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HETEROCYCLES, XXIV. SYNTHESIS OF OPTICALLY PURE 2,3-*TRANS*-5,7,3′,4′,5′-PENTAHYDROXYFLAVAN-3,4-DIOLS AND COMPARISON WITH NATURALLY OCCURRING LEUCODELPHINIDINS[1]

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ABSTRACT.—Two enantiomeric chalcone epoxides **4a** and **4b** have been synthesized in the optically pure state by the phase-transfer asymmetric epoxidation of the chalcone **3** accompanied by hplc separation. Stereoselective cyclization of **4a** and **4b** and subsequent methylation afford pure (+)- and (−)-ampelopsin pentamethyl ethers **6a** and **6b**, respectively. Reduction of **6a** and **6b** with $NaBH_4$/MeOH diastereoselectively gives the pure 2,3-*trans*-3,4-*trans*-flavan-3,4-diols **7a** and **7b**. On the other hand, reduction with $NaBH_4$/dioxane diastereoselectively furnishes the pure 2,3-*trans*-3,4-*cis*-flavan-3,4-diols **8a** and **8b**.

From the comparisons of the specific rotations and melting points, it is deduced that the natural leucodelphinidins isolated from *Cleistanthus collinus* and *Eucalyptus pilularis* may belong to the 2,3-*cis*-flavan-3,4-diols.

The occurrence and stereochemistry of the currently known leucoanthocyanidins have been well reviewed by Haslam (1) and Porter (2). However, the question of the natural occurrence of leucocyanidin (5,7,3′,4′-tetrahydroxyflavan-3,4-diol), leucodelphinidin (5,7,3′,4′,5′-pentahydroxyflavan-3,4-diol), and leucopelargonidin (5,7,4′-trihydroxyflavan-3,4-diol) has remained essentially unresolved. Also, unambiguous stereochemical assignment has not been achieved for these leucoanthocyanidins. Ganguly and Seshadri (3,4) assigned the 2*R*,3*R* configuration to (+)-leucocyanidin (*Butea frondosa*) and (−)-leucopelargonidin (*Eucalyptus calophylla* Kino), but the stereochemistry at the 4 position remained undecided. Recently, we (5,6) attempted to approach the stereochemistry of these leucoanthocyanidins synthetically and concluded that (+)-leucocyanidin has the 2*R*,3*S*,4*S*-configuration, but that the structure of (−)-leucopelargonidin is doubtful.

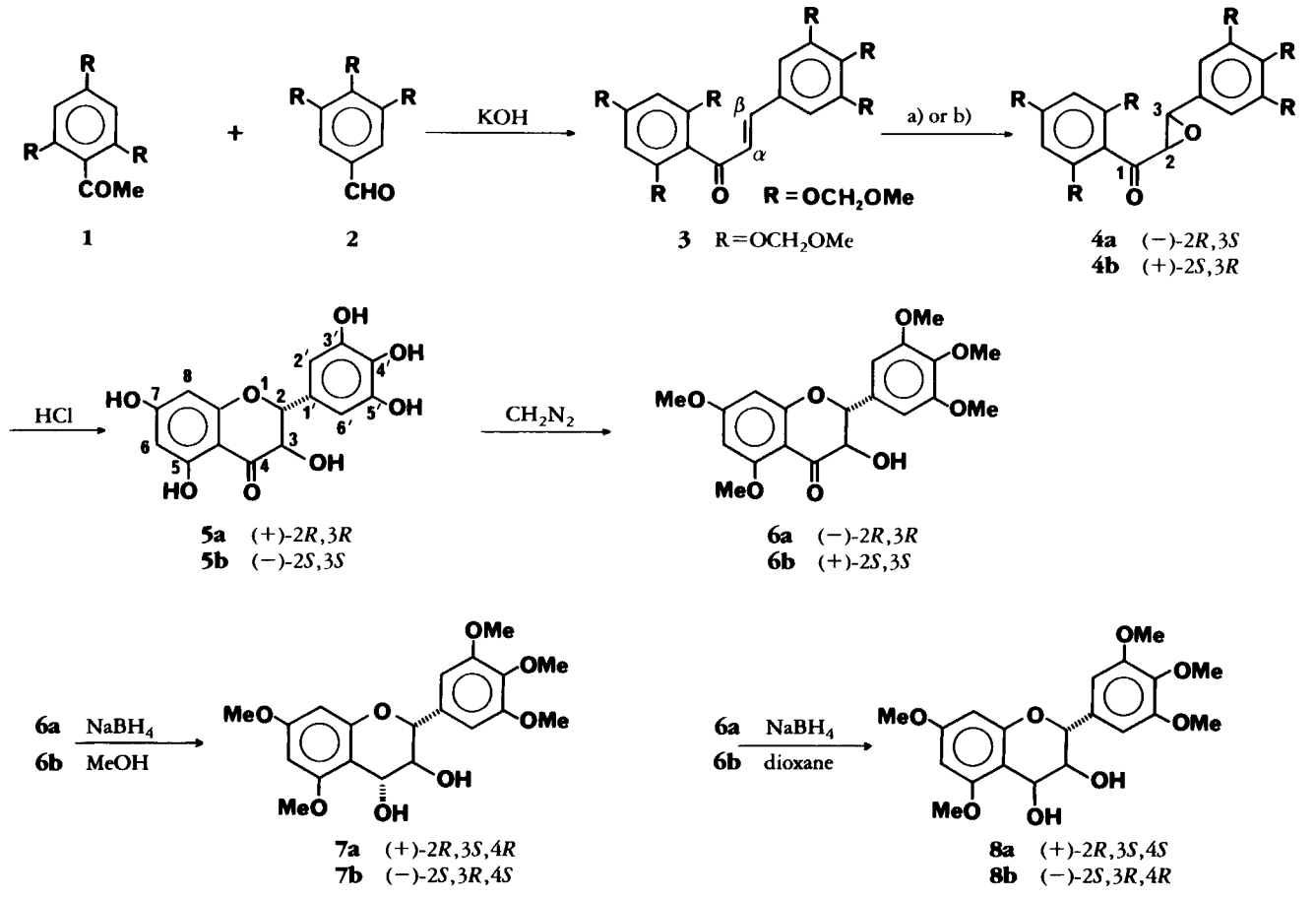
Ganguly *et al.* (7) isolated (−)- and (+)-leucodelphinidins from *Cleistanthus collinus* and *Eucalyptus pilularis*, respectively, and stated that these leucodelphinidins were not enantiomeric with each other. Their physico-chemical properties are listed in Table 1. For the completion of this series of work, we now report the stereoselective synthesis of the optically pure 2,3-*trans*-flavan-3,4-diols with the aim of examining the stereochemistry of the natural leucodelphinidins.

TABLE 1. Physico-chemical Properties of the Natural Leucodelphinidin Derivatives.[a]

Derivative	(−)-Leucodelphinidin	(+)-Leucodelphinidin
Pentamethyl ether	mp 160–164° $[\alpha]^{36}D$ −53.8°	mp 180–184° $[\alpha]^{32}D$ +72.9°
Pentamethyl ether diacetate . .	mp 218–220°	mp 225–230°

[a]The data in this table are from Ganguly *et al.* (7).

[1]For part XXIII, see Takahashi *et al.* (6).



SCHEME 1. a) *t*-BuO_2H/NaOH/BQdC/toluene for **4a**. b) *t*-BuO_2H/NaOH/BQC/toluene for **4b**. The drawings of the **b**-series compounds refer to the mirror images of those depicted for the **a**-series compounds.

RESULTS AND DISCUSSION

Condensation of the acetophenone **1** (8) with the benzaldehyde **2** using KOH/EtOH afforded the chalcone **3** (86%), to which the trans configuration was assigned by its ^{1}H-nmr spectrum ($J_{\alpha,\beta}$ = 16.5 Hz). Epoxidation of **3** with *t*-BuO_2H in the presence of 1-benzylquinidinium chloride (BQdC) and NaOH in toluene enantioselectively gave the epoxide **4a** (60%), $[\alpha]^{28}D$ −34.8°, whose enantiomeric excess (ee) was determined to be 62.3% by hplc analysis (9). The asymmetric epoxidation of **3** using 1-benzylquininium chloride (BQC) instead of BQdC under the same conditions as above yielded the epoxide **4b** (63%) (57.4% ee), $[\alpha]^{29}D$ +30.1°.

Preparative hplc of **4a** and **4b** obtained above furnished optically pure **4a**, $[\alpha]^{28}D$ −54.6°, and **4b**, $[\alpha]^{29}D$ +53.6°, in the approximate ratio corresponding to their initial ee (9). The 2*R*,3*S* and 2*S*,3*R* configurations (each 2,3-*trans*) were assigned to **4a** and **4b**, respectively, on the basis of their levo- and dextrorotations (10).

Treatment of **4a** (100%) with HCl/MeOH stereoselectively gave (+)-ampelopsin (dihydromyricetin) [**5a**] (70%), $[\alpha]^{27}D$ +24.2°, as the sole product, which was converted into the pentamethyl ether **6a** (40%) (100% ee), $[\alpha]^{25}D$ −28.2°, on methylation with CH_2N_2/Et_2O. The ^{1}H-nmr spectrum of **6a** ($J_{2,3}$ = 12.0 Hz) suggests that the aryl and hydroxyl groupings adopt a 2,3-diequatorial conformation. The 2*R*,3*R* configuration (2,3-*trans*) was determined for **6a** by its cd spectrum showing a positive Cotton effect at 337 nm ($n\mapsto\pi^*$) and a negative one at 290 nm ($\pi\mapsto\pi^*$) (11) (Figure 1).

Reduction of **6a** (100%) with $NaBH_4$/MeOH diastereoselectively afforded the flavan-3,4-diol **7a** (77%) (100% ee), mp 185–187°, $[\alpha]^{25}D$ +2.6° (MeOH), $[\alpha]^{27}D$ +6.8° ($CHCl_3$), as the sole product. On the other hand, reduction of **6a** (100%) with $NaBH_4$/dioxane diastereoselectively gave the flavan-3,4-diol **8a** (46%) (100% ee), mp 188–192°, $[\alpha]^{25}D$ +10.2° (MeOH), $[\alpha]^{27}D$ +17.6° ($CHCl_3$), as the sole product. The ^{1}H-nmr spectra of **7a** ($J_{2,3}$ = 10.2, $J_{3,4}$ = 7.5 Hz) and **8a** ($J_{2,3}$ = 10.2, $J_{3,4}$ = 4.2 Hz) assigned the 2*R*,3*S*,4*R* (2,3-*trans*, 3,4-*trans*) and 2*R*,3*S*,4*S* (2,3-*trans*, 3,4-*cis*) configurations to **7a** and **8a**, respectively. The above-obtained results suggest that the hydride ion attacks the carbonyl grouping axially in MeOH and equatorially in dioxane. The reduction mechanism will be presented elsewhere.

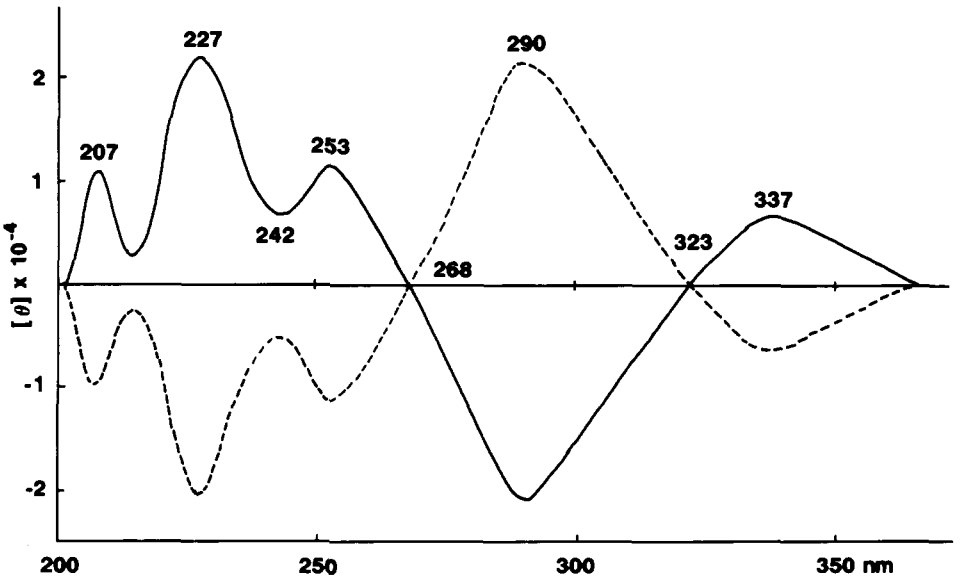
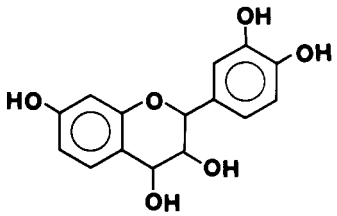


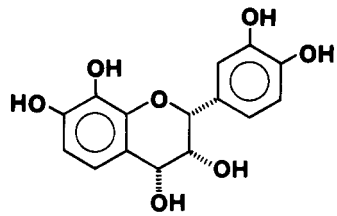
FIGURE 1. Cd spectra of **6a** and **6b** (each 100% ee).

The optically pure **b**-series compounds were prepared from **4b** (100% ee) by following the above procedures. Their absolute configurations were confirmed in the same way as employed for determining those of the **a**-series compounds.

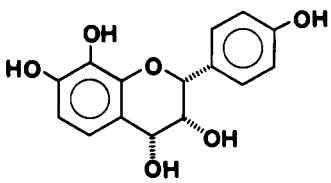
Although the melting point of (+)-leucodelphinidin pentamethyl ether is similar to those of **7a** and **8a**, the remarkable discrepancies are found in their specific rotations. Also, the melting point and specific rotation of (−)-leucodelphinidin pentamethyl ether are inconsistent with those of **7b** and **8b**. These observations suggest that the natural leucodelphinidins are not 2,3-*trans*-flavan-3,4-diols. The currently known 2,3-*cis*-leucoanthocyanidins in general show fairly large specific rotations compared to the 2,3-*trans* ones. The representatives (12–14) are shown in Figure 2. Thus, it is speculated that the natural leucodelphinidins isolated by Ganguly *et al.* (7) may belong to the 2,3-*cis*-flavan-3,4-diols on the basis of their specific rotations.



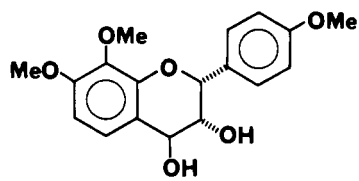
ent-epifisetinidol-4β-ol[a]
$[\alpha]^{20}D$ +49.0° (Me_2CO/H_2O)



melacacidin[b]
$[\alpha]^{16}D$ −75° (EtOH)
tetramethyl ether
$[\alpha]^{25}D$ −83.5° (EtOH)



teracacidin[c]
$[\alpha]^{20}D$ −73.3 ± 0.8° (EtOH)
trimethyl ether
$[\alpha]^{20}D$ −71.0 ± 0.7° (EtOH)



isoteracacidin
trimethyl ether[c]
$[\alpha]^{20}D$ −40.3 ± 0.9° (EtOH)

FIGURE 2. Specific rotations of the natural 2,3-*cis*-leucoanthocyanidins.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points (uncorrected) were determined on a micro hot-stage apparatus. Hplc was performed on a JASCO TRY ROTAR-V using a Chiralpak OT (+) column under the same conditions as previously described (9). Specific rotations were taken on a JASCO DPI-181 polarimeter. Spectra were recorded on the following spectrometers: uv, Hitachi EPS-2U; cd, JASCO J-600; ir, Hitachi 260-30; ^{1}H-nmr, Varian EM-390 (90 MHz) (reference TMS); hrms, JEOL JMS DX-300; elemental analysis, Perkin-Elmer 240B. The uv, ir, and ^{1}H-nmr spectra of the **b**-series compounds were superimposable on those of the corresponding **a**-series ones. The ee estimations were achieved by the ^{1}H-nmr spectra taken in the presence of Eu(hfc)$_3$ using the following signals: O-Me at δ 3.92 for **6a**, **6b**, 2′- and 6′-Hs for **7a**, **7b** and **8a**, **8b**, and 3- and 4-OAc for the **7a**, 7**b** and **8a**, **8b** diacetates. (These proton signals of racemic compounds appeared at two positions under the same conditions as employed for the optically pure compounds.)

[a]From Drewes and Ilsley (12).
[b]From Clark-Lewis and Mortimer (13).
[c]From Drewes and Roux (14).

3,4,5-TRIS (METHOXYMETHOXY) BENZALDEHYDE [**2**].—A mixture of 3,4,5-trihydroxy-benzaldehyde·H_2O (103 mg), $MeOCH_2Cl$ (296 mg), and K_2CO_3 (825 mg) in absolute Me_2CO (20 ml) was refluxed for 4 h. The reaction mixture was filtered, concentrated in vacuo and extracted with EtOAc. Workup of the organic layer gave an oily residue (164 mg) that was purified by preparative tlc [Si gel, Me_2CO-C_6H_6 (1:10)] to yield **2** (147 mg, 86%), R_f 0.55, as a colorless oil: ir ν max ($CHCl_3$) cm^{-1} 1690 (CH=O); hrms *m/z* $[M]^+$ 286.1047 (calcd for $C_{13}H_{18}O_7$, 286.1051). *Anal.* calcd for $C_{13}H_{18}O_7$, C 54.54, H 6.34; found C 54.45, H 6.39.

3,4,5,2′,4′,6′-HEXAKIS (METHOXYMETHOXY) CHALCONE [**3**].—A mixture of **1** (8) (157 mg), **2** (150 mg), and KOH (436 mg) in absolute EtOH (10 ml) was stirred at ambient temperature for 20 h. The reaction mixture was filtered, concentrated in vacuo, and extracted with EtOAc. Workup of the organic layer, followed by preparative tlc [Si gel, Me_2CO-C_6H_6 (1:5)] of the product (297 mg), afforded **3** (270 mg, 91%), R_f 0.36, as colorless needles of mp 102–102.5° (EtOH): ir ν max ($CHCl_3$) cm^{-1} 1640 (C=O); ^{1}H-nmr ($CDCl_3$) δ 7.22 (1H, d, J = 16.5 Hz, H-β), 6.84 (1H, d, J = 16.5 Hz, H-α); hrms *m/z* $[M]^+$ 568.2156 (calcd for $C_{27}H_{36}O_{13}$, 568.2154). *Anal.* calcd for $C_{27}H_{36}O_{13}$, C 57.03, H 6.38; found C 56.68, H 6.34.

(2*R*,3*S*)-(−)-2,3-EPOXY-1,2″,4″,6″-TRIS (METHOXYMETHOXY) PHENYL-3-3′,4′,5′-TRIS (METHOXYMETHOXY) PHENYLPROPANONE [**4a**] AND ITS ENANTIOMER **4b**.—A mixture of **3** (400 mg), *t*-BuO_2H (73%, 0.8 ml), BQdC (15) (160 mg) and 2 N aqueous NaOH (2 ml) in toluene (10 ml) was stirred at 40° for 4 h (see Scheme 1). Workup of the organic layer, followed by preparative tlc [Al_2O_3; Me_2CO-C_6H_6 (1:40)] of the product (405 mg), gave **4a** (247 mg, 60%) (62.3% ee), R_f 0.18, as colorless needles of mp 67–69° (EtOH): specific rotation $[\alpha]^{28}$ (nm) −34.8° (589), −37.5° (577), −45.4° (546), −123.9° (435), −469.6° (365) (*c* = 0.85, $CHCl_3$); ir ν max ($CHCl_3$) cm^{-1} 1695 (C=O); hrms *m/z* $[M]^+$ 584.2103 (calcd for $C_{27}H_{36}O_{14}$, 584.2103). *Anal.* calcd for $C_{27}H_{36}O_{14}$, C 55.47, H 6.21; found C 55.74, H 6.26. There was recovered unreacted **3** (135 mg, 34%).

A mixture of **3** (350 mg), *t*-BuO_2H (73%, 0.8 ml), BQC (15) (150 mg) and 2 N aqueous NaOH (2 ml) in toluene (10 ml) (see Scheme 1) was treated as above to yield unreacted **3** (103 mg, 29%) and **4b** (227 mg, 63%) (57.4% ee), R_f 0.18, as colorless needles of mp 71–74° (EtOH): specific rotation $[\alpha]^{29}$ (nm) +30.1° (589), +31.6° (577), +40.2° (546), +108.5° (435), +430.8° (365) (*c* = 0.90, $CHCl_3$); hrms *m/z* $[M]^+$ 584.2103 (calcd for $C_{27}H_{36}O_{14}$, 584.2103). *Anal.* calcd for $C_{27}H_{36}O_{14}$, C 55.47, H 6.21; found C 55.74, H 6.34.

PREPARATIVE HPLC OF **4a** AND **4b**.—A solution of **4a** (62.3% ee) (20.4 mg) in MeOH (3 ml) was chromatographed on a Chiralpak OT(+) column to yield **4a** (100% ee) (13.4 mg, 66%), Rt 15.5, as colorless needles of mp 65–67° (EtOH) and **4b** (100% ee) (3.0 mg, 15%), Rt 16.3, as colorless needles of mp 68–70° (EtOH).

A solution of **4b** (57.4% ee) (18.2 mg) in MeOH (3.0 ml) was treated as above to give **4a** (100% ee) (3.2 mg, 18%) and **4b** (100% ee) (12.4 mg, 68%).

Optical and spectral properties of **4a**–Specific rotation $[\alpha]^{29}$ (nm) −54.6° (589), −58.2° (577), −74.7° (546), −192.2° (435), −824.5° (365) (*c* = 0.80, $CHCl_3$); ^{1}H-nmr ($CDCl_3$) δ 3.89, 3.80 (each 1H, d, J = 1.8 Hz, H-2, H-3); hrms *m/z* $[M]^+$ 584.2105 (calcd for $C_{27}H_{36}O_{14}$, 584.2103). *Anal.* calcd for $C_{27}H_{36}O_{14}$, C 55.47, H 6.21; found C 55.47, H 6.18.

Optical and spectral properties of **4b**.—Specific rotation $[\alpha]^{29}$ (nm) +53.6° (589), +55.8° (577), +70.9° (546), +190.2° (435), +816.4° (365) (*c* = 0.81, $CHCl_3$); hrms *m/z* $[M]^+$ 584.2110 (calcd for $C_{27}H_{36}O_{14}$, 584.2103). *Anal.* calcd for $C_{27}H_{36}O_{14}$, C 55.47, H 6.21; found C 55.65, H 6.20.

(2*R*,3*R*)-(+)-AMPELOPSIN [**5a**] AND ITS ENANTIOMER **5b**.—A mixture of **4a** (100% ee) (200.0 mg) and HCl/absolute MeOH (12%, 1 ml) in absolute MeOH (0.8 ml) 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 product (108.4 mg), afforded **5a** (77.1 mg, 70%), R_f 0.15, as colorless needles of mp 189–190° (EtOH) [lit. (16) mp 245–248°]; specific rotation $[\alpha]^{27}$ (nm) +24.2° (589), +25.5° (577), +29.3 (546), +49.5° (435), +282.5° (365) (*c* = 0.99, MeOH) [lit. (16) $[\alpha]_D$ +18.08° (MeOH)]; ir ν max (KBr) cm^{-1} 3425, 3300 (OH), 1640 (C=O); ^{1}H-nmr (Me_2CO-d_6) δ 6.63 (2H, s, H-2′, H-6′), 5.98, 5.96 (each 1H, d, J = 1.8 Hz, H-6, H-8), 4.90 (1H, d, J = 12.0 Hz, H-2), 4.50 (1H, d, J = 12.0 Hz, H-3); hrms *m/z* $[M]^+$ 320.0534 (calcd for $C_{15}H_{12}O_8$, 320.0531).

A mixture of **4b** (100% ee) (150.7 mg), and HCl/absolute MeOH (12%, 1 ml) in absolute MeOH (1.0 ml) was treated as above to yield **5b** (46.2 mg, 56%) (100% ee), R_f 0.15, as colorless needles of mp 189–190° (EtOH); specific rotation $[\alpha]^{29}$ (nm) −21.7° (589), −23.0° (577), −26.4° (546), −47.1° (435), −280.2° (365) (*c* = 0.95, MeOH); hrms *m/z* $[M]^+$ 320.0524 (calcd for $C_{15}H_{12}O_8$, 320.0531).

(2*R*,3*R*)-(+)-AMPELOPSIN PENTAMETHYL ETHER [**6a**] AND ITS ENANTIOMER **6b**.—A solution

of **5a** ($[\alpha]^{27}D$ +24.2°) (63.4 mg) in absolute MeOH (10 ml) was methylated with a saturated solution of CH_2N_2 in absolute Et_2O (30 ml) in a sealed tube at 0° for 38 h. Workup of the reaction mixture, followed by preparative tlc [Si gel, Me_2CO-C_6H_6 (1:6)] of the product (60.1 mg), gave **6a** (30.6 mg, 40%) (100% ee), R_f 0.36, as colorless needles of mp 193–195° (EtOH) [lit. (16) mp 190°]; specific rotation $[\alpha]^{25}$ (nm) −28.2° (589), −31.4° (577), −37.9° (546), −90.4° (435) (c = 0.56, $CHCl_3$), −214.3° (365) (c = 0.056, $CHCl_3$); uv λ max (MeOH) nm (log ε) 315 (3.3), 284 (3.8), 226 (4.0), 210 (4.3); cd ($c = 1.28 \times 10^{-3}$, MeOH) $[\theta]^{25}$ (nm) +5600 (337) (positive maximum), 0 (323), −21400 (290) (negative maximum), 0 (268), +12000 (253) (positive maximum), +7300 (242) (negative maximum) +22000 (227) (positive maximum); ir ν max ($CHCl_3$) cm^{-1} 3475 (OH), 1670 (C=O); ^{1}H-nmr ($CDCl_3$) δ 6.80 (2H, s, H-2′, H-6′), 6.17 (2H, s, H-6, H-8), 5.97 (1H, d, J = 12.0 Hz, H-2), 4.43 (1H, d, J = 12.0 Hz, H-3), 4.09 (1H, s, 3-OH, exchangeable with D_2O), 3.92 (3H, s, OMe), 3.90 (6H, s, 2 × OMe), 3.85, 3.83 (each 3H, s, 2 × OMe); hrms *m/z* $[M]^+$ 390.1326 (calcd for $C_{20}H_{22}O_8$, 390.1313). *Anal.* calcd for $C_{20}H_{22}O_8 \cdot \frac{3}{4}H_2O$, C 59.47, H 5.86; found C 59.37, H 5.77.

Treatment of a solution of **5b** ($[\alpha]^{29}D$ −21.7°) (80.7 mg) in absolute MeOH (5 ml) and methylated with CH_2N_2/absolute Et_2O (30 ml) as above afforded **6b** (36.2 mg, 37%) (100% ee), R_f 0.36, as colorless needles of mp 192–193° (EtOH); specific rotation $[\alpha]^{29}$ (nm) +26.4° (589), +30.8° (577), +38.4° (546), +87.2° (435) (c = 0.55, $CHCl_3$), +204.8° (365), (c = 0.055, $CHCl_3$); cd ($c = 1.28 \times 10^{-3}$, MeOH) $[\theta]^{25}$ (nm) −5500 (337) (negative maximum), 0 (323), +21200 (290) (positive maximum), 0 (268), −12000 (253) (negative maximum), −5200 (242) (positive maximum), −21000 (227) (negative maximum); hrms *m/z* $[M]^+$ 390.1307 (calcd for $C_{20}H_{22}O_8$, 390.1313). *Anal.* calcd for $C_{20}H_{22}O_8 \cdot \frac{1}{2}H_2O$, C 60.14, H 5.81; found C 60.43, H 5.84.

(2*R*,3*S*,4*R*)-(+)-5,7,3′,4′,5′-PENTAMETHOXYFLAVAN-3,4-DIOL [**7a**] AND ITS ENANTIOMER **7b**.—$NaBH_4$ (13.6 mg) was added to a solution of **6a** (100% ee) (14.0 mg) in absolute MeOH (25 ml), and the whole was refluxed for 2 h. Workup of the reaction mixture, followed by preparative tlc [Si gel, Me_2CO-C_6H_6 (1:5)] of the product (12.2 mg), gave **7a** (10.8 mg, 77%) (100% ee), R_f 0.27, as colorless needles of mp 185–187° (EtOH): specific rotation $[\alpha]^{25}$ (nm) +2.6° (589), +5.1° (577), +8.2° (546), +11.0° (435), +24.5° (365) (c = 0.10, MeOH), $[\alpha]^{27}$ (nm) +6.8° (589), +8.1° (577), +17.4° (546), +28.0° (435), +64.2° (365), (c = 0.12, $CHCl_3$); ir ν max ($CHCl_3$) cm^{-1} 3580 (OH); ^{1}H-nmr ($CDCl_3$) δ 6.72 (2H, s, H-2′, H-6′), 6.14, 6.11 (each 1H, d, J = 1.8 Hz, H-6, H-8), 5.00 (1H, d, J = 7.5 Hz, H-4), 4.64 (1H, d, J = 10.2 Hz, H-2), 4.07 (1H, dd, J = 10.2, 7.5 Hz, H-3), 3.85 (9H, s, 3 × OMe), 3.82, 3.72 (each 3H, s, 2 × OMe), 2.59, 1.79 (each 1H, s, 3-OH, 4-OH, exchangeable with D_2O); hrms *m/z* $[M]^+$ 392.1452 (calcd for $C_{20}H_{24}O_8$, 392.1470). *Anal.* calcd for $C_{20}H_{24}O_8 \cdot \frac{1}{4}H_2O$, C 60.52, H 6.22; found C 60.37, H6.10.

The **7a** *diacetate*.—This compound was prepared from **7a** (100% ee) (8.2 mg) by acetylation with Ac_2O (0.3 ml)/C_6H_5N (2 drops) as a colorless oil (6.2 mg, 62%) (100% ee); specific rotation $[\alpha]^{27}$ (nm) +14.2° (589), +20.4° (577) +27.2° (546), +52.6° (435), +80.2° (365) (c = 0.10, MeOH); ir ν max ($CHCl_3$) cm^{-1} 1740 (OAc); ^{1}H-nmr ($CDCl_3$) δ 6.60 (2H, s, H-2′, H-6′), 6.14 (1H, d, J = 4.8 Hz, H-4), 6.12, 6.10 (each 1H, d, J = 2.4 Hz, H-6, H-8), 5.54 (1H, dd, J = 7.2, 4.8 Hz, H-3), 5.11 (1H, d, J = 7.2 Hz, H-2), 3.82 (6H, s, 2 × OMe), 3.80, 3.77, 3.73 (each 3H, s, 3 × OMe), 1.95, 1.79 (each 3H, s, 2 × OAc); hrms *m/z* $[M]^+$ 476.1691 (calcd for $C_{24}H_{28}O_{10}$, 476.1681). *Anal.* calcd for $C_{24}H_{28}O_{10} \cdot \frac{1}{2}H_2O$, C 59.37, H 6.02; found C 59.13, H 5.75.

Treatment of a solution of **6b** (100% ee) (10.1 mg) in absolute MeOH (25 ml) with $NaBH_4$ (10.6 mg) as above gave **7b** (6.7 mg, 66%) (100% ee), R_f 0.27, as colorless needles of mp 184–187° (EtOH): specific rotation $[\alpha]^{25}$ (nm) −3.1° (589), −5.4° (577), −7.6° (546), −10.2° (435), −26.1° (365) (c = 0.10, MeOH); $[\alpha]^{27}$ (nm) −7.4° (589), −8.4° (577), −18.0° (546), −27.6° (435), −68.1° (365) (c = 0.10, $CHCl_3$); hrms *m/z* $[M]^+$ 392.1473 (calcd for $C_{20}H_{24}O_8$, 392.1470). *Anal.* calcd for $C_{20}H_{24}O_8 \cdot \frac{1}{2}H_2O$, C 59.84, H 6.28; found C 60.05, H 6.25.

The **7b** *diacetate*.—A colorless oil: 100% ee; specific rotation $[\alpha]^{25}$ (nm) −13.8° (589), −22.0° (577), −26.2° (546), −48.1° (435), −84.0° (365) (c = 0.10, MeOH); hrms *m/z* $[M]^+$ 476.1680 (calcd for $C_{24}H_{28}O_{10}$, 476.1681).

(2*R*,3*S*,4*R*)-(+)-5,7,3′,4′,5′-PENTAMETHOXYFLAVAN-3,4-DIOL [**8a**] AND ITS ENANTIOMER **8b**.—$NaBH_4$ (3.0 mg) was added to a solution of **6a** (100% ee) (9.5 mg) in absolute dioxane (3 ml), and the whole was stirred at ambient temperature for 3 h. Workup of the reaction mixture, followed by preparative tlc [Si gel, Me_2CO-C_6H_6 (1:5)] of the product (8.7 mg), gave **8a** (4.8 mg, 46%) (100% ee), R_f 0.39, as colorless needles of mp 188–192° (EtOH): specific rotation $[\alpha]^{25}$ (nm) +10.9 (589), +13.6° (577), +14.5° (546), +23.6° (435), +40.9° (365) (c = 0.11, MeOH); $[\alpha]^{27}$ (nm) +17.6° (589), +18.8° (577), +21.0° (546), +39.1° (435), +79.6° (365) (c = 0.21, $CHCl_3$); ir ν max ($CHCl_3$) cm^{-1} 3620, 3570 (OH); ^{1}H-nmr ($CDCl_3$) δ 6.72 (2H, s, H-2′, H-6′), 6.12 (2H, s, H-6, H-8), 5.04 (1H, d, J = 4.2 Hz, H-4), 4.89 (1H, d, J = 10.2 Hz, H-2), 3.99 (1H, m, H-3), 3.86 (6H, s, 2 × OMe), 3.84, 3.82, 3.74

(each 3H, s, 3 × OMe), 2.66, 2.58 (each 1H, s, 3-OH, 4-OH, exchangeable with D_2O), hrms *m/z* $[M]^+$ 392.1457 (calcd for $C_{20}H_{24}O_8$, 392.1470). *Anal.* calcd for $C_{20}H_{24}O_8$, C 61.21, H 6.16; found C 60.90, H 6.11.

The **8a** *diacetate.*—Colorless needles of mp 190–193° (EtOH): 100% ee; specific rotation $[\alpha]^{29}$ (nm) +20.2° (589), +26.4° (577), +28.0° (546), +38.6° (435), +64.2° (365) (*c* = 0.10, MeOH); ir ν max ($CHCl_3$) cm^{-1} 1740 (OAc); ^{1}H-nmr ($CDCl_3$) δ 6.66 (2H, s, H-2′, H-6′), 6.43 (1H, d, *J* = 3.6 Hz, H-4), 6.10 (2H, s, H-6, H-8), 5.42 (1H, dd, *J* = 11.4, 3.6 Hz, H-3), 5.06 (1H, d, *J* = 11.4 Hz, H-2), 3.86 (6H, s, 2 × OMe), 3.82, 3.76, 3.73 (each 3H, s, 3 × OMe), 2.12, 1.83 (each 3H, s, 3-OAc, 4-OAc); hrms *m/z* $[M]^+$ 476.1657 (calcd for $C_{24}H_{28}O_{10}$, 476.1681).

Treatment of a solution of **6b** (100% ee) (12.5 mg) in absolute dioxane (5 ml) with $NaBH_4$ (3.4 mg) as above gave **8b** (4.6 mg, 37%) (100% ee), R_f 0.39, as colorless needles of mp 187–192° (EtOH); specific rotation $[\alpha]^{25}$ (nm) −9.4° (589), −11.6° (577), −12.2° (546), −21.9° (435), −37.4° (365) (*c* = 0.10, MeOH), $[\alpha]^{29}$ (nm) −15.2° (589), −16.5° (577), −20.7° (546), −37.1° (435), −76.2° (365), (*c* = 0.20, $CHCl_3$); hrms *m/z* $[M]^+$ 392.1472 (calcd for $C_{20}H_{24}O_8$, 392.1470). *Anal.* calcd for $C_{20}H_{24}O_8 \cdot \frac{1}{2}H_2O$, C 59.84, H 6.28; found C 59.78, H 6.19.

The **8b** *diacetate.*—Colorless needles of mp 191–194° (EtOH): 100% ee; specific rotation $[\alpha]^{27}$ (nm) −21.4° (589), −24.1° (577), −28.5° (546), −37.8° (435), −59.2° (365) (*c* = 0.10, MeOH); hrms *m/z* $[M]^+$ 476.1676 (calcd for $C_{24}H_{28}O_{10}$, 476.1681). *Anal.* calcd for $C_{24}H_{28}O_{10} \cdot \frac{1}{4}H_2O$, C 59.93, H 5.97; found C 59.95, H 6.24.

LITERATURE CITED

1. E. Haslam, in: "The Flavonoids: Advances in Research." Ed. by J.B. Harborne and T.J. Mabry, Chapman and Hall, London, 1982, p. 417.
2. L.J. Porter, in: "The Flavonoids: Advances in Research." Ed. by J.B. Harborne and T.J. Mabry, Chapman and Hall, London, 1988, p. 21.
3. A.K. Ganguly and T.R. Seshadri, *Tetrahedron*, **6**, 21 (1951).
4. A.K. Ganguly and T.R. Seshadri, *J. Chem. Soc.*, 2787 (1961).
5. H. Takahashi, S. Li, Y. Harigaya, and M. Onda, *Chem. Pharm. Bull.*, **36**, 1877 (1988).
6. H. Takahashi, S. Li, Y. Harigaya, and M. Onda, *J. Nat. Prod.*, **51**, 730 (1988).
7. A.K. Ganguly, T.R. Seshadri, and P. Subramanian, *Tetrahedron*, **3**, 225 (1958).
8. H. Takahashi, Y. Kubota, M. Iguchi, L. Fang, and M. Onda, *Heterocycles*, **24**, 369 (1986).
9. H. Takahashi, S. Li, Y. Harigaya, and M. Onda, *Heterocycles*, **26**, 3239 (1987).
10. B. Marsman and H. Wynberg, *J. Org. Chem.*, **44**, 2312 (1979).
11. W. Gaffield, *Tetrahedron*, **26**, 4093 (1970).
12. S.E. Drewes and A.H. Ilsley, *Phytochemistry*, **8**, 1039 (1969).
13. J.W. Clark-Lewis and P.I. Mortimer, *J. Chem. Soc.*, 4106 (1960).
14. S.E. Drewes and D.G. Roux, *Biochem. J.*, **98**, 493 (1966).
15. H. Takahashi, Y. Kubota, H. Miyazaki, and M. Onda, *Chem. Pharm. Bull.*, **32**, 4852 (1984).
16. P.K. Agrawal, S.K. Agarwal, and R.P. Rastogi, *Phytochemistry*, **19**, 893 (1980).

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