One-Pot Synthesis of 3-Methylflavones and Their Transformation into (*E*)-3-Styrylflavones via Wittig Reactions

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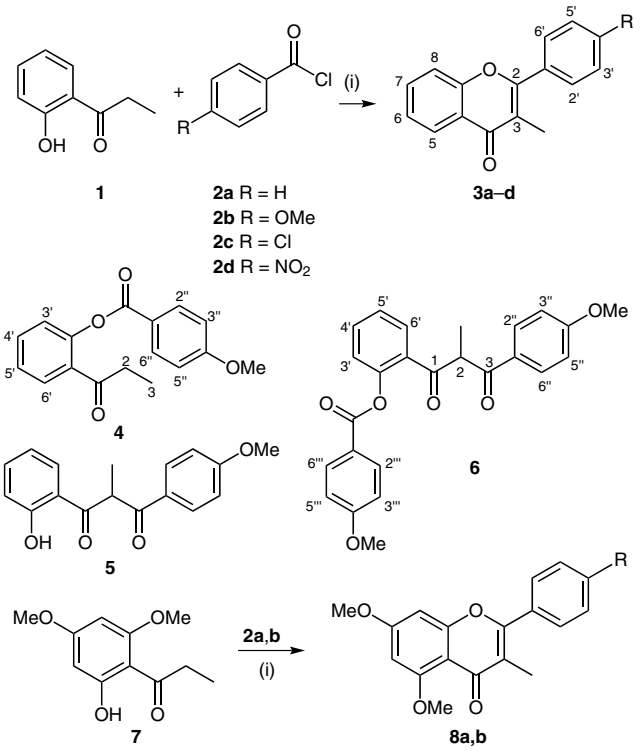
Abstract: An efficient one-pot synthesis of 3-methylflavone derivatives is established. Furthermore, their transformation into phosphorus ylides, which are then used in the diastereoselective synthesis of (*E*)-styrylflavones through Wittig reactions, is also studied.

Key words: 3-methylflavones, lithium bis(trimethylsilyl)amide, phosphonium salts, Wittig reaction, 3-styrylflavones

Flavone derivatives constitute one of the major classes of naturally occurring oxygen-containing heterocycles, and their abundance in plants, fruits and vegetables make them important human dietary constituents.[1,2] Their association with biological activities,[3] such as anticancer,[4] anti-inflammatory[5] and anti-oxidant[6] has important potential consequences. 3-Methylflavones are scarce in Nature, with only four derivatives having been isolated from the aerial parts of *Eugenia kurzii*: 3-methylapigenin, 3-methylluteolin and their 5-*O*-rhamnoside derivatives.[7] Synthetic derivatives are also uncommon; the methyl ethers of 3-methylapigenin and 3-methylluteolin were synthesized to confirm the structures of the natural aglycones,[7] and a few years ago we disclosed the synthesis of 3-methylluteolin[8] and reported on its potential to prevent low-density lipoproteins (LDL) oxidation.[9] In both cases the 3-methylflavones were obtained by modified Baker–Venkataraman transformations. As far as we are aware, only a single total synthesis of 3-methylluteolin has been published and the overall yield was very low (less than 20%).[8] The synthesis, anti-oxidant and antibacterial activities were reported for twenty 3-methylflavones,[10] these flavones having been obtained by cyclodehydrogenation of the corresponding 2′-hydroxy-α-methylchalcones in overall yields of below 50%.

We previously developed a new and efficient synthetic route toward 3-aroylflavones involving reactions of 2′-hydroxyacetophenones with aroyl chlorides in the presence of lithium bis(trimethylsilyl)amide.[11] The good yields and the experimental simplicity prompted us to use this method for the synthesis of 3-methylflavones (Scheme 1), not only because these derivatives can have potentially important biological activities, but also because they can be used to generate new chromone derivatives. In addition, we also studied their transformation into phosphonium salts, which were further used in Wittig reactions with various benzaldehydes to afford 3-styrylflavones (Scheme 2).



Scheme 1 Synthesis of 3-methylflavones **3a**–**d** and **8a**,**b**. *Reagents and conditions*: (i) (1) LiHMDS, anhydrous toluene, r.t.; (2) HCl (37%), r.t.

The synthetic approach to the 3-methylflavones started with the reaction of 2′-hydroxypropiophenone (**1**) with *p*-methoxybenzoyl chloride (**2b**) in the presence of an excess amount of lithium bis(trimethylsilyl)amide (LiHMDS),[12] followed by treatment with hydrochloric acid (Table 1, entry 1). Under these conditions the desired product, 3-methyl-4′-methoxyflavone (**3b**), was obtained in a low yield, whilst compounds **4**, **5** and **6** were obtained as the major products (Scheme 1).[13] Based on our previously established conditions for analogous transformations,[11] we decided to increase the amount of base and to use longer reaction times in both steps (Table 1, entry 2), particularly for the second step (after the addition of HCl), since the isolation of products **5** and **6** indicates that a longer reaction time is needed to allow the β-diketone intermediate to cyclize in the acidic medium. As can be seen in

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Table 1, it was necessary to optimize the reaction conditions (reaction time and/or amount of base) in each case, but eventually the flavone derivatives **3a–d** were obtained in good yields (Table 1, entries 2, 3, 5 and 6).[14] The results indicated that β-diketone formation was favored by the presence of strong electron-withdrawing or electron-donating groups (e.g., *p*-methoxybenzoyl and *p*-nitrobenzoyl chlorides, Table 1, entries 2 and 3), while the cyclization step was less affected by these substituents.

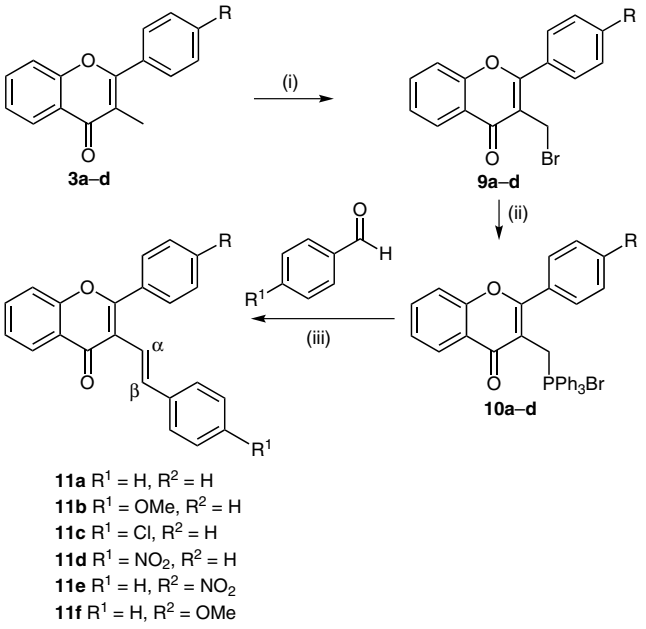
Taking into consideration that the available methodologies for synthesis of natural 5,7-dihydroxy-3-methylflavones involve several steps, and consequently reduced yields, we applied our procedure to the synthesis of new 3-methyl-5,7-dimethoxyflavones **8a**,**b** (Scheme 1). These flavones were obtained in moderate yields (Table 1, entries 7 and 8), but in view of the fewer steps and purifications required, this process represents a significant synthetic development for these materials.

Table 1 Optimization Studies on the Synthesis of 3-Methylflavones **3a–d** and **8a**,**b**

Entry	Product	Equiv of base	Time before HCl (h)	Time after HCl (h)	Yield (%)
1	**3b**	4.5	3	2	13
2	**3b**	4.7	5	45	80
3	**3d**	4.7	4.5	41	74
4	**3a**	5	19	44	40
5	**3a**	5	27	72	70
6	**3c**	5	19	44	90
7	**8a**	4.7	12	25	40
8	**8b**	4.7	12	25	31

The main feature of the ^{1}H NMR spectra of the 3-methylflavones was the singlet at δ 2.09–2.19 due to the 3-CH_3 proton resonance.[15] The aliphatic regions of the ^{1}H NMR spectra of 3-methyl-5,7-dimethoxyflavones **8a**,**b** also present singlets due to the 5- and 7-OCH_3 groups at δ 3.87–3.96. Other important signals of these new 3-methylflavones are the aromatic proton resonances of H-6 and H-8 at δ 6.34–6.36 and δ 6.44–6.45, respectively, with typical *meta*-coupling constants (^4J = 2.3 Hz).

Having established an efficient synthetic route for 3-methylflavones, we next sought to use them in Wittig reactions toward the synthesis of 3-styrylflavones. The reactions of 3-methylflavones with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide[16] afforded the desired 3-bromomethylflavones **9a–d** in good yields (50–87%) (Scheme 2).[17] Both the ^{1}H and ^{13}C NMR spectra confirmed the structures of flavones **9a–d**, the most important resonances being those due to the 3-CH_2Br group (δ_H 4.43–4.67; δ_C 24.4–33.7).[18]



Scheme 2 Synthesis of (*E*)-3-styrylflavones **11a–f**. *Reagents and conditions*: (i) NBS, benzoyl peroxide, CCl_4, reflux; (ii) Ph_3P, anhydrous toluene, reflux; (iii) NaH, anhydrous THF, r.t.

The next step in our strategy was the synthesis of the 3-(bromotriphenylphosphoranyl)methylflavones **10a–d** (Scheme 2), by the reaction of 3-bromomethylflavones **9a–d** with triphenylphosphine in anhydrous toluene.[19,20] In addition to the characteristic signals of the flavone moiety, significant features of the ^{1}H and ^{13}C NMR spectra of compounds **10a–d**[21] were the proton and carbon resonances of the methylene group, both appearing as doublets due to coupling with phosphorus (δ_H 5.19–5.48, J ~ 14 Hz; δ_C 23.3–23.8, J ~ 50 Hz).

Following our earlier work on the synthesis of 3-styrylchromones using the Wittig reaction,[22,23] 3-(bromotriphenylphosphoranyl)methylflavones **10a–d** were used as the sources of ylides for the synthesis of 3-styrylflavones **11a–f** (Scheme 2).[24,25] Products **11a–f** were obtained in moderate to good yields (45–80%) (Table 2), although all attempts to improve the yields of this transformation were not successful. However, careful analysis of the reaction mixture allowed the isolation of the corresponding 3-methylflavones **3a–d** in yields from 19–40%.[24] It was observed that an electron-withdrawing group on the benzaldehyde improved the yield (80%, Table 2, entry 10) compared with the unsubstituted case (70%, Table 2, entry 2); when an electron-donating group was present, it was necessary to heat the reaction and the yield was lower (65%, Table 2, entry 13).

It should be noted that all the 3-styrylflavones were obtained with a *trans*-configured vinylic system (J ~ 16 Hz), and this result is in accord with those previously reported for the Heck reaction.[26] The observed *trans* stereochemistry is in keeping with Wittig reactions involving stabilized ylides.[27,28] This indicates that the chromone nucleus acts

Table 2 Optimization of the Wittig Reactions in the Synthesis of (*E*)-3-Styrylflavones **11a–f**

Entry	Product	Equiv of base	Time to ylide formation (min)	Time after aldehyde addition (h)	Yield (%)
1	**11a**	1	50	48	55
2	**11a**	1.2	30	6	70
3	**11b**	1	60	4	23
4	**11b**	1	10	3	38
5	**11b**	1.2	5	3 h 50 min	45
6	**11c**	1.2	30	2 h 30 min	55
7	**11c**	1	15	3 h 50 min	45
8	**11d**	1.2	30	3	60
9	**11d**	1.2	20	2 h 40 min	67
10	**11e**	1.2	10	1	80
11	**11e**	1.2	30	1 h 20 min	75
12	**11f**	1.2	30	6	45
13	**11f**	1.2	30	2 (60 °C)	65

as an electron-withdrawing group and not as an electron-donating group, as might be anticipated on considering the conjugation present between the heterocyclic oxygen atom and the ylide.

In conclusion, we have established a very efficient route for the synthesis of 3-methylflavones, which can be successfully applied in the synthesis of natural derivatives. These compounds can also be transformed into phosphonium salts and used as the source of phosphorus ylides, which can be further used in diastereoselective syntheses of (*E*)-styrylflavones via a Wittig reaction.

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(13) **2-Propionylphenyl 4-Methoxybenzoate (4)**
Yield: 46 mg (15%). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.2 Hz, 3 H, H-3), 2.92 (q, *J* = 7.2 Hz, 2 H, H-2), 3.90 (s, 3 H, 4″-OCH_3), 7.00 (d, *J* = 9.0 Hz, 2 H, H-3″,5″), 7.22 (dd, *J* = 1.3, 8.1 Hz, 1 H, H-3′), 7.34 (ddd, *J* = 1.3, 7.0, 8.1 Hz, 1 H, H-5′), 7.55 (ddd, *J* = 1.3, 7.0, 8.1 Hz, 1 H, H-4′), 7.81 (dd, *J* = 1.3, 8.1 Hz, 1 H, H-6′), 8.16 (d, *J* = 9.0 Hz, 2 H, H-2″,6″).
1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-methylpropane-1,3-dione (5)
Yield: 137 mg (30%). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 7.0 Hz, 3 H, 2-CH_3), 3.87 (s, 3 H, 4″-OCH_3), 5.23 (q, *J* = 7.0 Hz, 1 H, H-2), 6.86 (ddd, *J* = 1.2, 7.2, 8.1 Hz, 1 H, H-5′), 6.95 (d, *J* = 8.1 Hz, 2 H, H-3″,5″), 7.00 (dd, *J* = 1.2, 8.1 Hz, 1 H, H-3′), 7.46 (ddd, *J* = 1.2, 7.2, 8.1 Hz, 1 H, H-4′), 7.69 (dd, *J* = 1.2, 8.1 Hz, 1 H, H-6′), 7.95 (d, *J* = 8.1 Hz, 2 H, H-2″,6″), 12.09 (s, 1 H, 2-O*H*).
2-[3-(4-Methoxyphenyl)-2-methyl-3-oxo-propanoyl]-phenyl 4-Methoxybenzoate (6)
Yield: 77 mg (25%). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 7.0 Hz, 3 H, 2-CH_3), 3.83 (s, 3 H, 4″-OCH_3), 3.88 (s, 3 H, 4‴-OCH_3), 5.07 (q, *J* = 7.0 Hz, 1 H, H-2), 6.80 (d, *J* = 9.0 Hz, 2 H, H-3″,5″), 6.93 (d, *J* = 9.0 Hz, 2 H, H-3‴,5‴), 7.20 (dd, *J* = 1.1, 8.1 Hz, 1 H, H-6′), 7.32 (ddd, *J* = 1.1, 7.0, 8.1 Hz, 1 H, H-5′), 7.53 (ddd, *J* = 1.1, 7.0, 8.1 Hz, 1 H, H-4′), 7.77 (dd, *J* = 1.1, 8.1 Hz, 1 H, H-3′), 7.81 (d, *J* = 9.0 Hz, 2 H, H-2″,6″), 8.04 (d, *J* = 9.0 Hz, 2 H, H-2‴,6‴).
(14) **3-Methylflavones 3a–d, 8a,b; General Procedure**
2′-Hydroxypropiophenone (**1**) (0.15 mL, 1.09 mmol) was dissolved in anhydrous toluene (5 mL) in a screw-cap vial, equipped with a magnetic stir bar and sealed with a septum. The solution was cooled to 0 °C under N_2 and LiHMDS (5.14 mL in THF, 5.13 mmol) was added quickly via a syringe. The solution was stirred for approximately 30 min before the addition of aroyl chloride **2a–d** (1.42 mmol) in one portion. The mixture was removed from the ice-bath and stirred at r.t. for the appropriate period of time (Table 1). HCl (4 mL, 37%) was added and the resulting solution stirred at r.t. for the requisite amount of time (Table 1). H_2O (50 mL)

and ice (30 g) were added and the mixture was extracted with EtOAc (3 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (gradient: PE→PE–EtOAc, 4:1). After solvent evaporation, the expected 3-methylflavones **3a–d** and **8a**,**b** were obtained in very good yields (see Table 1).

(15) **3-Methyl-5,7,4′-trimethoxyflavone (8b)**
Yield: 110 mg (31%); white powder; mp 188–190 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, 3-CH_3), 3.87 (s, 3 H, 4′-OCH_3), 3.88 (s, 3 H, 5-OCH_3), 3.95 (s, 3 H, 7-OCH_3), 6.34 (d, *J* = 2.3 Hz, 1 H, H-6), 6.44 (d, *J* = 2.3 Hz, 1 H, H-8), 7.01 (d, *J* = 6.9 Hz, 2 H, H-3′,5′), 7.58 (d, *J* = 6.9 Hz, 2 H, H-2′,6′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 11.6 (3-*C*H$_3$), 55.4 (5-O*C*H$_3$), 55.6 (4′-O*C*H$_3$), 56.2 (7-O*C*H$_3$), 92.2 (C-8), 95.7 (C-6), 108.0 (C-4a), 113.7 (C-3′,5′), 118.5 (C-3), 125.7 (C-1′), 130.4 (C-2′,6′), 158.1 (C-2), 159.6 (C-8a), 160.7 (C-7), 160.8 (C-4′), 163.6 (C-5), 177.8 (C-4). MS (ESI): *m*/*z* (%) = 327 (100) [M + H]$^+$, 349 (8) [M + Na]$^+$. HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}O_5$: 326.1154; found: 326.1153.

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(17) **3-Bromomethylflavones 9a–d; General Procedure**
To a solution of the appropriate 3-methylflavone **3a–d** (0.17 mmol) in CCl_4 (40 mL) was added benzoyl peroxide (8.2 mg, 0.033 mmol) and NBS (39 mg, 0.22 mmol). The mixture was heated at reflux temperature under an N_2 atm for 6–24 h (depending on the substituent). The solvent was evaporated and the residue was taken in $CHCl_3$ (40 mL) and the obtained solution washed with H_2O (3 × 20 mL). The organic layer was concentrated and purified by thin-layer chromatography (CH_2Cl_2–hexane, 8:2) affording 3-bromomethylflavones **9a–d** (**9a**, 87%; **9b**, 50%; **9c**, 50%; **9d**, 60%).

(18) **3-Bromomethyl-4′-methoxyflavone (9b)**
Yield: 30 mg (50%); yellow powder; mp 161–163 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, 4′-OCH_3), 4.67 (s, 2 H, 3-CH_2), 7.05 (d, *J* = 8.9 Hz, 2 H, H-3′,5′), 7.42 (br dd, *J* = 7.0, 8.0 Hz, 1 H, H-6), 7.49 (br d, *J* = 8.0 Hz, 1 H, H-8), 7.68 (ddd, *J* = 1.6, 7.0, 8.0 Hz, 1 H, H-7), 7.74 (d, *J* = 8.9 Hz, 2 H, H-2′,6′), 8.24 (dd, *J* = 1.6, 8.0 Hz, 1 H, H-5). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 30.9 (3-*C*H$_2$), 55.5 (4′-O*C*H$_3$), 114.2 (C-3′,5′), 117.9 (C-8), 118.1 (C-3), 122.7 (C-4a), 125.3 (C-6), 126.1 (C-5), 130.0 (C-2′,6′), 130.3 (C-1′), 133.9 (C-7), 156.0 (C-8a), 161.8 (C-4′), 163.8 (C-2), 176.6 (C-4). MS (ESI): *m*/*z* (%) = 345 (47) [^{79}Br, M]$^+$, 347 (40) [^{81}Br, M]$^+$, 367 (100) [^{79}Br, M + Na]$^+$, 369 (90) [^{81}Br, M + Na]$^+$. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}BrO_3$: 345.0133; found: 345.0142.

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(20) **3-(Bromotriphenylphosphoranyl)methylflavones 10a–d; General Procedure**
To a solution of the appropriate 3-bromomethylflavone **9a–d** (0.06 mmol) in anhydrous toluene (10 mL) was added PPh_3 (16 mg, 0.06 mmol). The mixture was heated at reflux temperature under an N_2 atm for 24 h, after which the solvent was evaporated to give the corresponding 3-(bromotriphenylphosphoranyl)methylflavone **10a–d** (**10a**, 67%; **10b**, 58%; **10c**, 64%; **10d**, 60%).

(21) **3-(Bromotriphenylphosphoranyl)methyl-4′-chloroflavone (10c)**
Yield: 21 mg (64%); white powder; mp 282–284 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.33 (d, *J* = 13.8 Hz, 2 H, 3-CH_2), 7.34 (ddd, *J* = 1.3, 7.0, 8.0 Hz, 1 H, H-6), 7.43 (br d, *J* = 8.0 Hz, 1 H, H-8), 7.46–7.52 (m, 8 H, PPh_3), 7.61–7.71 (m, 10 H, H-2′,6′, H-7 and 7 H of PPh_3), 7.77 (dd, *J* = 1.3, 8.0 Hz, 1 H, H-5), 7.87 (d, *J* = 9.0 Hz, 2 H, H-3′,5′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.6 (d, *J* = 50.0 Hz, 3-*C*H$_2$), 111.8 (C-3), 118.0 (C-8), 119.1 (C-4a), 121.3 (C-1′), 125.4 (C-5), 125.7 (C-6), 129.5 (C-1 of PPh_3), 129.7 (C-3,5 of PPh_3), 129.9 (C-4 of PPh_3), 130.6 (C-3′,5′), 133.9 (C-2,6 of PPh_3), 134.5 (C-7), 134.6 (C-2′,6′), 137.8 (C-4′), 155.6 (C-8a), 163.7 (C-2), 176.4 (C-4). MS (ESI): *m*/*z* (%) = 531 (100) [^{35}Cl, M]$^+$, 532 (56) [^{35}Cl, M + H]$^+$, 533 (40) [^{37}Cl, M]$^+$. HRMS (ESI): *m*/*z* calcd for $C_{34}H_{25}ClO_2P$: 531.1264; found: 531.1275.

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(24) **(*E*)-3-Styrylflavones 11a–f; General Procedure**
To a suspension of the appropriate 3-(bromotriphenylphosphoranyl)methylflavone **10a–d** (0.022 mmol) in THF (20 mL) was added NaH (0.5 mg, 0.022 mmol) and the mixture was stirred for the appropriate amount of time (Table 2). The appearance of coloration and the disappearance of the suspension due to the phosphonium salt was indicative of ylide formation. The appropriate benzaldehyde (2.3 μL, 0.022 mmol) was added and the mixture was stirred for the time given in Table 2. The solvent was evaporated and the residue was taken in CH_2Cl_2 (20 mL) and then washed with H_2O (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by thin-layer chromatography (CH_2Cl_2) to give the desired (*E*)-3-styrylflavones **11a–f** (see yields in Table 2) and 3-methylflavones **3a–d** (**3a**, 19%; **3b**, 40%; **3c**, 28%; **3d**, 20%).

(25) **(*E*)-3-(4-Nitrostyryl)flavone (11d)**
Yield: 6 mg (67%); orange powder; mp 174–176 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 16.2 Hz, 1 H, H-α), 7.26–7.30 (m, 1 H, H-4″), 7.33 (t, *J* = 7.9 Hz, 2 H, H-3″,5″), 7.38 (br d, *J* = 7.9 Hz, 2 H, H-2″,6″), 7.48 (ddd, *J* = 1.7, 7.2, 8.3 Hz, 1 H, H-6), 7.52 (dd, *J* = 1.7, 7.2 Hz, 1 H, H-8), 7.73 (ddd, *J* = 1.7, 7.2, 8.3 Hz, 1 H, H-7), 7.95 (d, *J* = 16.2 Hz, 1 H, H-β), 7.97 (d, *J* = 9.1 Hz, 2 H, H-2′,6′), 8.33 (dd, *J* = 1.7, 7.2 Hz, 1 H, H-5), 8.40 (d, *J* = 9.1 Hz, 2 H, H-3′,5′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 117.8 (C-8), 118.6 (C-α), 118.9 (C-3), 123.4 (C-4a), 123.7 (C-3′,5′), 125.5 (C-6), 126.4 (C-5), 126.6 (C-2″,6″), 128.1 (C-4″), 128.7 (C-3″,5″), 130.9 (C-2′,6′), 133.9 (C-7), 136.3 (C-β), 137.5 (C-1″), 139.2 (C-1′), 148.7 (C-4′), 155.4 (C-8a), 159.6 (C-2), 177.1 (C-4). MS (ESI): *m*/*z* (%) = 370 (60) [M + H]$^+$, 392 (99) [M + Na]$^+$. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{15}NO_4$: 369.1001; found: 369.1003.

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