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The First Enantioselective Synthesis of Optically Pure (*R*)- and (*S*)-5,5″-Dihydroxy-4′,4‴,7,7″-tetramethoxy -8,8″-biflavone and the Reconfirmation of Their Absolute Configuration

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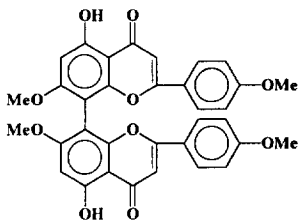
Abstract The first enantioselective synthesis of the optically pure (*R*)- and (*S*) - 5,5″-dihydroxy-4′,4‴,7,7″-tetramethoxy -8,8″-biflavone is described. The key steps involve the intramolecular oxidative coupling of the cyanocuprate intermediate and Friedel-Crafts rearrangement. Their absolute configuration was reconfirmed by CD spectra. © 1997, Elsevier Science Ltd. All rights reserved.

In 1968, Ilyas and his coworkers[1] isolated (-)-5,5″-dihydroxy-4′,4‴,7,7″-tetramethoxy -8,8″-biflavone (**1**) from *Araucaria cunninghamii* and *A. cooki* as the first optically pure biflavone. Since then, 13 other optically active biflavones of three groups, *i.e.*, cupressflavones, amentoflavones, and agathisflavones, have been isolated from a variety of plants. There is now ample evidence of the pharmacological effects of biflavones including inhibition of cyclic AMP phosphodiesterase[2a] and inhibition of lens aldose reducyase[2b], *etc.* In most cases, the biflavones proved to be more active than the monomeric species.



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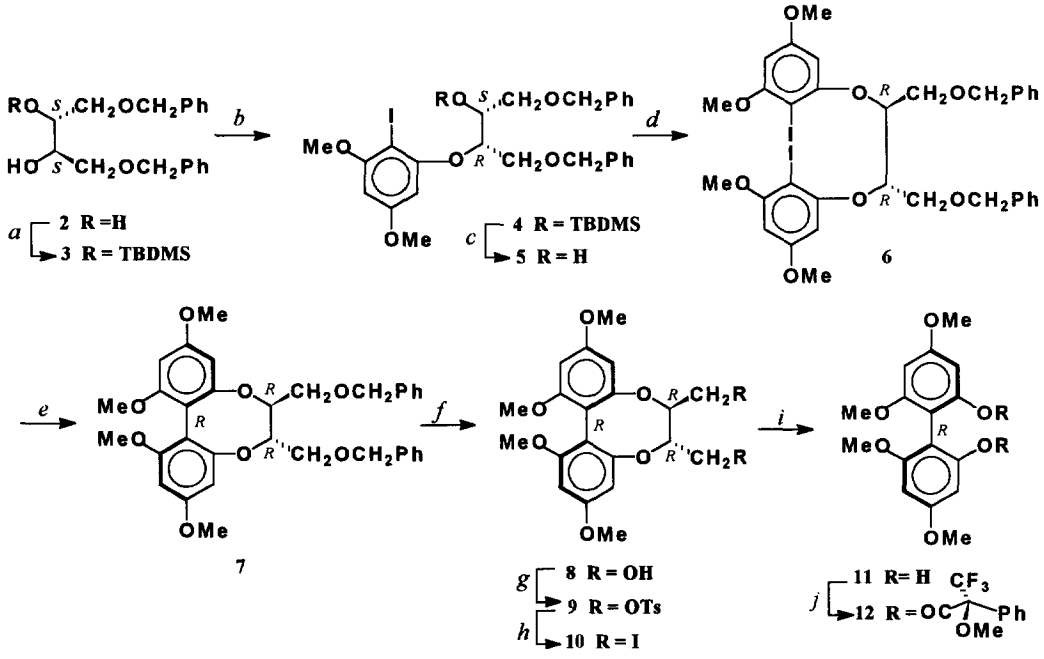
The chirality of those biflavones is due to the atropisomerism of the biflavone moiety. Although the racemic 5,5″-dihydroxy-4′,4‴,7,7″-tetramethoxy -8,8″-biflavone or its derivatives have been synthesized by various methods [3], and the absolute configuration of the naturally occurring 5,5″-dihydroxy-4′,4‴,7,7″-tetramethoxy -8,8″-biflavone was deduced as a*R* by Harada *et al.*[4] and later on confirmed by us [3g], to our knowledge, there was no report of enantioselective synthesis of the optically active (*R*)- or (*S*)-**1**. As a

continuation of our efforts in this area, we report here the first enantioselective synthesis of the optically pure (*R*)- and (*S*)-**1**, in which the asymmetric intramolecular oxidative coupling of the cyanocuprate intermediate of **6** developed by Lipshutz's group [5] and the Friedel-Crafts rearrangement of **13** were employed as the key steps. We have also reconfirmed their absolute configuration by CD spectra.

Scheme 1



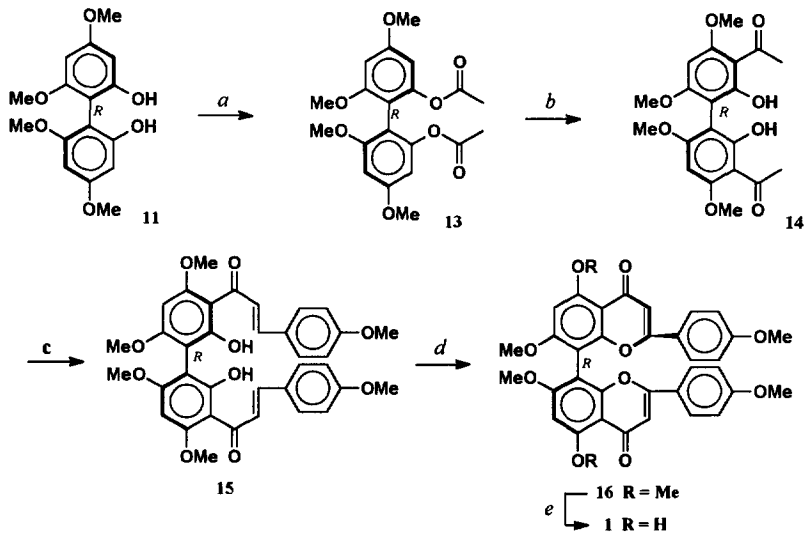
Reagents and conditions: a. TBDMSCl, imidazole, DMF, r.t, 24 h, 84%; b. 2-iodo-3,5-dimethoxyphenol, DEAD, *n*-Bu_3P, THF, r.t, 24 h, 68%; c. *n*-Bu_4NF, THF, 2 h, 90%; d. 2-iodo-3,5-dimethoxyphenol, DEAD, *n*-Bu_3P, THF, r.t, 42 h, 42%; e. *n*-BuLi, THF, -78°C, 1 h; CuCN-TMEDA(1:3), -78°C→ -40°C, 1 h; dry O_2, -78°C, 4 h, 75%; f. 10% Pd/C, H_2, EtOAc, 12 h, 100%; g. TsCl, py., 0 °C, 8 h, 92%; h. NaI, acetone, reflux, 3 h, 85%; i. activated Zn powder, EtOH, reflux, 1 h, 80%; j. (S)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride, 4-DMAP, Et_3N, CH_2Cl_2, r.t, 24 h, 90%.

As shown in scheme 1, 1,4-di-*O*-benzyl-D-threitol (**2**) [6] was converted to its monosilyl ether (**3**). Mitsunobu reaction [7] of **3** with 2-iodo-3,5-dimethoxyphenol [8], with the configuration transformation from *S* to *R* at the reaction center, gave **4** in 68% yield. Cleavage of the silyl ether of **4** with *n*-Bu_4NF in THF gave **5** in 90% yield, which was followed by treatment with 2-iodo-3,5-dimethoxyphenol again to give the (2*R*,3*R*)-tetraether (**6**)[9] in 42% yield. The low yield of the second Mitsunobu reaction was possibly caused by the steric hindrance at the coupling center. The attempt of the condensation of two molecules of 2-iodo-3,5-dimethoxyphenol to **2** in one step failed. Treatment of **6** with *n*-BuLi followed by addition of CuCN-TMEDA (1:3) led to formation *in situ* of a higher order cyanocuprate intermediate [5], which transformed to **7**[10] upon exposure to dry oxygen at -78°C in 75% yield. In order to obtain the biphenol (**11**) from **7**, a four-step process was designed to cleave the chiral auxiliary. Catalytic hydrogenation of **7** gave the threitol (**8**) in quantitative

yield. The threitol (**8**) was converted to the ditosylate (**9**) in 92% yield, which upon treatment with NaI gave the diiodide (**10**) in 85% yield. Reduction of **10** by activated zinc powder in ethanol provided the biphenol (**11**) in 80%. The diastereomeric excess of **11** was determined to be 81% by the examination of the ^{1}H NMR spectra of its corresponding (*S*)-Mosher's ester (**12**). The optically pure **11** [11] was obtained by recrystallization from ethyl acetate and hexane.

Subsequently, our efforts were made to complete the synthesis of the optically pure **1** (**Scheme 2**).

Scheme 2



Reagents and conditions: a. $(CH_3CO)_2O$, py., 2 h, 93%; b. $TiCl_4$, benzene, reflux, 1 h, 94%; c. *p*-anisaldehyde, KOH, cat. TEBACl, EtOH-H_2O(3:2), r.t, 48 h, 80%; d. I_2, DMSO, 150°C, 30 min., 60%; e. BCl_3, CH_2Cl_2, 0°C, 1 h, 84%.

The diacetate (**13**), generated from **11** by treatment with acetic anhydride in pyridine, underwent Friedel-Crafts rearrangement promoted by $TiCl_4$ as Lewis acid to afford **14**[12] in 94% yield. Treatment of **14** with *p*-anisaldehyde in presence of KOH and catalytic TEBACl as a phase-transfer reagent gave bichalcone (**15**) in 80% yield. Ring closure of **15** on heating with I_2–DMSO [3g] afforded **16** in 60% yield. Selective demethylation of **16** with BCl_3 [3d] in CH_2Cl_2 at 0°C gave (+)-**1**[13] in 84% yield. The absolute configuration of the synthetic (+)-**1**[$[\alpha]^{22}_D$ +76.6 (c 0.11, EtOH)] was assigned as a*R* and was determined to be optically pure by comparison of the specific rotation value of (*R*)-**1** [$[\alpha]^{18}_D$ +77 (c 0.2, EtOH) for (*R*)-**1**] with our previous report[3g]. The CD curves of the synthetic (+)-**1** were in accordance with that of the naturally occurring **1**, which was deduced as a*R* by Harada *et al.*[4]. This result was also in agreement with Lipshutz's conclusion[5] that the (2*R*,3*R*)-tetraether generally induced the formation of (*R*)-biaryl and the (2*S*,3*S*)-tetraether generally induced the formation of (*S*)-biaryl in the cyclization (**6**→**7**). Accordingly, the absolute configuration of the biaryls **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**,

15, **16** was all assigned as a*R*. In the same manner as that of preparation of (*R*)-**1**, the optically pure (*S*)-**1** [$[\alpha]^{22}_D$ -77.3 (c 0.13, EtOH)][13] was synthesized using 1,4-di-*O*-benzyl-L-threitol [6] as the chiral auxiliary and the CD curves of the synthetic (*S*)-**1** was contrary to that of the naturally occurring **1**.

In summary, we have accomplished the first enantioselective synthesis of the optically pure (*R*)- and (*S*)-5,5''-dihydroxy-4',4''',7,7''-tetramethoxy -8,8''-biflavone (**1**) and reconfirmed the absolute configuration of the naturally occurring **1** as a*R* by CD spectra.

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9. **6**. $[\alpha]^{22}_D$ -5.04 (c 2.10, $CHCl_3$). FT-IR (film): 2938, 2841, 1583, 1454, 1413, 1365, 1342, 1223, 1201, 1162, 1112, 1018, 812, 738, 698 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.27-7.32 (m, 10H), 6.39 (s, 2H), 6.15 (s, 2H), 4.82 (s, 2H), 4.53 (s, 4H), 4.09 (dd, 2H, *J*= 2.75, 10.20Hz), 3.90 (dd, 2H, *J*= 4.00, 9.84Hz), 3.86 (s, 6H), 3.66 (s, 6H) ppm. ^{13}C NMR (75.5HMz, $CDCl_3$) δ 162.162, 159.230, 138.116, 128.368, 127.855, 127.667, 94.002, 92.900, 78.936, 73.749, 69.100, 68.899, 56.527, 55.560 ppm. MS m/z (EI, 70ev): 826, 699, 572, 514, 466, 354, 191, 155, 127, 105, 91(100). Calcd. for $C_{34}H_{36}O_8I_2$: C, 49.41; H, 4.39. Found: C, 49.33; H, 4.49.
10. (a*R*)-**7**. $[\alpha]^{22}_D$ +34.7 (c 0.59, $CHCl_3$). FT-IR (film): 2937, 2840, 1603, 1547, 1496, 1463, 1454, 1436, 1414, 1369, 1353, 1319, 1280, 1215, 1199, 1151, 1094, 1064, 1024, 1007, 935, 909, 874, 826, 799, 739, 699, 635, 603, 522, 530 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.27-7.33 (m, 10H), 6.40 (d, 2H, *J*=2.39Hz), 6.34 (d, 2H, *J*=1.97Hz), 4.59, 4.58 (AB, 4H, J_{AB}= 12.04Hz), 4.10 (dd, 2H,*J*= 4.98, 6.67HZ), 3.73 (s, 12H), 3.72 (d, 2H, *J*=8.30Hz), 3.61 (tt, 2H, *J*= 2.59, 8.22Hz) ppm. ^{13}C NMR (75.5HMz, $CDCl_3$) δ 160.743, 160.056, 158.919, 138.315, 128.420, 127.708, 110.385, 99.121, 95.557, 85.136, 73.704, 70.682, 55.872, 55.365 ppm. MS m/z (EI, 70ev): 574, 573, 572 (19.5), 91(100). HRMS calcd. for $C_{34}H_{36}O_8(M^+)$: 572.2411, found 572.2460.
11. (a*R*)-**11**. m.p 165-166°C (EtOAc/hexane). $[\alpha]^{21}_D$ +76.5 (c 0.53, $CHCl_3$). FT-IR (KBr): 3410, 1612, 1584, 1523 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 6.29 (d, 2H, *J*=2.35Hz), 6.20 (d, 2H, *J*=2.31Hz), 3.83 (s, 6H), 3.74 (s, 6H) ppm. MS m/z (EI, 70ev): 308, 307, 306 (100), 289, 275, 259, 245, 231, 215, 193, 77. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.35; H, 5.96. for (a*S*)-**11**. m.p 164-166°C (EtOAc/hexane). $[\alpha]^{20}_D$ -76.3 (c 0.61, $CHCl_3$).
12. (a*R*)-**12**. m.p 253-254°C ($CHCl_3$/EtOH). $[\alpha]^{20}_D$ -27.6 (c 0.56, $CHCl_3$). CD (EtOH) λ_{ext} 298 nm (Δε -3.29), 276 (Δε +4.60), 241 (Δε -1.34), 235 (Δε -0.26), 229 (Δε -2.63), 212 (Δε +8.67). FT-IR (KBr): 2701, 1617, 1588, 1504 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 14.02 (s, 2H), 6.08 (s, 2H), 3.95 (s, 6H), 3.83 (s, 6H), 2.63 (s, 6H) ppm. MS m/z (EI, 70ev): 392, 391, 390 (100), 375, 359, 333. Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.07; H, 5.53. for (a*S*)-**12**. m.p 252-254°C ($CHCl_3$/EtOH). $[\alpha]^{19}_D$ +27.2 (c 0.40, $CHCl_3$). CD (EtOH) λ_{ext} 297 nm (Δε +3.38), 275 (Δε -2.03), 240 (Δε +3.78), 235 (Δε +2.43), 230 (Δε +3.78), 211 (Δε -6.21).
13. (a*R*)-**1**. m.p 152-153°C (MeOH). $[\alpha]^{22}_D$ +76.6 (c 0.11, EtOH). CD (EtOH) λ_{ext} 355 nm (Δε +17.0), 318 (Δε -30.8), 258 (Δε +14.0). FT-IR (KBr): 2934, 2833, 1615, 1609, 1588, 1511, 1486, 1427, 1373, 1337, 1264, 1241, 1206, 1179, 1123, 1029, 834, 572 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 13.23 (s, 2H), 7.43 (dd, 4H, *J*=2.02, 7.01Hz), 6.87 (dd, 4H, *J*=1.95, 7.06Hz), 6.60 (s, 2H), 6.59 (s, 2H), 3.82 (s, 6H), 3.80 (s, 6H) ppm. ^{13}C NMR (75.5HMz, $CDCl_3$) δ 183.030, 164.060, 163.504, 162.802, 154.817, 127.727, 123.455, 114.693, 105.427, 103.679, 99.692, 95.446, 56.347. 55.598 ppm. MS m/z (EI, 70ev): 597 (1.75), 596 (9.64), 595 (39.25), 594 (M^+,100), 433 (1.74), 297 (8.91), 135 (16.38), 77 (3.15). HRMS calcd. for $C_{34}H_{26}O_{10}(M^+)$: 594.1526, found 594.1553. for (a*S*)-**1**. m.p 153-154°C (MeOH). $[\alpha]^{22}_D$ -77.3 (c 0.13, EtOH). CD (EtOH) λ_{ext} 359 nm (Δε -23.2), 323 (Δε +54.8), 264 (Δε -15.2).

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