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EFFICIENT SYNTHESIS OF BIFLAVONES HAVING A RING-A RING OF TWO FLAVONE UNITS USING SUZUKI CROSS-COUPLING REACTIONS

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Abstract – Biflavones having a A ring-A ring of two flavone units were easily prepared by using Suzuki cross-coupling reaction of borylated flavones with bromoflavones or flavone-5-triflate in good to excellent yields.

INTRODUCTION

Flavonoids belong to a important class of natural compounds and occur naturally in fruits, vegetables, nuts, seeds, flowers, and barks.[1] Natural flavonoids are known to exhibit a wide range of biological activity such as antioxidant, anti-inflammatory, antiviral *etc*.,[2] and are increasingly being used as dietary supplement. Many other related compounds have been classified in this group, and new ones continue to be isolated and identified from various plants.

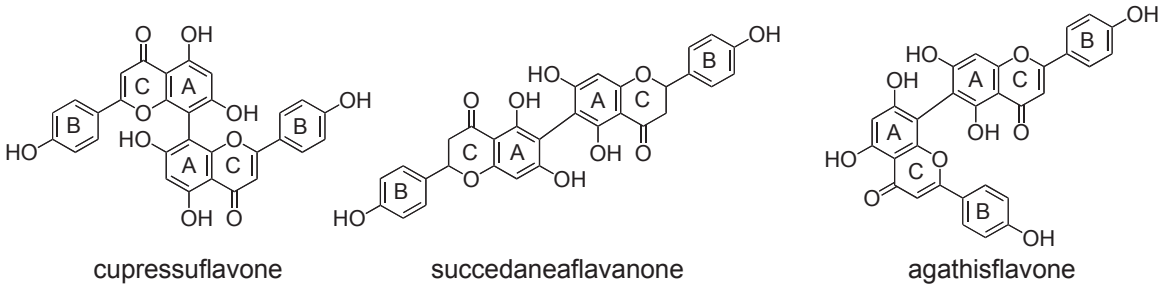


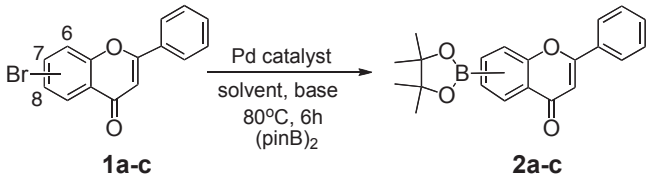
Figure 1. Biflavonoids having linkages at A ring-A ring

Biflavonoids form a subclass of flavonoids, of which they are dimers. Unlike the other flavonoids, the biflavones are distributed in only a limited area in plants. Their major presence is in the gymnosperms. Most biflavonoids are derived from carbon-carbon linking of two similar flavone units, but mixed dimers

such as flavone-flavanone and flavanone-chalcone are also known. Furthermore, some biflavonoids such as cupressflavone, succedaneaflavanone and agathisflavone, which are composed of two flavone units linking at each A ring, have been identified in plants (Figure 1). Some attempts have been made at constructing a biflavone framework.[3] With regard to the biflavone units, however, there has been to our knowledge no attempt to prepare unsymmetric biflavones with a flavone-flavone unit linked at each A ring. Thus, our research has focused on the synthesis of biflavones having various patterns of linkage in the A ring based on Suzuki cross-coupling using a borylated compound. We describe in this paper the details of a new and efficient synthetic method utilizing Suzuki coupling for biflavones having an A ring-A ring linkage.

RESULTS AND DISCUSSION

We first examined the reactions of 6-, 7-, and 8-bromoflavone (**1a-c**)[4] with bis(pinacolato)diboron (pin_2B_2) in the presence of palladium catalysts to afford borylated compound **2a** using a precursor for the the synthesis of biflavones (Scheme 1).



1a-c **2a-c**

a: 6-Br, **b**: 7-Br, **c**: 8-Br

Scheme 1. Borylation reaction of **1**

The borylation reaction using pin_2B_2 was carried out in the presence of Pd catalysts and KOAc in DMSO at 80 °C under a nitrogen atmosphere.[5] First, the effect of palladium catalyst were examined. The results

Table 1. Catalyst effects in the borylation of **1a**

Run	Pd catalyst	Yield of **2a** [%][a)]	Yield of **3aa** [%][b)]
1	$Pd(OAc)_2$	27	—
2	$PdCl_2(dppf)$	98	—
3	$PdCl_2(PPh_3)_2$	98	—
4	$PdCl_2(PPh_3)_2$+2PPh_3	98	—
5	$PdCl_2(PPh_3)_2$+2dppf	65	—
6	$PdCl_2(PPh_3)_2$+2P(*o*-tol)$_3$	98	—
7	$Pd(PPh_3)_4$	62	—
8	$Pd(dba)_2$	85	13
9	$Pd_2(dba)_3$	83	15

a) Isolated yield.
b) Isolated yield.

are summarized in Table 1. It can be seen that the Pd-catalysts used were effective in the borylation reactions, except in the case of $Pd(OAc)_2$ or $Pd(PPh_3)_4$ (runs 1 and 7). The reaction using $Pd(OAc)_2$ as a catalyst progressed slowly under the conditions employed to afford **2a** in poor yield (27%, run 1), likely due to the lack of a factor to reduce Pd(II) to Pd(0) (run 1). $Pd(PPh_3)_4$ was also relatively ineffective (run 7), and the yield was moderate (62%), probably due to the formation of phenyl-boronate derived from the coupling with a phosphine-bounded phenyl group.[6] In contrast, a small amount of 6,6''-biflavone **3aa** was formed as a by-product (13%, run 9: 15%, run 8) in the reactions using $Pd(dba)_2$ or $Pd_2(dba)_3$.

Table 2. Base effects in the borylation reaction of **1a**

Run	Pd catalyst	Base	Yield [%][a)]	
			2a	**3aa**
1	$PdCl_2(PPh_3)_2$	Na_2CO_3	33	62
2	"	K_2CO_3	41	54
3	"	KOAc	98	0
4	"	NaOAc	98	0
5	$PdCl_2(PPh_3)_2$-$2PPh_3$	Na_2CO_3	50	43
6	"	KOAc	98	0

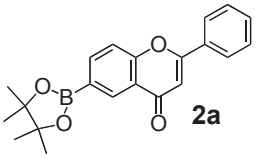
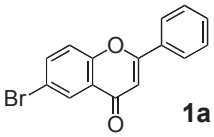
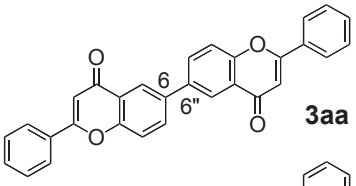
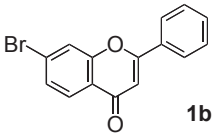
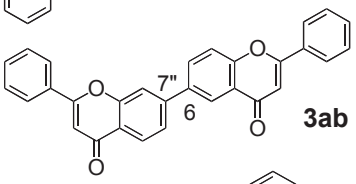
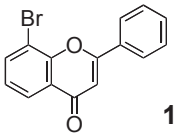
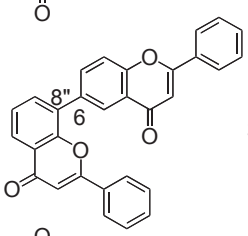
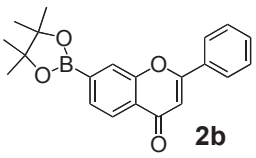
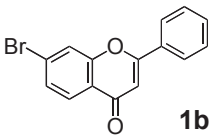
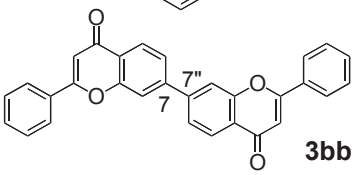
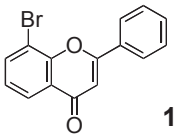
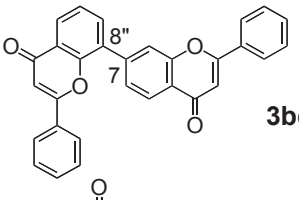
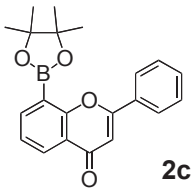
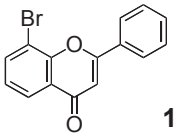
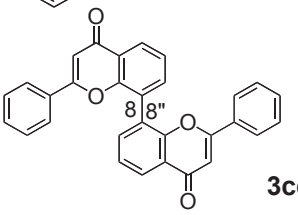
a) Isolated yield.

Next, the effects of a base in this borylation reaction were examined. In general, it has been well known that Pd-catalyzed boron-containing cross-coupling reactions are strongly accelerated by suitable base.[5] Thus, the reaction were carried out using several bases with the best catalysts $PdCl_2(PPh_3)_2$ or $PdCl_2(PPh_3)_2$-$2PPh_3$ (Table 2).

The bases such as KOAc or NaOAc afforded **2a** in almost quantitative yields (runs 3, 4 and 6). In contrast, a mixture of dimers **3aa** and **2a** was obtained by using stronger bases such as K_2CO_3 or Na_2CO_3 (runs 1, 2 and 5). Although the reason for this difference is not clear, a strong base might promote the further reaction of the prepared **2a** with **1a** to afford biflavone **3aa**. The borylation reactions of 7- and 8-bromoflavones **1b**,**c** were also attempted with pin_2B_2 under the optimized conditions ($PdCl_2(PPh_3)_2$+$2PPh_3$, KOAc system). As a result, the reactions using **1b** or **1c** afforded the desired borylated compounds **2b,c** in moderate to good yields (**2b**: 82%, **2c**: 68%).

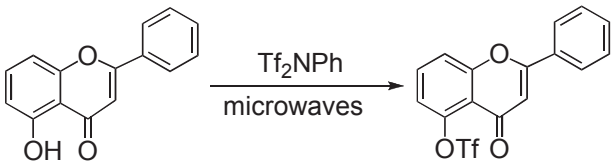
We next tried the Suzuki cross-coupling of bromoflavones **1a-c** with borylated compounds **2a-c**, respectively, to obtain biflavones **3** (Table 3). The reactions of **2a-c** with **1a-c** carried out under the employed conditions (2M-Na_2CO_3, in benzene, reflux, for 16 h)[7] using $Pd(PPh_3)_4$ as a catalyst gave **3** in a wide range of yields. Although the coupling reaction is usually carried out using a slightly excess of boron compound, we utilized an excess of **1** to prevent the homocoupling of **2a**.

Table 3. Cross-coupling reaction of **2** with **1**

Entry	Borylated flavone (**2**)	Bromoflavone (**1**)	Product (**3**)	Yield of **3** [%][a)]
1	 **2a**	 **1a**	 **3aa**	67
2		 **1b**	 **3ab**	68
3		 **1c**	 **3ac**	4
4	 **2b**	 **1b**	 **3bb**	35
5		 **1c**	 **3bc**	3
6	 **2c**	 **1c**	 **3cc**	4

a) Isolated yield.

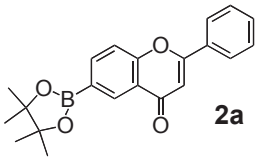
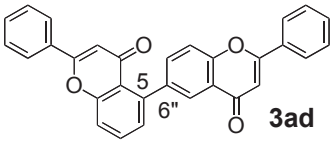
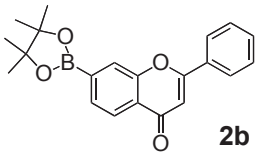
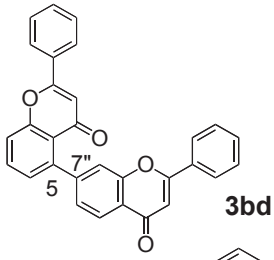
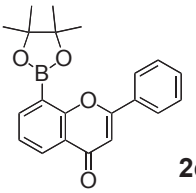
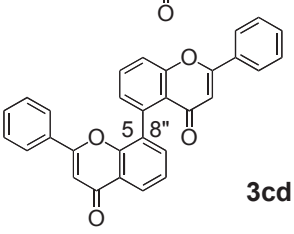
The reactions of borylated flavone **2a** with bromoflavones **1a**-**c** gave the corresponding biflavones (**3a, 3ab,** and **3ac**) in 68%, 67% and 4% yields, respectively (entries 1-3). In addition, the combinations of **2b** with **1b,c**, respectively, afforded the corresponding biflavones **3bb** or **3bc**. It is clear from these results that the formation of unsymmetric biflavone is difficult to achieve. This difficulty might be due to the highly steric factors in the structures of unsymmetric flavones **3ac** and **3bc**. The cross-coupling reaction of **2c** with **1c** was also carried out to prepare the unsymmetric biflavones 8,8”-biflavone **3cc**. However, the formation of this sterically bulkier **3cc** was almost not observed (entry 2). We examined the cross-coupling reactions of **2a-c** with flavone-5-triflate **1d** under the above-mentioned conditions (Table 4). Triflate **1d** was easily prepared from the reaction of 5-hydroxyflavone with Tf_2NPh **4** under microwave conditions according to the procedure by Fitzmaurice *et al* (Scheme 2).[8]



Scheme 2. Triflation of 5-hydroxyflavone

As a result, the corresponding unsymmetric biflavones **3ad**, **3bd** and **3cd** were obtained in fairly good yields in every case (entries 1-3).

Table 4. Cross-coupling reaction of **2** with **1d**

Entry	Borylated flavone (**2**)	Product (**3**)	Yield of **3** [%][a)]
1	 **2a**	 **3ad**	90
2	 **2b**	 **3bd**	93
3	 **2c**	 **3cd**	93

a) Isolated yield

In conclusion, we have developed an efficient synthesis for obtaining unsymmetric and symmetric bisflavone by the Suzuki cross-coupling of borylated flavones **2a-c** with bromoflavones **1a-c** or flavone-5-triflate **1d** in good to excellent yields. Further studies to examine the scope and limitations of our new synthetic methodology for the synthesis of flavonoids are now in progress.

EXPERIMENTAL

Unless otherwise stated, all chemicals and reagents were commercially available grades and were used without further purification. All reactions were performed under a nitrogen atmosphere and monitored by

thin-layer chromatography (TLC) using silica gel 60 F254 on aluminium pre-coated plates (0.25 mm). Column chromatography was performed on silica gel (Wakogel C-200). ^{1}H NMR and ^{13}C NMR spectra were recorded at 270 MHz and 67.8 MHz on a JEOL JNM-EX 270 FT NMR SYSTEM in $CDCl_3$ using tetramethylsilane as an internal standard**.**

General procedure for the preparation of borylated flavones (2a-c). The mixture of bis(pinacolato)diboron (0.55 mmol), $PdCl_2(PPh_3)_2$ (3 mol%), PPh_3 (6 mol%), **1** (0.5 mmol), KOAc (1.5 mmol) which was dried by oven for 1 h, and DMSO (3 mL), were stirred for 6 h at 80 ˚C under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, the products were extracted with $CHCl_3$. The organic layer was washed with water and brine, followed by dried over anhydrous $MgSO_4$ and filtered. After the filtrate was concentrated, Kugelrohr distillation *in vacuo* gave flavone boronates (**2**).

6-Pinacolatoborylflavone (2a). Colorless needles; mp 158-160 °C; ^{1}H NMR ($CDCl_3$, 270MHz, ppm) δ 1.37 (12H, s), 6.84 (1H, s), 7.52-7.55 (3H, m), 7.56 (1H, d, *J*=8. 4 Hz), 7.91-7.95 (2H, m), 8.10 (1H, dd, *J*=8.4, 1.6 Hz), 8.74 (1H, d, *J*=1.6 Hz); ^{13}C NMR($CDCl_3$, 65MHz, ppm): δ 24.9, 84.2, 107.9, 117.4, 123.2, 126.3, 129.1, 131.6, 131.7, 133.3, 139.6, 158.2, 163.2, 178.4.[9]

7-Pinacolatoborylflavone (2b). Colorless needles; mp 172-173 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 1.35 (12H, s), 6.81 (1H, s), 7.47-7.50 (3H, m), 7.78 (1H, d, *J*=7.6 Hz), 7.85-7.92 (2H, m), 8.01 (1H, s), 8.18 (1H, d, *J*=7.8 Hz); 13C NMR($CDCl_3$, 68 MHz, ppm): δ 24.8, 84.5, 107.5, 124.5, 124.6, 125.5, 126.2, 129.0, 130.6, 131.6, 131.6, 155.6, 163.3, 178.5.

8-Pinacolatoborylflavone (2c). Colorless needles; mp 178-179 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 1.38 (12H, s), 6.82 (1H, s), 7.35(1H, dd, *J*=7.7, 7.3 Hz), 7.43-7.46 (3H, m), 8.07 (1H, dd, *J*=7.3, 1.9 Hz), 8.15-8.18 (2H, m), 8.27 (1H, dd, *J*=7.7, 1.9 Hz); ^{13}C NMR($CDCl_3$, 68 MHz, ppm): δ 25.1, 84.1, 106.5, 123.6, 124.7, 126.7, 128.7, 129.0, 131.5, 133.8, 141.6, 160.0, 163.3, 178.9.

General procedure for the preparation of biflavone (3). The mixture of borylated flavone (**2**) (0.55 mmol), tetrakis(triphenylphosphine)palladium as a catalyst (3 mol%), bromoflavone or flavone-5-triflate (**1**) (0.5 mmol), 2M Na_2CO_3 (1 mL), and benzene (3 mL) were stirred for 16 h at reflux temperture under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, the products were extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$

and filtered. After the filtrate was concentrated, biflavones (**3**) were isolated by silicagel column chromatoglaphy.

6,6''-Biflavone (**3aa**). Colorless needles; mp 312-313 °C (lit.,[10] 312-313 °C); 1H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.89 (2H, s) 7.55-7.58 (6H, m), 7.72 (2H, d, *J*=8.9 Hz), 7.96-7.99 (4H, m), 8.09 (2H, dd, *J*=8.9, 2.4 Hz), 8.53 (2H, d, *J*=2.4 Hz); $_{13}$C NMR($CDCl_3$, 68 MHz, ppm): δ 107.7, 119.0, 123.7, 124.2, 126.4, 129.1, 132.0, 131.8, 132.7, 136.5, 156.0, 163.6, 178.3; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1207.

6,7''-Biflavone (3ab). Colorless needles; mp 236-238 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.88 (1H, s), 6.90 (1H, s), 7.52-7.59 (6H, m), 7.74(1H, d, *J*=8.8 Hz), 7.76 (1H, dd, *J*=8.1, 1.5 Hz), 7.93 (1H, d, *J*=1.5 Hz), 7.96-8.00 (4H, m), 8.06 (1H, dd, *J*=8.8, 2.3 Hz), 8.33 (1H, d, *J*=8.1 Hz), 8.58 (1H, d, *J*=2.3 Hz); ^{13}C NMR($CDCl_3$, 68 MHz, ppm): δ 107.8, 107.8, 116.4, 119.2, 123.1, 124.2, 124.4, 126.3, 126.4, 126.6, 129.2, 131.6, 131.7, 131.9, 132.5, 136.2, 144.9, 156.4, 156.7, 163.7, 178.2; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1207.

6,8''-Biflavone (3ac). Colorless needles; mp 292-293 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.91 (1H, s), 6.93 (1H, s), 7.41-7.62 (6H, m), 7.54 (1H, dd, *J* =7.9, 7.4 Hz), 7.75 (1H, d, *J*=8.6 Hz), 7.75-7.81 (2H, m), 7.83 (1H, dd, *J*=7.4, 1.8 Hz), 7.96-8.03 (2H, m), 8.04 (1H, dd, *J*=5.8, 3.0 Hz), 8.31 (1H, dd, *J*=7.9, 1.7 Hz), 8.59 (1H, d, *J*=2.0 Hz); ^{13}C NMR($CDCl_3$, 68 MHz, ppm): δ 107.4, 107.8, 118.3, 124.1, 124.6, 125.4, 125.8, 126.4, 126.8, 129.2, 130.1, 131.6, 131.7, 131.8, 133.4, 134.9, 135.1, 153.1, 156.0, 163.5, 163.7, 178.1, 178.4; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1199.

7,7''-Biflavone (3bb). Colorless needles; mp 356-358 °C (lit.,[10] 346 °C); ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.90 (2H, s), 7.52-7.61 (6H, m), 7.77 (2H, dd, *J*=8.3, 1.7 Hz), 7.92 (2H, d, *J*=1.5 Hz), 7.95-8.01 (4H, m), 8.37 (2H, d, *J*=8.3 Hz) ; ^{13}C NMR($CDCl_3$, 68 MHz, ppm): δ 107.9, 116.9, 123.7, 124.4, 126.4, 126.4, 129.2, 131.6, 131.8, 144.7, 156.6, 163.8, 178.0; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1207.

7,8''-Biflavone (3bc). Colorless needles; mp 293-294 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.94 (2H, s), 7.44-7.60 (5H, m), 7.57 (1H, dd, *J*=7.5, 7.9 Hz), 7.76-7.80 (2H, m), 7.78 (1H, dd, *J*=8.3 1.5 Hz), 7.84 (1H, dd, *J*=7.9, 1.7 Hz), 7.91 (1H, d, *J*=1.5 Hz), 7.95-7.99 (2H, m), 8.36 (1H, dd, *J*=7.9, 1.7 Hz), 8.40 (1H, d, *J*=8.3 Hz); ^{13}C NMR($CDCl_3$, 68 MHz, ppm:) δ 107.4, 107.9, 119.1, 123.4, 124.6, 125.4,

125.7, 126.2, 126.3, 126.5, 126.9, 129.2, 129.2, 129.9, 131.4, 131.6, 131.9, 134.8, 142.1, 153.0, 156.3, 163.4, 163.7, 178.2; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1207.

8,8”-Biflavone (3cc). Colorless needles; mp 289-290 °C (lit.,[10] 290-291 °C); ^{1}H NMR ($CDCl_3$, 270 MHz, ppm:) δ 6.85 (2H, s), 7.24-7.30 (4H, m), 7.35-7.41 (6H, m), 7.62 (2H, dd, *J*=7.9, 7.3 Hz), 7.86 (2H, dd, *J*=7.3, 1.8 Hz), 8.42 (2H, dd, *J*=7.9, 1.8 Hz); ^{13}C NMR(CDCl3, 68 MHz, ppm): δ 107.1, 124.2, 125.1, 125.7, 126.3, 126.4, 129.0, 131.0, 131.6, 135.6, 135.4, 163.2, 178.3; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1207.

5,6”-Biflavone (3ad). Colorless needles; mp 235-238 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.69 (1H, s), 6.86 (1H, s), 7.28 (1H, dd, *J*=7.09, 1.49 Hz), 7.50-7.55 (6H, m), 7.58 (1H, d, *J*=8.6 Hz), 7.63 (1H, dd, *J*=8.4, 1.5 Hz), 7.70 (1H, dd, *J*=8.4, 7.1 Hz), 7.72 (1H, dd, *J*=8.6, 2.1 Hz), 7.91-7.97 (4H, m), 8.19 (1H, d, *J*=2.1 Hz); ^{13}C NMR(CDCl3, 68 MHz, ppm): δ 107.7, 108.6, 116.7, 118.4, 121.1, 123.3, 124.6, 126.1, 126.2, 128.6, 129.0, 131.4, 131.5, 131.5, 131.9, 132.6, 135.6, 138.5, 141.1, 155.6, 157.4, 162.0, 163.3, 178.1, 178.4; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1205.

5,7”-Biflavone (3bd). Colorless needles; mp 271-273 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.71 (1H, s), 6.85 (1H, s), 7.25 (1H, dd, *J*=6.9, 1.6 Hz), 7.38 (1H, dd, *J*=8.1, 1.5 Hz), 7.49-7.55 (6H, m), 7.56 (1H, d, *J*=1.5 Hz), 7.67 (1H, dd, *J*=8.4, 1.7 Hz), 7.73 (1H, dd, *J*=8.4, 6.9 Hz), 7.90-7.95 (4H, m), 8.24 (1H, d, *J*=1.5 Hz); ^{13}C NMR(CDCl3, 68 MHz, ppm): δ 107.8, 108.7, 117.8, 118.8, 121.3, 122.7, 124.6, 126.2, 126.3, 126.5, 128.0, 129.0, 129.1, 131.4, 131.4, 131.7, 132.0, 132.7, 141.0, 147.5, 155.7, 157.3, 162.3, 163.4, 177.9, 178.4; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1207.

5,8”-Biflavone (3cd). Colorless needles; mp 208-209 °C; ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.61 (1H, s), 6.80 (1H, s), 7.20-7.35 (3H, m), 7.33 (1H, dd, *J*=6.68, 1.90 Hz), 7.42-7.58 (5H, m), 7.48 (1H, dd, *J*=7.9, 7.3 Hz), 7.61 (1H, dd, *J*=7.3, 1.7 Hz), 7.75 (1H, dd, *J*=8.5, 1.9 Hz), 7.80 (1H, dd, *J*=8.5, 6.7 Hz), 7.89-7.93 (2H, m); ^{13}C NMR($CDCl_3$, 68 MHz, ppm): δ 107.3, 108.5, 119.0, 122.3, 123.4, 124.6, 124.9, 125.9, 126.2, 128.5, 128.8, 129.1, 131.2, 131.3, 131.7, 131.8, 131.9, 133.0, 133.2, 136.3, 153.9, 157.0, 162.3, 162.7, 177.9, 178.7; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found: 442.1207.

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