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Microwave-Promoted, One-Pot, Solvent-Free Synthesis of 4-Arylcoumarins from 2-Hydroxybenzophenones

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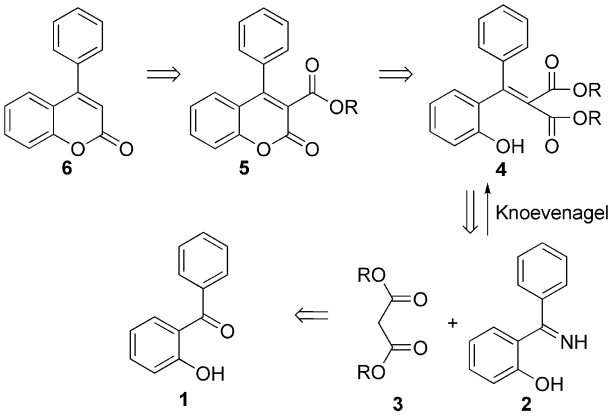
4-Arylcoumarins are synthesized in very good yields through solvent-free microwave irradiation of 2-hydroxybenzophenones and alkyl malonate in the presence of DBU. The one-pot synthesis is carried out with Knoevenagel condensation, intramolecular lactonization, and decarboxylation reactions. The method can be applied to a broad scope of neoflavonoids.

Introduction

The coumarin nucleus is widely distributed in natural products, such as neoflavonoids (4-arylcoumarins) and 3-arylcoumarins. In particular, 4-aryl derivatives constitute a subgroup of flavonoids that have received considerable attention, as they exhibit important biological activities such as anti-HIV,[1] antimalarial,[2,3] antibacterial,[4] and cytotoxic properties.[5] Several natural and synthetic polyoxygenated 4-arylcoumarins have been evaluated as the nonisomerizable analogues of combretastatin A-4, which is an important antitubulin agent that interacts with the binding site of colchicine.[6,7]

The use of microwave irradiation in the synthesis of coumarins has been extensively studied.[8,9] Microwave-assisted organic synthesis (MAOS) has shown to be a valuable tool for reducing reaction times, getting cleaner reactions, improving yields, simplifying workup, and designing energy-saving protocols. The increasing demand for clean and efficient "ecofriendly" chemical syntheses has focused general interest on solvent-free reactions, which when combined with microwave irradiation, have advantages from economical and environmental standpoints.[10–13] One of the predominantly employed strategies for the synthesis of coumarins is based on the Knoevenagel condensation of salicyl aldehydes and active methylene compounds. Besides the use of aldehydes,[14,15] there are some reports on the use of 2-hydroxyacetophenones[16] for the synthesis of 4-methylcoumarins[17] and on the use of 2-hydroxybenzophenones for the synthesis of 3,4-diphenylcoumarins by condensation with phenylacetic acids,[18] but no reports on the use of 2-hydroxybenzophenones for the synthesis of 4-arylcoumarins are known. There are also some papers on Knoevenagel condensation of benzophenones with different activated methylene compounds, but the reactions proceed to give products in moderate yields.[19–21] These precedents, as well as prior work by Charles[22–28] and Bihlmayer[29] on the reactivity of benzophenones towards active methylene compounds, and which reported higher reactivity for diarylketimines in Knoevenagel condensation, led us to design a retrosynthetic approach to neoflavonoids on the basis of the imine of 2-hydroxybenzophenone **2** instead of ketone **1** (Scheme 1).



Scheme 1. Retrosynthetic analysis of 4-arylcoumarins.

The key step in the retrosynthesis outlined in Scheme 1 is a microwave Knoevenagel condensation. Subsequent lactonization of intermediate **4** followed by decarboxylation should lead to the formation of the neoflavonoid skeleton (i.e., **6**).

Results and Discussion

As a model, the synthesis of the basic 4-phenylcoumarin skeleton was studied. So, benzophenone **1a** was trans-

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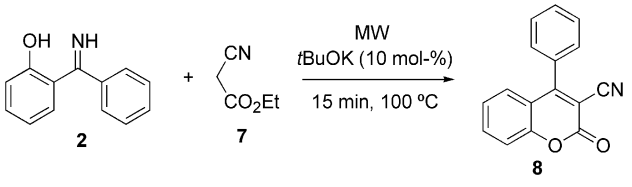
formed into corresponding imine **2** following the method described by Perlmutter et al.[30] for benzophenones with a hydroxy group at the 2-position. The procedure is very simple and is carried out in the absence of solvent,[31] providing 50% yield of the product. The study of the Knoevenagel condensation with compounds containing an active methylene group was limited to symmetric compounds, as unsymmetric substrates will give mixtures of *E*/*Z* isomers and only one of them can lactonize to the neoflavonoid skeleton. Thus, Meldrum's acid was treated with **2** under microwave irradiation under different conditions, in the absence or in the presence of bases such as *t*BuOK or piperidine, but in no case was the product obtained in significant quantities.

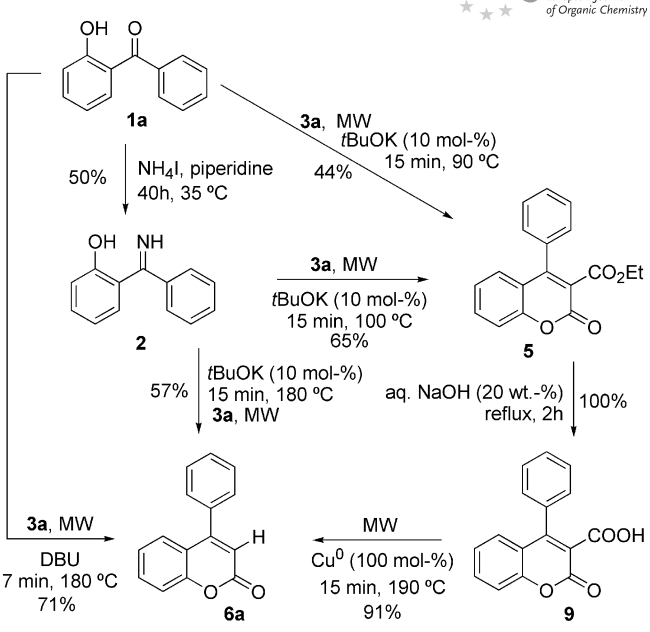
Meldrum's acid was replaced by malononitrile because there were precedent in the literature that it condensed with the imine of benzophenone.[26,32] As in the previous case, numerous tests were conducted in the absence and presence of a base (piperidine or *t*BuOK) and under different conditions, but unfortunately none of them provided the desired compound.

Despite the drawbacks discussed earlier about the use of unsymmetrical active methylene groups, we decided to test the condensation of ethyl cyanoacetate, which has an intermediate pK_a value of 13.1, which is between those of malononitrile (pK_a = 11.1) and diethyl malonate (pK_a = 16.4). Thus, ethyl cyanoacetate and imine **2** were irradiated with microwaves (10 min, 180 °C) in the presence of *t*BuOK (10 mol-%). *t*BuOK was the base chosen, as it has proven to be particularly useful in MAOS and has been applied successfully to obtain various skeletons (4-aminoquinazolines,[33] indolines,[34] and pyrazole [3,4-*d*] pyrimidine[35]). This allowed us to isolate a compound whose characterization confirmed that the condensation had taken place, and as expected, the cyclization occurred spontaneously to form the neoflavonoid skeleton, obtaining compound **8** in 47% yield (Scheme 2).



Scheme 2.

Although the yield achieved was moderate, one must recall that the Knoevenagel reaction leads to both the *E* and *Z* isomers, yet only the *Z* isomer can cyclize. This result raised the possibility of using diethyl malonate (**3a**), whose symmetry would avoid the existence of geometric isomers and both ester functions are able to build the coumarin nucleus. When imine **2** was treated with diethyl malonate (**3a**) in the presence of *t*BuOK (10 mol-%) under microwave irradiation for 15 min at 100 °C the reaction was successful, and the condensation–cyclization took place to give neoflavonoid **5** in 65% yield (Scheme 3).



Scheme 3.

Hydrolysis of the ester group in the 3-position of the coumarin with aqueous NaOH gave 2-oxo-4-phenyl-2*H*-chromene-3-carboxylic acid (**9**) in quantitative yield. This acid was decarboxylated by using copper salts, as this method was described as being compatible with microwave irradiation to decarboxylate aromatic carboxylic acids[36] or indoles.[37] Several tests were conducted with copper metal or copper(II) salts (carbonate and chloride) under solvent-free conditions or in the presence of the ionic liquid 1-butyl-3-methyl imidazolium chloride. In all cases, the decarboxylated compound was obtained, but the best performance (91%) was obtained with copper metal (100 mol-%). The optimized conditions were irradiation in a single-mode microwave oven for 15 min at 190 °C at a power of 300 W (Scheme 3).

Therefore, the 4-phenylcoumarin (**6a**) neoflavonoid skeleton was successfully synthesized. The route consists of four steps with an overall yield of 30%. Two stages are carried out in a microwave oven and two with conventional heating. The starting materials, 2-hydroxybenzophenone and diethyl malonate, are easily affordable.

In an effort to improve the process, the condensation, cyclization, hydrolysis, and decarboxylation sequence was attempted in one pot by raising the temperature (180 °C) to favor the decarboxylation step. In this way, **6a** was obtained from imine **2** in 57% yield (Scheme 3). Although the overall yield of the reaction from 2-hydroxybenzophenone is similar (29%), the process was carried out in two stages, with the consequent savings in effort, energy, and reagents.

These results caused us to think about bypassing the imine formation stage, because it occurs in moderate yield. However, because it was already reported that the direct condensation of 2-hydroxybenzophenone with diethyl malonate was low yielding, we decided to check its enhancement by microwave irradiation and performed the

Table 1. Synthesis of 4-arylcoumarins **6** from 2-hydroxybenzophenones **1**.

Entry	2-Hydroxybenzophenone				Alkyl malonate	4-Arylcoumarin	Yield [%][a]
		R^1	R^2	R^3			
1	**1a**	H	H	H	**3a**	**6a**	71
2	**1a**	H	H	H	**3b**	**6a**	77
3	**1b**	H	OMe	H	**3b**	**6b**	75
4	**1c**	H	OMe	Me	**3b**	**6c**	76
5	**1d**	OMe	H	H	**3b**	**6d**	75
6	**1e**	OMe	OMe	H	**3b**	**6e**	75
7	**1f**	OMe	H	*t*Bu	**3b**	**6f**	62
8	**1g**	OH	H	H	**3b**	**6d**	75
9	**1g**	OH	H	H	**3a**	**6g** (R^1 = OEt)	62 (23, R^1 = OH)[b]
10	**1h**	OH	H	*t*Bu	**3b**	**6f**	79
11	**1h**	OH	H	*t*Bu	**3a**	**6h** (R^1 = OEt)	73 (14, R^1 = OH)[b]
12	**1i**	Cl	H	H	**3b**	**6i**	55

[a] Reactions were heated at 180 °C for 7 min. All yields are for isolated products with previous purification by flash chromatography with 2-hydroxybenzophenone/alkyl malonate/DBU (1:1.5:0.5). [b] Yield of nonalkylated neoflavonoid is given in parentheses.

whole process in one pot. Hence, the use of *t*BuOK as a base under different conditions (temperature, irradiation power, time, and molar ratio of *t*BuOK) showed that at moderate temperatures (90 °C) the neoflavonoid skeleton in coumarin **5** was obtained directly, but in moderate yield (44%), and in no case could the formation of decarboxylated product **6a** be detected (Scheme 3). In this way, the synthesis of neoflavonoid **6a** was conducted in three stages: two steps were performed in a microwave oven, and the product was obtained in a slightly improved overall yield of 40% from benzophenone **1a**. This reduced the reaction time and avoided the imine formation step. Presumably, the decarboxylation should require higher temperatures (≈180 °C), as for the decarboxylation of **9** or in the direct synthesis of **6a** from imine **2**. However, irradiation of benzophenone **1a** with diethyl malonate (**3a**) and *t*BuOK at high temperatures led to carbonization. Therefore, other bases were tested and DBU was found to yield better results. With this base and in only one step, the synthesis of neoflavonoid **6a** was achieved from 2-hydroxybenzophenone and diethyl malonate. To optimize the conditions, the influences of temperature, reaction time, and molar ratio between reagents were analyzed. The optimum conditions were thus irradiation of a mixture of **1a/3a/**DBU (molar ratio 1:1.5:0.5) for 7 min at 180 °C, leading to neoflavonoid **6a** in good yield (71%; Scheme 3; Table 1, Entry 1).

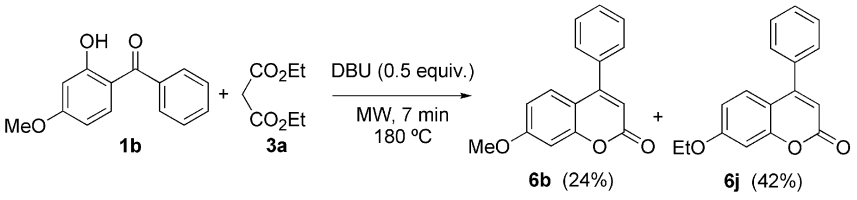
The synthetic routes to 4-phenylcoumarin are summarized in Scheme 3. The drastic reduction in the reaction time, reagents, and energy requirements achieved with the use of DBU, as well as the substantial increase in the overall performance, are quite remarkable.

With the optimized conditions in hand, a series of substituted 2-hydroxybenzophenones were subjected to explore the generality and scope of the process. Thus, 2-hydroxy-4-methoxybenzophenone (**1b**) was treated with diethyl malonate and DBU under the optimized conditions (7 min at 180 °C in a single-mode microwave oven). As might be expected, neoflavonoid **6b** was the result of the Knoevenagel condensation, cyclization, and subsequent decarboxylation sequence. However, it was only obtained in 24% yield, and additionally, **6j** was obtained in 42% yield (Scheme 4).

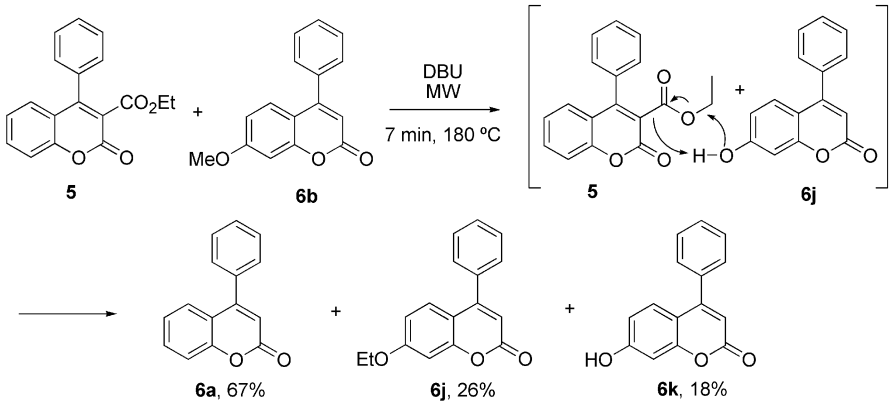
This result was surprising, and one might suppose that the exchange of the methoxy group by the ethoxy group was due to the presence of diethyl malonate. The demethylation should be helped by DBU. To provide evidence for this path, 4,4′-dimethoxybenzophenone was irradiated for 7 min at 180 °C in the presence of DBU (50 mol-%), as this compound – lacking a hydroxy group in the 2-position – would not be able to cyclize to the coumarin skeleton. DBU is not an overly strong base, and it is not described as a demethylating agent. Nonetheless, in the presence of DBU (in the absence of diethyl malonate) and under microwave irradiation 4,4′-dimethoxybenzophenone underwent demethylation to give 4-hydroxy-4′-methoxybenzophenone in low yield (16%). To detect the way in which the ethyl group was transferred, the molar ratio of diethyl malonate (**3a**) with respect to 2-hydroxy-4-methoxybenzophenone (**1b**) was increased; this should encourage the formation of ethoxylated coumarin **6j**. However, when a mixture of **1b/3a/**DBU (1:3:1) was irradiated, the percentage of **6j** did not increase. Therefore, the ethyl group must come from another species in the reaction, and the only remaining compound bearing an ethyl group is coumarin **5**. To test this alternative, a mixture of **5/6b/**DBU (1:1:1) was irradiated under the described conditions and afforded products **6a**, **6j**, and **6k** (Scheme 5). These results are consistent with the possibility that the transferred ethyl group, at least in part, comes from intermediate **5**.

To prevent the formation of mixtures of products and the production of only coumarins with methoxy groups, we decided to exchange ethyl malonate (**3a**) for methyl malonate (**3b**). Under these conditions, only product **6b** was obtained in a similar yield (75%) to the model 4-phenylcoumarin (Table 1, Entries 2 and 3).

To extend the study of this one-step synthesis for neoflavonoids, other 2-hydroxybenzophenones with different positions and natures of the substituents were tested (Scheme 6). Thus, when a methyl group is present in the 4′-position, neoflavonoid **6c** was obtained also in good yield (Table 1, Entry 4). The presence of a methoxy group in the *para* position to the hydroxy group, or two methoxy groups, resulted in the same yield (75%; Table 1, Entries 5 and 6).

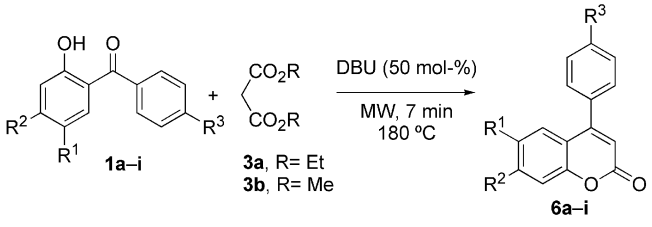


Scheme 4.



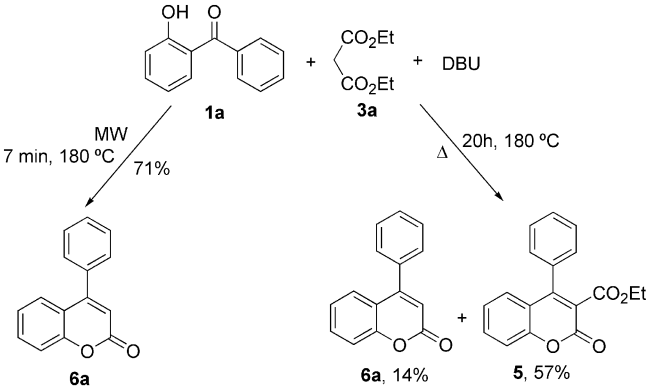
Scheme 5.

A slightly lower yield was obtained when a *t*Bu group was present in ring C of the coumarin (Table 1, Entry 7). As expected, the presence of a second hydroxy group in the aromatic ring resulted in alkylation of the phenol. The reaction occurs in good yield with or without substituents in ring C (Table 1, Entries 8–11). The alkylation step is more effective when it is done with dimethyl malonate instead of diethyl malonate, as evidenced by the presence of some nonalkylated coumarins (Table 1, Entries 9 and 11). The presence of a halogen leads to **6i**, also in good yield (Table 1, Entry 12).



Scheme 6.

To study the influence of microwaves on the formation of neoflavonoids, a mixture of 2-hydroxybenzophenone, diethyl malonate, and DBU was conventionally heated at 180 °C (the same temperature as that reached in the microwave method). After 7 min, the reaction time necessary for the reaction in the microwave method, a considerable amount of **1a** remained unchanged together with the formation of **5**. Compounds **1a** and **5** were in a molar ratio of approximately 2:3, as determined by ^{1}H NMR spectroscopy. The reaction was followed by thin-layer chromatography up to the total consumption of the starting material, which required 20 h. After this time, the mixture was worked up and purified by column chromatography on silica gel, yielding only 14% of neoflavonoid **6a** (Scheme 7). Whereas microwave irradiation leads to neoflavonoids in just 7 min with high yield, conventional heating is less efficient, and the time required is much longer and the decarboxylation process of **5** is much less favored. Because this reaction was found to be thermally driven, the use of microwave irradiation resulted in a considerably reduced reaction time and the yield was significantly increased. The beneficial effect of microwave irradiation may be associated with the quicker formation of dipolar intermediates.



Scheme 7. Microwave versus conventional procedure.

Conclusions

In summary, we have developed a highly efficient and direct solvent-free microwave-assisted synthesis of neoflavonoids from alkyl malonates and 2-hydroxybenzophen-

ones in the presence of DBU, applicable to a broad substrate scope on substituted 2-hydroxybenzophenones. The key step is a Knoevenagel-type condensation followed by lactonization and decarboxylation all in a one-pot reaction. The presence of an additional methoxy group allowed us to detect the existence of a secondary reaction consisting of demethylation and alkylation, where the alkylating agent might be intermediate carboxyalkylcoumarin **5** produced in the reaction. The use of methyl instead of ethyl malonate avoided the formation of mixtures of ethoxylated and methylated compounds. When the reaction is heated by conventional methods the yield is very low, which establishes the importance of the microwave irradiation for the good performance of the reaction. Synthesized neoflavonoids **6b**[38,39] and **6e**[40] show interesting pharmacological properties.

Experimental Section

General: Melting points were measured in open capillaries with a Gallenkamp MPD350.BM.2.5. ^{1}H NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ with a Varian Mercury 300. Low-resolution mass spectra were recorded with a Thermo Finnigan Trace-DSQ spectrometer. Infrared spectra were measured with an FTIR ABB Bomen MB102 instrument with a SPECAC Golden Gate™ accessory. Reaction mixtures were irradiated in an open vessel with a single-mode Discover CEM microwave.

Representative Procedure for the Synthesis of Coumarins 6: A mixture of 2-hydroxy-4-methoxybenzophenone (**1d**; 228 mg, 1 mmol), methyl malonate (**3b**; 240 mg, 1.5 mmol), and DBU (76 mg, 0.5 mmol) was treated with microwave irradiation in an open vessel (100 W, temperature control set at 180 °C measured with an IR sensor) for 7 min. The crude product was dissolved in dichloromethane and purified by flash chromatography (AcOEt/hexane, 1:9) to give **6d** (189 mg, 75%), as a solid.

6d: M.p. 154–155 °C (hexane; ref.[41] 109–110 °C). UV (MeOH): λ = 206, 226, 252, 282, 347 nm. IR (Golden-Gate): $\tilde{\nu}$ = 1714 (C=O), 1564, 1420, 1235, 1178, 1031, 942, 875, 821 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H, OCH_3), 6.35 (s, 1 H, COCH), 6.92 (d, J = 3.0 Hz, 1 H, ArH), 7.11 (dd, J = 9.0, 3.0 Hz, 1 H, ArH), 7.32 (d, J = 9.0 Hz, 1 H, ArH), 7.42–7.48 (m, 2 H, ArH), 7.48–7.57 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.0 (q, OCH_3), 110.3 (d, C-3), 115.9 (d, C-5), 118.4 (d, C-7), 119.2 (d, C-8), 119.7 (s, C-4a), 128.5 (d, C-2′,6′), 129.1 (d, C-3′,5′), 129.9 (d, C-4′), 135.5 (s, C-1′), 148.8 (s, C-8a), 155.5 (s, C-4), 156.1 (s, C-6), 161.0 (s, C=O) ppm. MS: m/z (%) = 253 (18) $[M + 1]^+$, 252 (100) $[M]^+$, 224 (57), 209 (25), 181 (33), 165 (26), 153 (42), 152 (74), 127 (26), 77 (32), 58 (33), 51 (32). $C_{16}H_{12}O_3$ (252.08): calcd. C 76.18, H 4.79; found C 75.72, H 4.81.

6c: M.p. 152–153 °C (AcOEt/hexane; ref.[42] 152 °C). IR (Golden-Gate): $\tilde{\nu}$ = 1718 (C=O), 1602, 1373, 1280, 1145, 1118, 1022, 814 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 6.20 (s, 1 H, COCH), 6.78 (dd, J = 8.9, 2.4 Hz, 1 H, ArH), 6.89 (d, J = 2.4 Hz, 1 H, ArH), 7.32 (m, 4 H, ArH), 7.41 (d, J = 8.9 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (q, CH_3), 56.0 (q, OCH_3), 101.3 (d, C-8), 111.9 (d, C-3), 112.4 (d, C-6), 112.9 (s, C-4a), 128.2 (d, C-5), 128.5 (d, C-2′, 6′), 129.7 (d, C-3′, 5′), 133.0 (s, C-1′), 140.0 (s, C-4′), 156.0 (s, C-4), 156.3 (s, C-8a), 161.4 (s, C-2), 163.0 (s, C-7) ppm. MS: m/z (%) = 267 (20) $[M + 1]^+$, 266 (100) $[M]^+$, 239 (23), 238 (91), 223 (19), 222 (30), 195 (11), 165 (27), 152 (16). $C_{17}H_{14}O_3$ (266.09): calcd. C 76.68, H 5.30; found C 76.39, H 5.27.

6e: M.p. 143–145 °C ($EtOH/CH_2Cl_2$; ref.[43] 145–146). UV (MeOH): λ = 207, 238, 259, 299, 351 nm. IR (Golden-Gate): $\tilde{\nu}$ = 1715 (C=O), 1512, 1273, 1229, 1149, 999, 852 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.23 (s, 1 H, COCH), 6.85 (s, 1 H, ArH), 6.90 (s, 1 H, ArH), 7.43–7.53 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6 (q, 2 OCH_3), 100.6 (C-8), 107.6 (d, C-5), 111.6 (s, C-4a), 112.5 (C-3), 128.5 (d, C-2′, 6′), 129.1 (d, C-3′, 5′), 129.8 (d, C-4′), 136.1 (s, C-1′), 146.4 (s, C-8a), 150.4 (s, C-6), 153.2 (s, C-7), 155.8 (s, C-4), 161.4 (s, C=O) ppm. MS: m/z (%) = 283 (29) $[M + 1]^+$, 282 (100) $[M]^+$, 254 (24), 239 (15), 235 (22), 168 (6), 152 (6), 127 (15). $C_{17}H_{14}O_4$ (282.09): calcd. C 72.33, H 5.00; found C 71.93, H 5.47.

6f: M.p. 158–160 °C (AcOEt/hexane). UV (MeOH): λ = 206, 224, 283, 345 nm. IR (Golden-Gate): $\tilde{\nu}$ = 2963, 1714 (C=O), 1567, 1462, 1273, 1237, 1030, 934, 845, 821 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 3.75 (s, 3 H, OCH_3), 6.35 (s, 1 H, COCH), 7.01 (d, J = 2.8 Hz, 1 H, ArH), 7.11 (dd, J = 9.0, 2.9 Hz, 1 H, ArH), 7.32 (d, J = 9.0 Hz, 1 H, ArH), 7.39 (d, J = 8.3 Hz, 2 H, ArH), 7.53 (d, J = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5 [q, $C(CH_3)_3$], 35.1 [s, $C(CH_3)_3$], 56.1 (q, OCH_3), 110.7 (d, C-3), 115.6 (d, C-5), 118.3 (d, C-7), 118.9 (d, C-8), 119.8 (s, C-4a), 126.1 (d, C-3′, 5′), 128.4 (d, C-2′, 6′), 132.6 (s, C-1′), 148.9 (s, C-8a), 153.3 (s, C-4′), 155.5 (s, C-4), 156.0 (s, C-6), 161.2 (s, C=O) ppm. MS: m/z (%) = 309 (23) $[M + 1]^+$, 308 (100) $[M]^+$, 294 (20), 293 (81), 265 (22), 251 (13), 152 (7), 133 (12). $C_{20}H_{20}O_3$ (308.14): calcd. C 77.90, H 6.54; found C 78.15, H 6.65.

6g: M.p. 157–160 °C (hexane). UV (MeOH): λ = 203, 227, 251, 282, 349 nm. IR (Golden-Gate): $\tilde{\nu}$ = 1714 (C=O), 1565, 1488, 1232, 1043, 822 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.0 Hz, 3 H, CH_3), 3.92 (q, J = 7.0 Hz, 2 H, CH_2), 6.34 (s, 1 H, COCH), 6.90 (d, J = 2.9 Hz, 1 H, ArH), 7.10 (dd, J = 9.0, 2.9 Hz, 1 H, ArH), 7.30 (d, J = 9.0 Hz, 1 H, ArH), 7.41–7.46 (m, 2 H, ArH), 7.47–7.56 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (q, OCH_2CH_3), 64.4 (t, OCH_2CH_3), 111.1 (d, C-3), 115.8 (d, C-5), 118.3 (d, C-7), 119.6 (d, C-8), 119.7 (s, C-4a), 128.5 (d, C-2′,6′), 129.1 (d, C-3′, 5′), 129.9 (d, C-4′), 135.6 (s, C-1′), 148.8 (s, C-8a), 155.48 and 155.54 (2s, C-4 and C-6), 161.0 (s, C=O) ppm. MS: m/z (%) = 267 (22) $[M + 1]^+$, 266 (100) $[M]^+$, 252 (10), 238 (34), 237 (34), 210 (78), 181 (30), 153 (19), 152 (32), 127 (15). $C_{17}H_{14}O_3$ (266.09): calcd. C 76.68, H 5.30; found C 77.06, H 5.52.

6h: M.p. 131–132 °C (hexane). UV (MeOH): λ = 206, 225, 283, 350 nm. IR (Golden-Gate): $\tilde{\nu}$ = 2966, 1716 (C=O), 1571, 1429, 1235, 1179, 1048, 938, 819 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.38 (m, 12 H, CH_3), 3.95 (q, J = 6.9 Hz, 2 H, CH_2), 6.33 (s, 1 H, COCH), 6.99 (d, J = 2.7 Hz, 1 H, ArH), 7.09 (dd, J = 9.0, 2.7 Hz, 1 H, ArH), 7.29 (d, J = 9.0 Hz, 1 H, ArH), 7.38 (d, J = 8.2 Hz, 2 H, ArH), 7.52 (d, J = 8.2 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (q, OCH_2CH_3), 31.5 [q, $C(CH_3)_3$], 35.0 [s, $C(CH_3)_3$], 64.4 (t, OCH_2CH_3), 111.5 (d, C-3), 115.6 (d, C-5), 118.2 (C-7), 119.3 (d, C-8), 119.8 (s, C-4a), 126.0 (d, C-3′, 5′), 128.4 (d, C-2′, 6′), 132.6 (s, C-1′), 148.7 (s, C-8a), 153.3 (s, C-4′), 155.4 and 155.5 (2s, C-4 and C-6), 161.2 (s, C=O) ppm. MS: m/z (%) = 323 (23) $[M + 1]^+$, 322 (100) $[M]^+$, 307 (35), 279 (32), 237 (9), 152 (6), 57 (10). $C_{21}H_{22}O_3$ (322.15): calcd. C 78.23, H 6.88; found C 78.28, H 7.14.

6j: M.p. 101–103 °C (hexane). UV (MeOH): λ = 204, 237, 256, 327 nm. IR (Golden-Gate): $\tilde{\nu}$ = 1730 (C=O), 1604, 1376, 1281, 1153, 1106, 1039, 1003, 814 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, J = 7.0 Hz, 3 H, CH_3), 4.09 (q, J = 7.0 Hz, 2 H, CH_2), 6.18 (s, 1 H, COCH), 6.76 (dd, J = 8.9, 2.5 Hz, 1 H, ArH), 6.85

(d, J = 2.5 Hz, 1 H, ArH), 7.34 (d, J = 8.9 Hz, 1 H, ArH), 7.40–7.44 (m, 2 H, ArH), 7.47–7.51 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7 (q, OCH_2CH_3), 64.4 (t, OCH_2CH_3), 101.9 (d, C-8), 112.0 (d, C-3), 112.6 (s, C-4a), 112.9 (d, C-6), 128.1 (d, C-5), 128.6 (d, C-2′, 6′), 129.0 (d, C-3′, 5′), 129.7 (d, C-4′), 135.9 (s, C-1′), 156.0 (s, C-4), 156.3 (s, C-8a), 161.4 (s, C=O), 162.4 (s, C-7) ppm. MS: m/z (%) = 267 (20) $[M + 1]^+$, 266 (100) $[M]^+$, 252 (63), 238 (36), 224 (32), 210 (31), 210 (57), 209 (23), 181 (35), 165 (35), 153 (29), 152 (47). $C_{17}H_{14}O_3$ (266.09): calcd. C 76.68, H 5.30; found C 76.27, H 5.03.

Supporting Information (see footnote on the first page of this article): Experimental procedures and analytical data for compounds **8**, **5**, **9**, **6a**–**c**, and **6e**–**j**; copies of the respective ^{1}H and ^{13}C NMR spectra.

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