3.6 Hz, H-4), 4.88 (1H, d, *J* = 10.2 Hz, H-2), 3.82 (1H, m, H-3), 3.87 (6H, s, Me × 2), 3.82, 3.72 (each 3H, s, Me × 2), 3- and 4-OH signals were not observed; hrms *m/z* calcd for $C_{19}H_{22}O_7$: $[M]^+$ 362.1366, found $[M]^+$ 362.1367. These flavan-3,4-diols were confirmed to be 100% ee by ^1H nmr spectroscopy (see above).

The flavanonol **4b** (100% ee) (36.6 mg) gave **5b** (23.1 mg, 63.0%) and **6b** (12.3 mg, 33.0%).

The flavan-3,4-diol **5b**.—Colorless needles of mp 170–172° (EtOH); specific rotation $[\alpha]^{28}$ (nm) −4.2° (589), −8.0° (577), −12.1° (546), −30.0° (435), −54.2° (365) (*c* = 0.08, EtOH); hrms *m/z* calcd for $C_{19}H_{22}O_7$: $[M]^+$ 362.1366, found $[M]^+$ 362.1367.

The flavan-3,4-diol **6b**.—Colorless fine prisms of mp 191–193° (EtOH); specific rotation $[\alpha]^{28}$ (nm) −33.4° (589), −36.8° (577), −42.6° (546), −75.4° (435), −128.0° (365) (*c* = 0.10, EtOH); hrms *m/z* calcd for $C_{19}H_{22}O_7$: $[M]^+$ 362.1366, found $[M]^+$ 362.1374. The ir and the ^1H-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 ^1H-nmr spectroscopy (see above).

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