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Synthesis, Resolution, and Absolute Configuration of Optically Pure 5,5″-Dihydroxy-4′,4‴,7,7″-tetramethoxy-8,8″-biflavone and Its Derivatives

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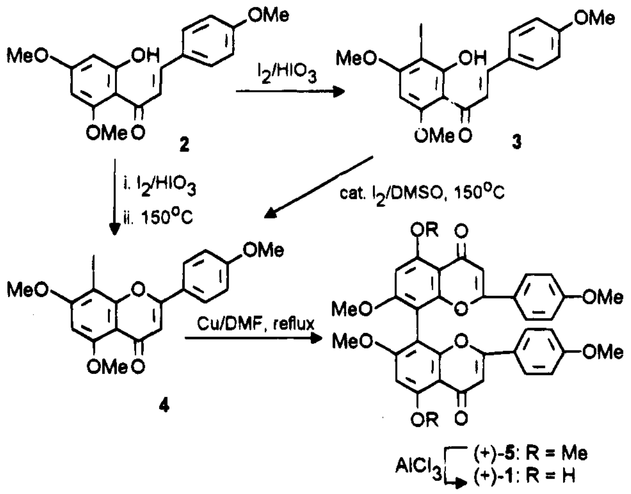
Optically pure 5,5″-dihydroxy-4,4‴,7,7″-tetramethoxy-8,8″-biflavone (**1**) and its dimethyl derivative **5** were synthesized for the first time. Resolution of the racemic (±)-**1**, prepared by a modified literature procedure, was performed *via* the formation and recrystallization of its (+)- and (−)-camphorsulfonate **6**. Hydrolysis of the (+)- or (−)-camphorsulfonate **6** afforded optically pure (+)- or (−)-**1**, which was then methylated to give (+)- or (−)-**5**. The absolute configurations of (+)-**1** and (−)-**1**, assigned as (a*R*) and (a*S*), respectively, were confirmed in an unambiguous manner by X-ray single crystal analysis and from their CD spectra.

In 1968, (−)-5,5″-dihydroxy-4′,4‴,7,7″-tetramethoxy-8,8″-biflavone ((−)-**1**) was isolated from *Araucaria cunninghamii* and *A. cooki* as the first optically active biflavone.[1] Since then, 13 other optically active biflavones have also been isolated from a variety of plants. These unique biflavones have been classified into three groups, i.e., cupressuflavones,[1−4] amentoflavones,[5−8] and agathisflavones.[5,9] Their chirality is due to the atropisomerism of the biflavone moiety. Although their planar structures have been established on the basis of synthesis,[10] less attention has been paid to their absolute stereochemistry. Two theoretical studies on the absolute configuration of (−)-**1** have been reported. In 1989, Parveen *et al.*[11] assigned the configuration of (−)-**1** as a*S*. However, two years later, Harada *et al.*[4] determined the absolute configuration of (−)-**1** to be a*R*. Furthermore, a synthesis of optically pure biflavones has not been achieved.

In this paper, we report the first synthesis of optically pure 5,5″-dihydroxy-4′,4‴,7,7″-tetramethoxy-8,8″-biflavone (**1**) and its methylated derivative **5** and the determination of their absolute configurations based on X-ray analysis and CD spectra.

Scheme 1



Results and Discussion

Synthesis of (±)-1. Compound (±)-**1** was synthesized by modification of the known method,[12] as outlined in Scheme 1. The chalcone **2**, generated from 1,3,5-trihydroxybenzene in three steps, was iodinated to give **3** (90%),[13] which underwent ring closure on heating with I_2−DMSO to afford **4** (84%). More conveniently, **4** was prepared in a one-pot reaction. Thus, **2** was iodinated with I_2/HIO_3 in DMSO at 40 °C until completion of the reaction, and the mixture was then heated at 150 °C for 20 min to give **4** in 83% yield. Treatment of **4** with Cu powder in dry DMF at reflux for 20 h afforded the 8,8″-biflavone ((±)-**5**) in 40% yield. Finally, compound **5** was selectively demethylated in the presence of $AlCl_3$ to give (±)**1** in nearly quantitative yield.

Optical Resolution of (±)-1. Upon treatment with (+)-camphorsulfonyl chloride in the presence of Et_3N, (±)-**1** was converted into a diastereomeric mixture, which was crystallized from CH_2Cl_2/petroleum ether to give

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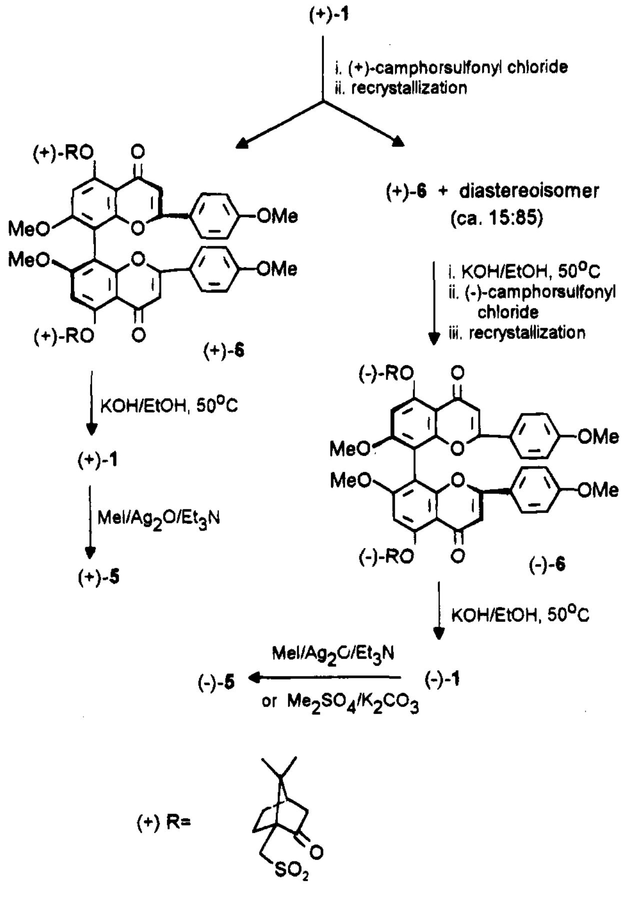
Scheme 2



(-) R means the enantiomer of (+)- R

crystalline (+)-**6** in 76% yield [based on (±)-**1**]. (+)-**6** was hydrolyzed with ethanolic KOH to give (+)-**1** in 84% yield.

Removal of the solvent from the mother liquor gave a semisolid which contained the other diastereomer as the main component together with ca. 15% of (+)-**6**. This semisolid was hydrolyzed and then treated with (−)-camphorsulfonyl chloride to furnish another diastereomeric mixture, from which (−)-**6** was separated *via* recrystallization in 76% yield [based on (−)-**1**]. Hydrolysis of (−)-**6** afforded (−)-**1** in 84% yield.

Methylation of (+)-**1** with $CH_3I/Ag_2O/Et_3N$ or Me_2SO_4/K_2CO_3 gave (+)-**5** in 94% yield. In the same manner, (−)-**1** was also converted into (−)-**5** (Scheme 2).

Determination of the Optical Purities of the Optically Active 8,8″-Biflavones. The optical purities of these 8,8″-biflavones were determined by ^1H NMR spectroscopy. As shown in Figure 1, in the ^1H NMR (600 MHz) spectra of the mixture of (+)-**6** and its diastereomer, the (+)-camphorsulfonate of (−)-**1**, two well-separated sets of AB system signals due to the methylene groups ($-CH_2SO_2-$) were observed at 4.06 (2 H, d, J = 15.0 Hz) and 4.15 (2 H, d, J = 15.0 Hz) and 4.05 (2 H, d, J = 15.0 Hz) and 4.18 (2H, d, J = 15.0 Hz) ppm, respectively. Only one set of signals was observed in the case of (+)-**6**, indicating that (+)-**6** was optically pure. The enantiomeric excess of (+)-**1** was determined after conversion into ester (+)-**6** and was found to be >99%. In a similar manner, (−)-**6** and (−)-**1** were also shown to be optically pure.

The enantiomeric purities of (+)- and (−)-**5** were established by ^1H NMR (300 MHz) spectra in the presence of the chiral shift reagent $Eu(hfc)_3$. Both (+)- and (−)-**5** presented only one set of signals in the presence of a 0.89 molar ratio of $Eu(hfc)_3$, whereas (±)-**5** showed two sets of signals under the same conditions. Thus, (+)- and (−)-**5** were enantiomerically pure. Furthermore, when the sample of (+)-**5** was mixed with that of (−)-**5**, the same two sets of signals appeared in the ^1H NMR spectrum.

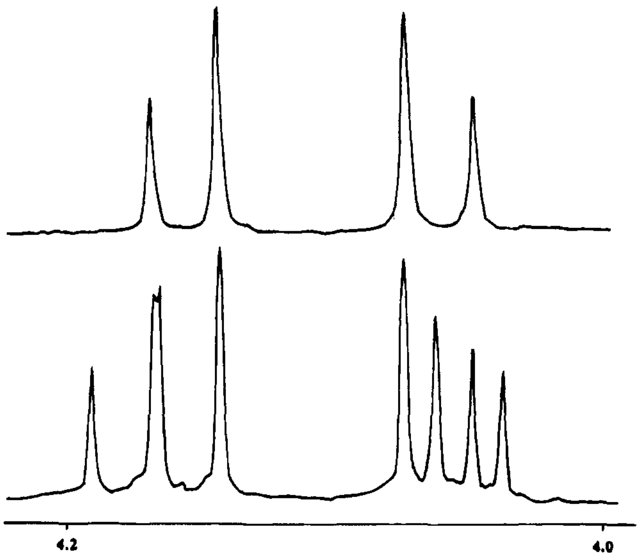


Figure 1. Top curve: ^1H NMR (600 MHz) spectra of the differentiated methylene group ($-CH_2SO_2-$) of (+)-**6**. Bottom curve: spectra of the mixture of (+)-**6** and its diastereoisomer, (+)-camphorsulfonate of (−)-**1**.

Absolute Stereochemistry of the Optically Pure 8,8″-Biflavones. A single crystal of (+)-**6**, obtained by recrystallization of (+)-**6** from ethyl acetate, was subjected to X-ray analysis.[15] The absolute configuration of (+)-**6** (biflavone moiety) was elucidated as a*R* by correlation with the known configurations of the camphorsulfonate groups in (+)-**6**. Unambiguous stereochemical assignments were thus established for the other optically active 8,8″-biflavones, as (+)-**1**(a*R*), (+)-**5**(a*R*), (−)-**1**(a*S*), (−)-**5**(a*S*), and (−)-**6**(a*S*).

The X-ray crystallographic analysis of (+)-**6** represents to the best of our knowledge the first reported diffraction study of an optically active biflavone. There are two important features of this analysis. First, the dihedral angle between the two A-ring planes is 112.1°, which is quite different from the theoretically calculated value for (−)-**1** (91°).[4] Second, the flavone moiety is not truly planar as described for (−)-**1**.[4] There is a dihedral angle of 8.9° (or 9.4°) between the C-ring plane and the B-ring plane. However, the A-ring and B-ring are coplanar.

CD spectra of all the optically active 8,8″-biflavones further confirmed their absolute assignments. As shown in Figure 2, the shapes of the curves representing the Cotton effects in the 240−360 nm region were similar for the 8,8″-biflavones with the same configuration, and this general trend was not influenced by the substituents. A comparison of the CD spectrum of our synthetic (+)-**1** (a*R*) with that of (−)-**1** (a*R*) reported by Harata *et al.*[4] shows agreement. Our experimentally-determined absolute configuration of the 8,8″-biflavone confirms the theoretical result of Parveen.[11] But it should be pointed

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(15) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

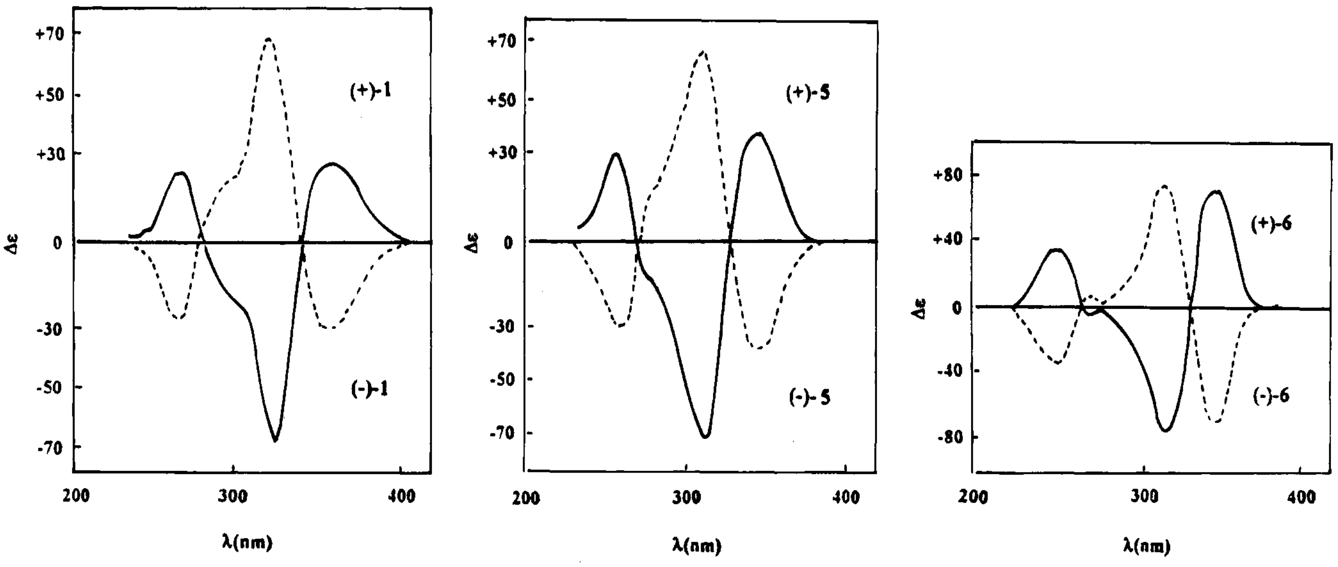

Figure 2. CD spectra of the optically pure 8,8″-biflavones (c 8 μg/mL, ethanol). The dashed lines refer to (+)-**1**, (+)-**5**, and (+)-**6**. The solid lines refer to (−)-**1**, (−)-**5**, and (−)-**6**.

out that our synthetic (+)-**1** differs in sign and value of optical rotation from those of the reported (−)-**1**. Furthermore, the optical rotations of (+)- and (−)-**1** are markedly affected by solvent. The values of $[\alpha]_D$ in MeOH for (+)- and (−)-**1** are very low, while in EtOH, the values are much higher (see Experimental Section). This phenomenon might be due to the effect of the solvent on the intramolecular hydrogen bond between the hydroxyl group at the 5-position and the carbonyl group at the 4-position.

In conclusion, we have described a method for the resolution of the 8,8″-biflavones (±)-**1** *via* their camphorsulfonates. All of the resolved 8,8″-biflavones and their methyl derivatives were determined to be optically pure. The atropisomers were found to be stable enough that they remained unracemized under conditions of hydrolysis with ethanolic potassium hydroxide at 50 °C or methylation in boiling acetone with dimethyl sulfate and potassium carbonate. The successful resolution of the racemic 8,8″-biflavones will now permit their structure−activity relationship to be investigated.

Experimental Section

Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded (ppm) in $CDCl_3$ using TMS as an internal standard.

8-Iodo-4′,5,7-trimethoxyflavone (4). Method 1. To a solution of 2′-hydroxy-3′-iodo-4,4′,6′-trimethoxychalcone (**3**)[13] (440 mg, 1.0 mmol) in DMSO (5 mL) at 150 °C was added iodine (15 mg, 0.06 mmol) with stirring. After being stirred for 0.5 h, the mixture was poured into a cold solution of $Na_2S_2O_3$ (1.0 g) and KOH (1.0 g) in water (50 mL). The solids were collected and crystallized from CH_2Cl_2/EtOH to give **4** (378 mg, 84%) as a yellowish solid: mp 240−241 °C (lit.[13] mp 239−241 °C); ^{1}H NMR, δ 3.88 (s, 3H), 4.02 (s, 6H), 6.43 (s, 1H), 6.64 (s, 1H), 7.02 (d, 2H, J = 8.8 Hz), 8.01 (d, 2H, J = 8.8 Hz).

Method 2. To a solution of iodic acid (130 mg, 0.74 mmol) in water (1.5 mL) was added a solution of chalcone **2**[12] (942 mg, 3.0 mmol) and iodine (350 mg, 1.38 mmol) in DMSO (18 mL). The mixture was stirred at 40 °C for 1 h and then at 150 °C for 20 min and poured into a cold solution of $Na_2S_2O_3$ (3.0 g) and KOH (3.0 g) in water (150 mL). The solids were collected and recrystallized from CH_2Cl_2/EtOH to give **4** (1.11 g, 83%) as a yellowish solid: mp 240−241 °C.

4′,4‴,5,5″,7,7″-Hexamethoxy-8,8″-biflavone (±)-5. A mixture of **4** (1.78 g, 4.06 mmol), copper powder (0.98 g, 0.15 mmol), and dry DMF (15 mL) was refluxed with stirring under N_2 for 20 h and then filtered. The solid was washed with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel using EtOAc and EtOAc/EtOH (1:1) as eluants to afford (±)-**5** (500 mg, 40%) as a yellowish solid: mp 296−298 °C (CH_2Cl_2/EtOH) (lit.[14] mp 294−295 °C); ^{1}H NMR (300 MHz) δ 3.78 (s, 6 H), 3.86 (s, 6 H), 4.13 (s, 6 H), 6.59 (s, 2 H), 6.61 (s, 2 H), 6.78 (dd, 4 H, J = 2.0, 7.3 Hz), 7.30 (dd, 4 H, J = 2.0, 7.3 Hz).

5,5″-Dihydroxy-4′,4‴,7,7″-tetramethoxy-8,8″-biflavone (±)-1. To a solution of (±)-**5** (420 mg, 0.68 mmol) in dry toluene (8 mL) at 100 °C was added anhydrous $AlCl_3$ (181 mg, 1.36 mmol) with stirring. After the mixture was stirred at 100 °C for 5 h, the solvent was removed under reduced pressure. Then 3 N HCl (20 mL) was added, and the mixture was stirred at 80 °C for 15 min. The solids were collected by filtration and recrystallized from MeOH to give (±)-**1** (404 mg, 96%) as a yellow needle: mp 256−258 °C (lit.[14] mp 260−262 °C); ^{1}H NMR δ 3.80 (s, 6 H), 3.82 (s, 6 H), 6.59 (s, 2 H), 6.60 (s, 2 H), 6.86 (dd, 4 H, J = 2.0, 7.0 Hz), 7.43 (dd, 4 H, J = 2.0, 7.0 Hz); MS (EI) m/z 594 (9.3), 297 (12.5), 149 (33.2), 135 (21.3), 85 (100).

Optical Resolution of (±)-1. To a stirred solution of (±)-**1** (356 mg, 0.6 mmol) in dry CH_2Cl_2 (9 mL) and dry triethylamine (3 mL) was added (+)-camphorsulfonyl chloride (450 mg, 1.8 mmol). The mixture was stirred at rt for 2 h, and then CH_2Cl_2 (20 mL) was added. The mixture was subsequently washed with cold 1 N HCl (3 × 30 mL), a saturated aqueous solution of $NaHCO_3$ (25 mL), and water (20 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed. The residue was chromatographed on silica gel (3/7, 4/6 EtOAc/petroleum ether) to afford a 1:1 diastereomeric mixture (570 mg, 93%). This mixture was dissolved in CH_2Cl_2 (2.5 mL) at 40 °C, followed by addition of petroleum ether (5 mL) dropwise with stirring. The resulting mixture was allowed to stand at rt overnight and then filtered to give (+)-**6** [230 mg, 76% based on (+)-**1**] as a white solid: mp 229−230 °C; $[\alpha]^{18}_D$ +110° (c 0.2, $CHCl_3$); CD (EtOH) λ_{max} 348 nm (Δε +71.7), 314 (−79.4), 249 (+33.9); UV (EtOH) λ_{max} 328 nm (ε 67 800), 212 (21 300); IR (KBr) 1750, 1640, 1600 cm^{-1}; ^{1}H NMR (300 MHz) δ, 1.02 (s, 6 H), 1.25 (s, 6 H), 1.40−1.55 (m, 2 H), 1.82−1.93 (m, 2 H), 2.00 (d, 2 H, J = 18.4 Hz), 2.10−2.21 (m, 4 H), 2.46 (dt, 2 H, J = 18.4, 3.0 Hz), 2.55−2.64 (m, 2 H), 3.81 (s, 6 H), 3.86 (s, 6 H), 4.06 (d, 2 H, J = 15.0 Hz), 4.15 (d, 2 H, J = 15.0 Hz), 6.63 (s, 2 H), 6.88 (s, 4 H, J = 9.0 Hz), 7.15 (s, 2 H), 7.30 (d, 4 H, J = 9.0 Hz). Anal. Calcd for $C_{54}H_{54}O_{16}S_2$: C, 63.39; H, 5.32. Found: C, 63.51; H, 5.11.

To a mixture of (+)-**6** (160 mg, 0.16 mmol) in ethanol (24 mL) was added to a solution of KOH (160 mg) in 95% ethanol (8 mL). After the mixture was stirred at 50 °C for 20 min, cold 3 N HCl (30 mL) was added. The mixture was extracted with three 10 mL portions of dichloromethane. The combined organic layer was washed with water (3 × 30 mL) and dried over Na_2SO_4. Evaporation of the solvent furnished a yellow solid which was recrystallized from methanol to give (+)-**1** (78 mg, 84%) as a yellow needle: mp 152−154 °C (lit.[1] mp 151 °C); $[\alpha]^{20}_{650}$ −18°, $[\alpha]^{20}_{D}$ + 1°, $[\alpha]^{20}_{550}$ + 12°, $[\alpha]^{20}_{500}$ +82°, $[\alpha]^{20}_{450}$ + 357° (c 0.2, MeOH); $[\alpha]^{18}_{D}$ + 77° (*c* 0.2, EtOH) (lit.[4] $[\alpha]^{27}_{D}$ −25.3° (*c* 0.3, MeOH); CD (EtOH) λ_{max} 360 nm ($\Delta\epsilon$ + 28.1), 324 (−66.4), 267 (+24.8); UV (EtOH) λ_{max} 326 nm (ϵ 39 800), 274 (40 400), 228 (50 500), 208 (53 400); IR (HBr) 3400, 1660, 1600 cm^{-1}; MS (EI) *m/z* 594 (9.2), 297 (10), 135 (15), 85(100); HRMS calcd for $C_{34}H_{26}O_{10}$ 594.1526, found 594.1484.

The mother liquor which contained the diastereoisomer of (+)-**6** as the main component (ca. 85% determined by ^{1}H NMR) was concentrated to give 330 mg of semisolid material. This mixture was treated with ethanolic KOH at 50 °C as described for the hydrolysis of (+)-**6**. The resulting mixture was acidified with cold 3 N HCl (40 mL) and extracted with dichloromethane (3 × 15 mL). The organic layer was washed with water (3 × 30 mL) and dried (Na_2SO_4). Evaporation of the solvent gave crude (−)-**1** (188 mg) as a yellow solid. This crude (−)-**1** (188 mg, 0.32 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and dry triethylamine (1.5 mL). (−)-Camphorsulfonyl chloride (250 mg, 1 mmol) was added with stirring. The mixture was stirred at room temperature for 2 h, and then dichloromethane (15 mL) was added. The whole was washed with cold 1 N HCl (3 × 20 mL), $NaHCO_3$ solution (20 mL), and water (20 mL). The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (3/7, 4/6 EtOAc/petroleum ether) to give a diastereomeric mixture, which was recrystallized from CH_2Cl_2/petroleum ether to afford (−)-**6** [232 mg, 76% based on (−)-**1** used] as a white solid: mp 230−231 °C; $[\alpha]^{18}_{D}$ −111° (*c* 0.2, $CHCl_3$); CD (EtOH) λ_{max} 348 nm ($\Delta\epsilon$-67.8), 314 (+72.7), 250 (−32.9); IR (KBr) 1750, 1660, 1505, 1375, 1115 cm^{-1}; ^{1}H NMR (600 MHz) δ, 1.196 (s, 6H), 1.419 (s, 6H), 1.679 (dt, 2H, J = 9.2, 3.2 Hz), 2.060 (dt, 2H, J = 9.2, 4.9 Hz), 2.173 (d, 2H, J = 18.4 Hz), 2.354 (t, 2H, J = 4.2 Hz), 2.635 (dt, 2H, J = 18.08, 4.2 Hz), 2.760 (m, 2H), 3.981 (s, 6H), 4.030 (s, 6H), 4.231 (d, 2H, J = 15 Hz), 4.326 (d, 2H, J = 15 Hz), 6.799 (s 2H), 7.049 (d, 4H, J = 8.9 Hz), 7.438 (s, 2H), 7.471 (d, 4H, J = 8.9 Hz).

(−)-**6** (160 mg, 0.16 mmol) was hydrolyzed with ethanolic KOH according to the procedure used for (+)-**6** described above. The workup of the reaction mixture and recrystallization from methanol gave (−)-**1** (78 mg, 84%) as a yellow needle: mp 152−154 °C; $[\alpha]^{20}_{650}$ +17°, $[\alpha]^{20}_{D}$ −2°, $[\alpha]^{20}_{550}$ −12°, $[\alpha]^{20}_{500}$ −78°, $[\alpha]^{20}_{450}$ −345° (*c* 0.2, MeOH); $[\alpha]^{18}_{D}$ −78° (*c* 0.2, EtOH); CD (EtOH) λ_{max} 359 nm ($\Delta\epsilon$ −29.3), 323 (+68.6), 267 (−25.9); HRMS calcd 594.1526, found 594.1545.

(−)-4′,4‴,5,5″,7,7″-Hexamethoxy-8,8″biflavone (−)-5. Method A. To a mixture of (−)-**1** (30 mg, 0.05 mmol), Ag_2O (46 mg, 0.2 mmol), and Et_3N (0.1 mL) in DMF (1 mL) was added CH_3I (70 mg, 0.5 mmol). The mixture was stirred at room temperature for 1 h and then filtered. The solids were washed with $CHCl_3$ (10 mL). The filtrate was washed with 3 N HCl (2 × 5 mL) and water (2 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel using EtOAc/petroleum ether (1:1) and EtOAc as eluants to give (−)-**5** (29 mg, 94%) as a semisolid, which was recrystallized from EtOAc/petroleum ether to afford a white solid: mp 159−162 °C; $[\alpha]^{25}_{D}$ −29.0° (*c* 0.2, EtOH); CD (EtOH) λ_{max} 344 nm ($\Delta\epsilon$ −41.2), 310 (+70.1), 260 (−31.8); UV (EtOH) λ_{max} 320 nm (ϵ 42 500), 270 (51 100), 216 (60 900), 208 (61 900).

Method B. The mixture of (−)-**1** (20 mg, 0.03 mmol), dimethyl sulfate (15 mg, 0.12 mmol), and K_2CO_3 (250 mg, 1.8 mmol) in acetone (2 mL) was refluxed with stirring for 1 h and then filtered. The solid was washed with acetone, and the filtrate was evaporated. The residue was chromatographed on silica gel using EtOAc/petroleum ether (1:1) and EtOAc as eluants to afford (−)-**5** (19 mg, 91%) as a white solid: mp 159−162 °C (EtOAc/petroleum ether); $[\alpha]^{25}_{D}$ −28° (c 0.2, EtOH).

(+)-4′,4‴,5,5″,7,7″-Hexamethoxy-8,8″-biflavone (+)-5. The methylation of (+)-**1** (30 mg, 0.05 mmol), performed under the same reaction conditions (method A) described for the enantiomer (−)-**1**, gave (+)-**5** (28 mg, 91%) as a white solid: mp 159−162 °C (EtOAc/petroleum ether) (lit.[1] mp 161 °C); $[\alpha]^{25}_{D}$ + 28° (*c* 0.2, EtOH); λ_{max} 344 nm ($\Delta\epsilon$ +38.9), 310 (−69.1), 258 (+29.5).

Single-Crystal X-ray Diffraction Analysis of (+)-6.[15] Crystal data: $C_{54}H_{54}O_{16}S_2$, Fw = 1023.15; tetragonal; space group $P4_12_12$; $a = b = 20.81(1)$ Å, $c = 24.90(1)$ Å; $V = 10785(1)$ Å^3; $D_{calcd} = 1.26$ g/cm^3; $Z = 8$; $\mu = 3.6$ mm^{-1} (Cu Kα, Ni filter). Single crystal were grown from a solution of (+)-**6** in ethyl acetate. A crystal of (+)-**6** with approximate dimensions of 0.6 × 0.6 × 0.6 mm covered with epoxy resin was used. Intensity data were collected at 24 °C on a Rigaku AFC 5R four-circle diffractometer using a $\theta - 2\theta$ scan with scan speed 8.0° min^{-1}. 3936 ($|F_o| > 3.92\sigma|F_o|$) unique reflections were measured with $2\theta_{max} = 120°$. No decay was found during data collection. All data were corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by direct methods program SHELXS on a micro VAX II. The chirality of the asymmetric carbon atom C_{19} (C_{49}) was known as *S* form, and therefore, the absolute configuration of the biflavone moiety was established as (a*R*). Block-full-matrix least-squares refinements with anisotropic non-hydrogen atoms and fixed riding hydrogens converged to a final residual factor of $R = 0.096$ and $R_w = 0.103$ with $\omega = \sigma^2(F + 0.001F^2)$. The final difference electron density map was featureless with ±0.32 eÅ^3.

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Supporting Information Available: Copies of the ORTEP drawings of (+)-**6** and selected ^{1}H NMR spectra data of (±)-**5**, (+)-**5**, and (−)-**5** in the presence of Eu(hfc)$_3$ (3 pages). This material is contained in libraries on microfiche, immediately follows this articles in the microfilm version of the journal and can be ordered from the ACS; see any current masthead page for ordering information.

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