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New Developments in the Synthesis of (*E*)-8-Styrylflavones

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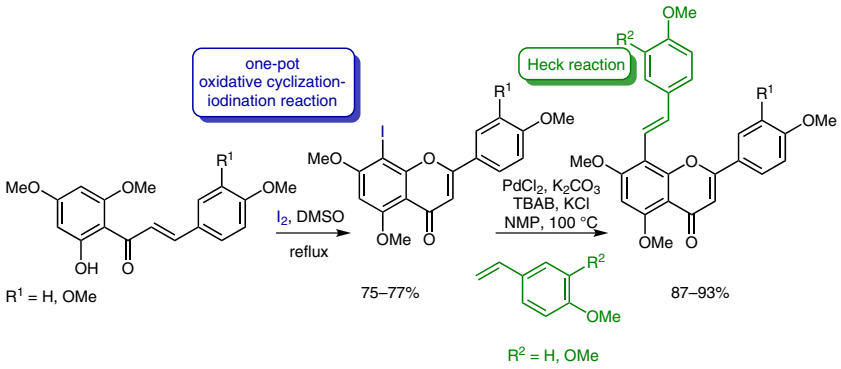

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Abstract A novel route for the synthesis of new (*E*)-8-styrylflavones is reported. This methodology involves the regio- and stereoselective Heck cross-coupling reaction of 8-iodoflavones and styrene derivatives. The Heck precursors, 8-iodoflavones, were obtained through an efficient regioselective one-pot oxidative cyclization–iodination reaction of (*E*)-2′-hydroxychalcones by applying the iodine/dimethyl sulfoxide system.

Keywords palladium, Heck reaction, styrylflavones, iodoflavones, cyclodehydrogenation

Flavones are an important class of flavonoids based on a 2-aryl-4*H*-chromen-4-one framework.[1,2] These compounds are widespread in the plant kingdom as secondary metabolites[2] and can be found in all parts of plants.[3] They are also part of the human diet, being present in various herbs, vegetables, and fruits.[4]

Depending on their substitution pattern, flavones exhibit several biological properties,[5] being the antioxidant activity one of the most explored.[6,7] Easily dissociable phenolic hydroxyl groups, maximum extended conjugated system, and electron-donating substituents in the aromatic rings are crucial structural features to a potent antioxidant activity.[8] Flavones possessing a 3′,4′-dihydroxy substitution at the B ring are highly active antioxidants and, as the number of hydroxyl groups increases, their scavenging potential also increases.[9] Like flavones, 2- and 3-styrylchromones (the vinylogues of flavones and isoflavones, respectively) possess multiple activities with potential therapeutic applications.[10,11]

The interesting biological properties of flavones and styrylchromones led us to attempt the synthesis of new flavones bearing a styryl moiety.

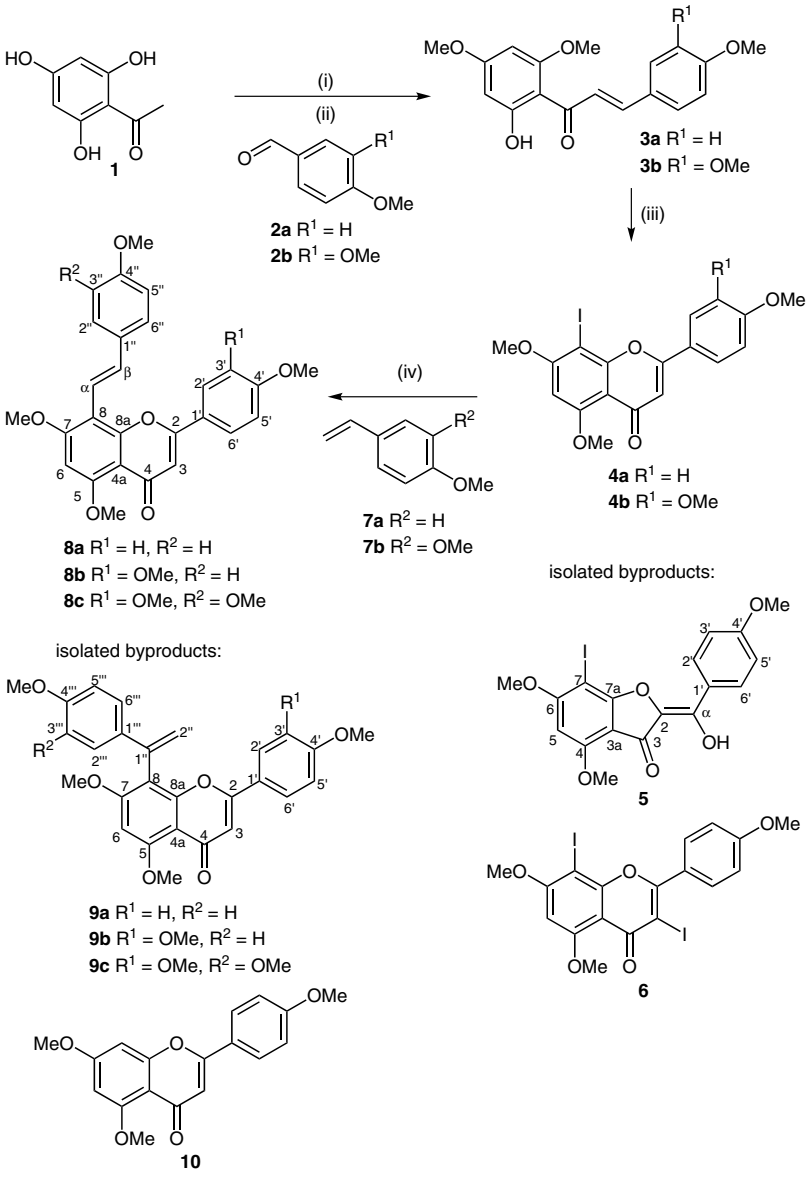
In recent years, there have been reported several studies on the application of Heck reactions in the synthesis of alkenylated chromones and flavones (including styrylflavones). Dawood performed the synthesis of 3-styryl-4*H*-chromen-4-one through a Heck cross-coupling reaction of 3-bromo-4*H*-chromen-4-one with styrene using benzothiazole oxime based palladium(II) precatalysts, in the presence of triethylamine, under thermal and microwave heating.[12] Patonay et al. have demonstrated that 3-, 6-, 7-, or 8-bromochromones can be coupled successfully under modified Jeffery's conditions to various terminal alkenes in a diastereoselective fashion.[13,14] Under similar conditions, 3-, 6-, or 7-bromoflavones can also be treated with multiple terminal alkenes, including styrene derivatives, to give the corresponding alkenylated flavones in moderate to good yields.[15] Luthman et al. have efficiently coupled methyl acrylate to the 3-, 6-, and 8-positions of flavone scaffolds using microwave heating as an alternative energy source.[16] Silva et al. performed an efficient Heck cross-coupling reaction of 3-bromoflavones with styrene derivatives, under microwave irradiation, leading to the corresponding (*E*)-3-styrylflavones.[17] Besides Heck reaction, other methods for the synthesis of styrylflavones are reported in the literature, including Wittig reaction of 3-methylflavone[18] and condensation of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones with phenylacetaldehydes.[19]

Iodoflavones can be excellent Heck precursors, and they are typically iodinated at 3-, 6-, or 8-positions. Synthesis of 6,8-diiodoflavones can be performed by oxidative cyclization–iodination of 2′-benzyloxy-6′-hydroxychalcones with iodine/dimethyl sulfoxide or by iodination of 5-hydroxy- or 5,7-dihydroxyflavones, using iodine/dimethyl sulfoxide[20] or I_2 in a mixture of acetic acid/nitric acid,[21] respectively. Alternatively, 6,8-diiodoflavones can be synthesized by diacetoxyiodobenzene-catalyzed iodination of 2′-hydroxychalcones with tetra-*n*-butylammonium iodide in acetic acid in

the presence of sodium perborate as a terminal oxidant.[22] The regioselective 8-iodination of 5,7-dibenzyloxyflavone can be accomplished using iodine/dimethyl sulfoxide.[23] Similarly, 5,7-dimethoxyflavone can be iodinated at 8-position using iodine in a mixture of acetic acid/nitric acid,[24] *N*-iodosuccinimide,[25] or iodine monochloride.[26] On the other hand, the regioselective 6-iodination of 5-hydroxy-7-methoxyflavones can be performed using *N*-iodosuccinimide[25] or iodine with thallium(I) salts.[27] In addition, 3-iodoflavones may be synthesized by using iodine monochloride,[28] iodine/cerium ammonium nitrate,[29] lithium diisopropylamide followed by iodine[30] and bis(trifluoroacetoxyiodo)benzene/iodine.[31]

In the present communication we report a new strategy for the synthesis of novel (*E*)-8-styrylflavones based on the selective one-pot oxidative cyclization–iodination of (*E*)-2′-hydroxychalcones followed by the Heck reaction of the obtained 8-iodoflavones (Scheme 1).

The preparation of the iodinated partner, in this case the 8-iodoflavones, started with the selective dimethylation of 2′,4′,6′-trihydroxyacetophenone (**1**) in good yield (82%), following a modification of the Khanna and Seshadri's method (Scheme 1).[10a,32,33] Then, (*E*)-2′-hydroxychalcones **3a**,**b**[34] were synthesized in good yields (77% and 61%, re-



Scheme 1 *Reagents and conditions*: (i) Me_2SO_4, K_2CO_3, acetone, reflux, 20 min; (ii) NaOH (aq, 60%), MeOH, r.t., 3–4 h; (iii) I_2, DMSO, reflux, N_2, 45 min; (iv) Pd cat., solvent, temperature, K_2CO_3, KCl, TBAB, 24 h, N_2.

spectively) by a base-catalyzed aldol condensation of the obtained acetophenone with benzaldehyde derivatives **2a**,**b**, using sodium hydroxide in methanol (Scheme 1).[35]

In order to prepare the iodinated flavones to be used as Heck precursors we attempted the one-pot oxidative cyclization–iodination of (*E*)-2′-hydroxychalcones **3a**,**b** by applying the I_2/DMSO system. Optimatizion of reaction conditions by changing the amount of iodine, temperature, and reaction time, was performed based on the ^{1}H NMR spectra of the crude reaction mixture. Molar quantity of iodine is determinant in the composition of the resulting reaction mixture. Best results were achieved using one equivalent of I_2 in refluxing DMSO for 45 min.[36] Under these conditions, 8-iodoflavone **4a** was isolated in good yield (77%, Scheme 1). Increasing the amount of iodine to two or three equivalents did not promote diiodination, resulting in lower yields of 8-iodoflavone **4a** together with an increase of degradation compounds and the identification of α-hydroxy-7-iodo-4,4′,6-trimethoxyaurone **5**[37] as a byproduct. Oxidative cyclization–iodination reaction of (*E*)-2′-hydroxychalcone **3a** can be performed at 130 °C, although better performances were attained in refluxing DMSO. Increasing the reaction time to 90 min led to a substantial decrease of 8-iodoflavone **4a** yield (43%) with no significant improvement of 3,8-diiodo-4′,5,7-trimethoxyflavone **6**[38] yield (4% → 9%), resulting in higher degradation products. Under the optimized conditions, 8-iodoflavone **4b**[39] was synthesized in good yield (75%) from (*E*)-2′-hydroxychalcone **3b**. It is worthy to note that in all the assays performed the iodination occurred regioselectively at C-8, the 6-iodoflavone isomer was never isolated, which is consistent with related studies.[21,23,24]

Following our interest on the synthesis of new 8-styrylflavones, we studied the Heck reaction of 8-iodoflavones **4a**,**b** with styrenes **7a**,**b**. Optimization of the experimental conditions was performed with 8-iodoflavone **4a** and 4-methoxystyrene **7a** under Jeffery's conditions, already described for the coupling of bromoflavones with several alkenes[13,14] (Table 1, entries 1–9). Among the different palladium catalysts used, palladium(II) led generally to better results than palladium(0) (Table 1, entries 1, 3–7). $PdCl_2$ had the largest effect on the reaction yield giving the expected (*E*)-8-styrylflavone **8a**[40] in very good yield (83%, Table 1, entry 7). Of the two polar aprotic solvents tested, 1-methylpyrrolidin-2-one (NMP) had the best performance leading to a slight improvement of (*E*)-8-styrylflavone **8a** yield (83% → 87%, Table 1, entries 7 and 8).

Increasing the temperature from 100 °C to 130 °C when using $PdCl_2(PPh_3)_2$ in DMF slightly enhanced the yield of **8a** (70% → 72%, Table 1, entry 2), although when using $PdCl_2$ in NMP the increase of temperature to 155 °C led to a lower yield of (*E*)-8-styrylflavone **8a** (47%, Table 1, entry 9) together with the presence of more degradation products. The optimized reaction conditions therefore consists in the use of $PdCl_2$ (6 mol%), K_2CO_3 (1.5 equiv), KCl (1 equiv), TBAB (1.5 equiv), and NMP at 100 °C.[41] These optimized conditions were applied to the other derivatives leading to (*E*)-8-styrylflavones **8b** and **8c** in excellent yields (90% and 93%, Table 1, entries 10 and 11).

Table 1 Optimization of the Heck Reaction Conditions in the Synthesis of (*E*)-8-Styrylflavones **8a**–**c**[a]

Entry	Product	Catalyst	Solvent	Temp (°C)	Yield (%)
1	**8a**	$PdCl_2(PPh_3)_2$	DMF	100	70
2	**8a**	$PdCl_2(PPh_3)_2$	DMF	130	72
3	**8a**	$Pd_2(dba)_3$	DMF	100	45
4	**8a**	$Pd(PPh_3)_4$	DMF	100	53
5	**8a**	$Pd(acac)_2$	DMF	100	65
6	**8a**	$Pd(OAc)_2$	DMF	100	66
7	**8a**	$PdCl_2$	DMF	100	83
8	**8a**	$PdCl_2$	NMP	100	87
9	**8a**	$PdCl_2$	NMP	155	47
10	**8b**	$PdCl_2$	NMP	100	90
11	**8c**	$PdCl_2$	NMP	100	93

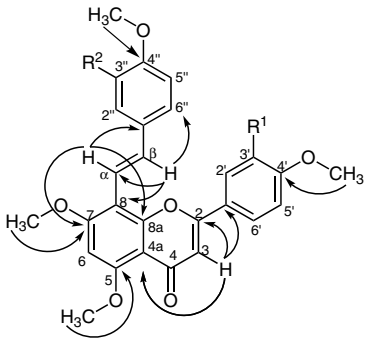
[a] All the reactions were performed in a 0.09 mmol scale of 8-iodoflavone **4** in the presence of the appropriate styrene **7** (0.45 mmol), Pd cat. (6 mol%), K_2CO_3 (0.14 mmol), KCl (0.09 mmol), TBAB (0.14 mmol) for 24 h under N_2.

Heck cross-coupling reaction of 8-iodoflavones **4a**,**b** with styrenes **7a**,**b** is regioselective to the C-β of the styrene which is activated by conjugation and less steric hindered, although in most assays, 8-[1-(4-metoxyphenyl)vinyl]-4′,5,7-trimethoxyflavone **9a**,[42] as well as **9b**,**c**, were isolated as byproducts in very low yields (traces to 11%).

4′,5,7-Trimethoxyflavone **10**,[43] formed by palladium-catalyzed dehalogenation of 8-iodoflavone **4a**, was only observed when using $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ (2% and <13%, respectively, Table 1, entries 1 and 4).

The most important features in the ^{1}H NMR spectra of (*E*)-8-styrylflavones **8a**–**c** are the presence of: i) two singlets at δ = 6.62–6.65 and 6.46–6.48 ppm assigned to the resonances of H-3 and H-6, respectively, and ii) two doublets at δ = 7.27–7.30 and 7.40–7.45 ppm assigned to the resonances of H-α and H-β, respectively, with a coupling constant of *J* = ca. 16 Hz which indicates a *trans* configuration of this vinylic system. HMBC correlations between H-α and C-7 (which correlates also with methoxyl protons) and C-8a allowed the confirmation of the 8-[2-(4-metoxyphenyl)vinyl] substituent (Figure 1). No correlation between H-α and C-5 was observed.

In conclusion, a new synthetic route to (*E*)-8-styrylflavones was developed, based firstly on an efficient one-pot oxidative cyclization–iodination of (*E*)-2′-hydroxychalcones leading to the corresponding 8-iodoflavones in a regioselective fashion, and secondly on the regio- and stereoselective



8

Figure 1 Main HMBC connectivities of compounds **8**

synthesis of (*E*)-8-styrylflavones by the Heck cross-coupling reaction of 8-iodoflavones and styrene derivatives with excellent overall yields.

Acknowledgment

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(33) **Optimized Experimental Procedure for the Synthesis of 2′-Hydroxy-4′,6′-dimethoxyacetophenone**
K_2CO_3 (7.23 g, 52.32 mmol) and Me_2SO_4 (2.48 mL, 26.16 mmol) were added to a solution of 2′,4′,6′-trihydroxyacetophenone (**1**, 2.00 g, 11.89 mmol) in acetone (50 mL). The reaction mixture was refluxed for 20 min under nitrogen atmosphere. After that, K_2CO_3 was filtered off, the acetone evaporated, and the residue recrystallized in EtOH affording the 2′-hydroxy-4′,6′-dimethoxyacetophenone in good yield (82%, 1.91 g).
(34) **Physical Data of (*E*)-2′-Hydroxy-3,4,4′,6′-tetramethoxychalcone (3b)**
Yellow needles; mp 156–157 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.84 and 3.92 (2 s, 2 × 3 H, 4′- and 6′-OCH_3), 3.94 (s, 3 H, 4-OCH_3), 3.95 (s, 3 H, 3-OCH_3), 5.98 (d, 1 H, *J* = 2.3 Hz, H-5′), 6.12 (d, 1 H, *J* = 2.3 Hz, H-3′), 6.90 (d, 1 H, *J* = 8.4 Hz, H-5), 7.13 (d, 1 H, *J* = 1.8 Hz, H-2), 7.22 (dd, 1 H, *J* = 1.8, 8.4 Hz, H-6), 7.78 (AB, 1 H, *J* = 15.6 Hz, H-β), 7.83 (AB, 1 H, *J* = 15.6 Hz, H-α), 14.41 (s, 2′-OH, 1 H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 55.6, 55.8, 55.9, and 56.0 (3-, 4-, 4′-, and 6′-OCH_3), 91.3 (C-5′), 93.8 (C-3′), 106.3 (C-1′), 110.4 (C-2), 111.2 (C-5), 122.6 (C-6), 125.4 (C-α), 128.6 (C-1), 142.7 (C-β), 149.1 (C-3), 151.1 (C-4), 162.4 and 166.1 (C-4′ and C-6′), 168.4 (C-2′), 192.5 (C=O) ppm. ESI$^+$-MS: *m/z* (%) = 345 (17) [M + H]$^+$, 367 (100) [M + Na]$^+$, 711 (5) [2M + Na]$^+$. Anal. Calcd (%) for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 65.99; H, 5.77.
(35) **General Optimized Experimental Procedure for the Synthesis of (*E*)-2′-Hydroxychalcones 3a,b**
NaOH (aq, 60%, 37 mL) was added to a solution of 2′-hydroxy-4′,6′-dimethoxyacetophenone (1.50 g, 7.645 mmol) in MeOH (37 mL; in the case of derivative **a**), or in MeOH–DMSO (v/v, 37:4.5 mL; in the case of derivative **b**). After that, the appropriate benzaldehyde **2a**,**b** (15.04 mmol) was added, and the reaction mixture was stirred for 3 h (derivative **a**) and 4 h (derivative **b**) at r.t. Then, the mixture was poured into ice (50 g) and H_2O (100 mL) and the pH adjusted to 4 with a solution of HCl (20%). After filtration, the precipitate was taken in CH_2Cl_2, washed repeatedly with a sat. solution of $KHCO_3$ (1 × 300 mL) and H_2O (3 × 300 mL), and the organic layer was dried over anhydrous Na_2SO_4. Subsequently, after solvent evaporation, the residue was recrystallized in EtOH giving the correspondent (*E*)-2′-hydroxychalcones **3a**,**b** in good yields [**3a** (77%, 1.78 g); **3b** (61%, 1.61 g)].
(36) **General Optimized Experimental Procedure for the Synthesis of 8-Iodoflavones 4a,b**
I_2 (0.100 g; 0.3181 mmol) was added to a solution of the appropriate (*E*)-2′-hydroxychalcone **3a**,**b** (0.3181 mmol) in DMSO (1.0 mL), and the reaction mixture was refluxed for 45 min under N_2 atmosphere. After that, the reaction mixture was poured into ice (25 g), H_2O (50 mL), and $Na_2S_2O_3{\cdot}5H_2O$ (1 g). The obtained solid was filtered, taken in CH_2Cl_2 (100 mL), and washed with $Na_2S_2O_3$ (aq, 20%) (100 mL) and H_2O (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 concentrated and purified by flash column chromatography with a mixture of EtOAc–CH_2Cl_2(4:1) leading to 8-iodoflavones **4a**,**b** in good yields [**4a** (77%, 107.3 mg); **4b** (75%, 111.7 mg)].
(37) **Physical Data of α-Hydroxy-7-iodo-4,4′,6-trimethoxyaurone (5)**
White powder. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, 4′-OCH_3), 4.03 and 4.06 (2 s, 2 × 3 H, 5-OCH_3 and 7-OCH_3), 6.18 (s, 1 H, H-5), 6.84 (d, 2 H, *J* = 8.9 Hz, H-3′,5′), 7.77 (d, 2 H, *J* = 8.9 Hz, H-2′,6′) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 55.6 (4′-OCH_3), 56.6 and 57.3 (4- and 6-OCH_3), 58.2 (C-7), 90.0 (C-5), 101.3 (C-2), 103.6 (C-3a), 114.4 (C-3′,5′), 124.3 (C-1′), 132.2 (C-2′,6′), 161.0 (C-4 or C-6), 165.0 (C-4′), 168.2 (C-4 or C-6), 172.2 (C-7a), 188.5 (C-α), 190.5 (C-3) ppm. ESI$^+$-MS: *m/z* (%) = 493 (100) [M + K]$^+$.
(38) **Physical Data of 3,8-Di-iodo-4′,5,7-trimethoxyflavone (6)**
White powder. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, 4′-OCH_3), 4.03 (s, 6 H, 5,7-OCH_3), 6.45 (s, 1 H, H-6), 7.03 (d, 2 H, *J* = 8.8 Hz, H-3′,5′), 8.02 (d, 2 H, *J* = 8.8 Hz, H-2′,6′) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 55.5 (4′-OCH_3), 56.6 and 56.8 (5- and 7-OCH_3), 63.9 (C-8), 89.2 (C-3), 92.0 (C-6), 106.2 (C-4a), 113.4 (C-3′,5′), 126.2 (C-1′), 132.0 (C-2′,6′), 157.6 (C-8a), 161.7 (C-2, C-5, C-7, or C-4′), 161.8 (C-2, C-5, C-7, or C-4′), 161.9 (C-2, C-5, C-7, or C-4′), 162.9 (C-5 or C-7), 172.7 (C-4) ppm. ESI$^+$-MS: *m/z* (%) = 565 (94) [M + H]$^+$, 587 (100) [M + Na]$^+$.
(39) **Physical Data of 8-Iodo-3′,4′,5,7-tetramethoxyflavone (4b)**
Pale yellow powder; mp 273–275 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, 4′-OCH_3), 4.00 (s, 3 H, 3′-OCH_3), 4.04 (s, 6 H, 5- and 7-OCH_3), 6.44 (s, 1 H, H-6), 6.67 (s, 1 H, H-3), 6.99 (d, 1 H, *J* = 9.0 Hz, H-5′), 7.63–7.67 (m, 2 H, H-2′,6′) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 56.08 and 56.14 (3′- and 4′-OCH_3), 56.6 and 56.8 (5- and 7-OCH_3), 64.9 (C-8), 91.8 (C-6), 107.0 (C-3), 109.2 (C-2′), 109.9 (C-4a), 111.2 (C-5′), 119.9 (C-6′), 123.6 (C-1′), 149.2 (C-3′), 151.8 (C-4′), 157.5 (C-8a), 160.9 (C-2), 162.0 and 162.6 (C-5 and C-7), 177.5 (C-4) ppm. ESI$^+$-MS: *m/z* (%) = 469 (100) [M + H]$^+$, 491 (11) [M + Na]$^+$, 959 (40) [2M + Na]$^+$. Anal. Calcd (%) for $C_{19}H_{17}IO_6$: C, 48.74; H, 3.66. Found: C, 48.90; H, 3.64.
(40) **Physical Data of (*E*)-8-[2-(4-Methoxyphenyl)vinyl]-4′,5,7-trimethoxyflavone (8a)**
Pale yellow powder; mp 224–225 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, 4″-OCH_3), 3.88 (s, 3 H, 4′-OCH_3), 4.03 (s, 3 H, 5-OCH_3), 4.04 (s, 3 H, 7-OCH_3), 6.46 (s, 1 H, H-6), 6.62 (s, 1 H, H-3), 6.93 (d, 2 H, *J* = 8.7 Hz, H-3″,5″), 6.98 (d, 2 H, *J* = 8.8 Hz, H-3′,5′), 7.30 (d, 1 H, *J* = 16.6 Hz, H-α), 7.45 (d, 1 H, *J* = 16.6 Hz, H-β), 7.48 (d, 2 H, *J* = 8.7 Hz, H-2″,6″), 7.86 (d, 2 H, *J* = 8.8 Hz, H-2′,6′) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 55.4 and 55.5 (4′- and 4″-OCH_3), 56.0 and 56.4 (5- and 7-OCH_3), 91.6 (C-6), 107.4 (C-3), 108.0 (C-8), 109.1 (C-4a), 114.2 (C-3″,5″), 114.5 (C-3′,5′), 115.7 (C-α), 124.2 (C-1′), 127.4 (C-2″,6″), 127.9 (C-2′,6′), 131.3 (C-1″), 132.4 (C-β), 156.2 (C-8a), 159.2 (C-4″), 159.7 (C-5), 161.0 (C-2), 161.2 (C-7), 162.0 (C-4′), 178.2 (C-4) ppm. ESI$^+$-MS: *m/z* (%) = 445 (100) [M + H]$^+$, 467 (11) [M + Na]$^+$, 911 (60) [2M + Na]$^+$. EI$^+$-HRMS: *m/z* calcd for [$C_{27}H_{24}O_6$]: 444.1573; found: 444.1572.
(41) **General Optimized Experimental Procedure for the Synthesis of (*E*)-8-Styrylflavones 8a–c**
The appropriate styrene **7a**,**b** (0.45 mmol) was added to a mixture of the appropriate 8-iodoflavone **4a**,**b** (0.09 mmol), KCl (0.09 mmol), TBAB (0.14 mmol), K_2CO_3 (0.14 mmol), and $PdCl_2$ (5.4 μmol) in NMP (1.5 mL). Each reaction mixture was heated to 100 °C for 24 h under N_2 atmosphere. After this time, the mixture was poured into H_2O (100 mL) and the pH was adjusted to 5 by adding dropwise a solution of HCl (50%). Afterwards, the

obtained residue was extracted with CH_2Cl_2 (100 mL), washed with H_2O (4 × 200 mL) and the organic layer dried over anhydrous Na_2SO_4. To remove any traces of NMP, the residue was dissolved in toluene and evaporated to dryness. Purification by TLC [two mixtures were used as eluent: first CH_2Cl_2–MeOH (9:1) and then CH_2Cl_2–acetone (4:1)] with subsequent recrystallization in EtOH lead to (*E*)-8-styrylflavones **8a–c** in good yields [**8a** (87%, 34.8 mg); **8b** (90%, 38.4 mg); **8c** (93%, 42.2 mg)].

(42) **Physical Data of 8-[1-(4-Methoxyphenyl)vinyl]-4′,5,7-trimethoxyflavone (9a)**

Pale yellow powder; mp 151–152 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.78, 3.82, 3.88, and 4.05 (4 s, 4 × 3 H, 4′-, 4‴-, 5-, and 7-OCH_3), 5.25 (d, 1 H, *J* = 0.7 Hz, H-2″$_a$), 6.02 (d, 1 H, *J* = 0.7 Hz, H-2″$_b$), 6.50 (s, 1 H, H-6), 6.55 (s, 1 H, H-3), 6.83 (d, 2 H, *J* = 8.8 Hz, H-3′,5′ or H-3‴,5‴), 6.84 (d, 2 H, *J* = 8.9 Hz, H-3′,5′or H-3‴,5‴), 7.32 (d, 2 H, *J* = 8.8 Hz, H-2‴,6‴), 7.46 (d, 2 H, *J* = 8.9 Hz, H-2′,6′) ppm. ESI$^+$-MS: *m/z* (%) = 445 (100) [M + H]$^+$, 467 (32) [M + Na]$^+$, 911 (19) [2M + Na]$^+$. ESI$^+$-HRMS: *m/z* calcd for [$C_{27}H_{24}O_6$ + H$^+$] 445.1646; found: 445.1639.

(43) **Physical Data of 4′,5,7-Trimethoxyflavone (10)**

White powder; mp 154–156 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, 4′-OCH_3), 3.91 (s, 3 H, 7-OCH_3), 3.96 (s, 3 H, 5-OCH_3), 6.37 (d, 1 H, *J* = 2.2 Hz, H-6), 6.56 (d, 1 H, *J* = 2.2 Hz, H-8), 6.60 (s, 1 H, H-3), 7.00 (d, 2 H, *J* = 8.8 Hz, H-3′,5′), 7.83 (d, 2 H, *J* = 8.8 Hz, H-2′,6′) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 55.5 (4′-OCH_3), 55.8 (7-OCH_3), 56.5 (5-OCH_3), 92.8 (C-8), 96.1 (C-6), 107.7 (C-3), 109.2 (C-4a), 114.4 (C-3′,5′), 123.9 (C-1′), 127.6 (C-2′,6′), 159.9 (C-8a), 160.1 (C-2), 160.9 (C-5), 162.0 (C-4′), 163.9 (C-7), 177.7 (C-4) ppm. ESI$^+$-MS: *m/z* (%) = 313 (43) [M + H]$^+$, 335 (27) [M + Na]$^+$, 647 (100) [2M + Na]$^+$.