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Synthesis of Benzopyran-Fused Flavone Derivatives via Microwave-Assisted Intramolecular C–H Activation

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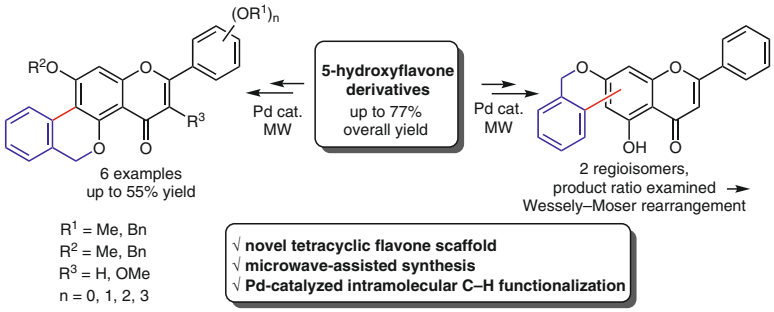
Dedicated to the memory of Prof. Tamás Patonay



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Abstract A microwave-assisted intramolecular direct arylation method for the synthesis of benzopyran-fused flavone derivatives containing natural flavone backbones is described. Different polyalkoxy flavones were synthesized and functionalized with 2-bromobenzyl bromide. The resulting compounds were subjected to palladium-catalyzed intramolecular direct arylation reactions supported by microwave irradiation to produce fused tetracyclic flavones. In the case of the 7-substituted chrysin derivative, the regioselectivity of the coupling was also examined.

Key words flavones, C–H bond activation, palladium, intramolecular direct arylation, microwave chemistry

The 2*H*-benzopyran (2*H*-chromene) moiety is a frequent constituent of natural products and potentially bioactive synthetic compounds.[1] It commonly occurs condensed to other oxygen containing heterocyclic compounds, such as xanthones,[2] chromones,[3] flavones[4] or coumarins,[5] constituting rigid polycyclic structures (Figure 1).

Dibenzopyrans, in particular, are valuable synthetic targets as they offer potent biological activity,[6] can be involved in the design of fluorescent conjugated polymer nanoparticles for cell imaging, and can also be components of polymer solar cells as promising wide band gap polymer donors.[7]

Polycyclic flavone derivatives with fused benzopyran subunit were also isolated from natural sources. These compounds were found to exhibit various biological activities such as immunosuppressive,[8] cytotoxic,[9] antibacterial and antifungal,[10] as well as antitobacco mosaic virus (anti-TMV)[11] activities. The roots of *Baeckea frutescens*, containing Baeckeins A and B (Figure 2), have been used in the traditional Chinese medicine for treating rheumatism and snake bites.[12]

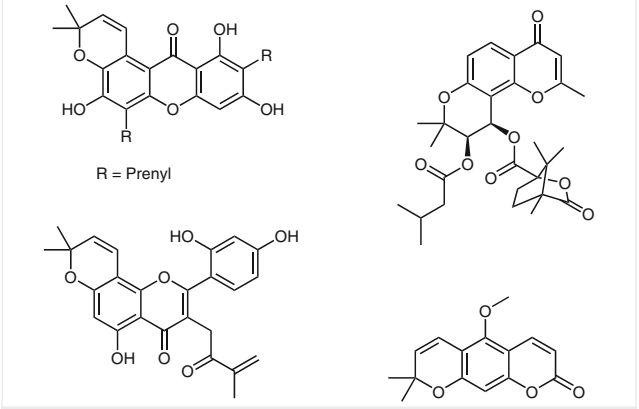


Figure 1 Examples of O-heterocycles fused to a benzopyran moiety

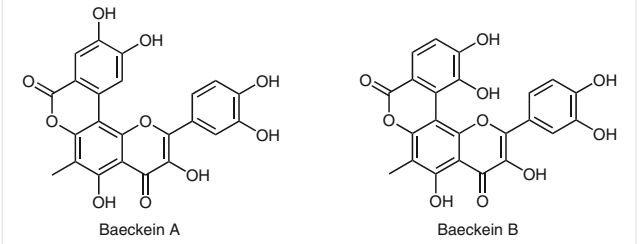


Figure 2 Baeckeins A and B, naturally occurring fused tetracyclic flavones

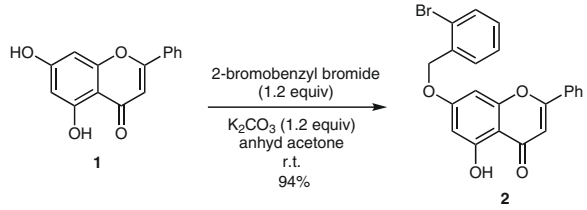
The different palladium-catalyzed cross-coupling reactions have been extensively used in various fields of organic chemistry in the formation of new carbon–carbon and carbon–heteroatom bonds ever since their discovery.[13] However, these methods require the use of metalated arenes,

which often can be synthesized only in multiple steps. Therefore, the C–H arylation of aromatic compounds has attracted attention recently from the researchers as a feasible alternative pathway for the classical cross-coupling methods, providing better atom economy.[14]

Since the pioneering work of Ames,[15] extensive effort has been made to study the palladium-catalyzed direct intramolecular arylation and extend its substrate scope, using various compounds bearing a (pseudo)halogen atom as a leaving group in the *ortho* position to the linker.[16,17] Palladium-catalyzed syntheses of polycyclic flavones have been reported recently,[18] as well as copper-catalyzed preparation of benzofuran fused flavone derivatives.[19] Pardo and coworkers reported the palladium/pivalic acid co-catalyzed synthesis of benzopyran fused 2-pyrone derivatives.[20]

Herein, we report the microwave irradiation-assisted palladium-catalyzed direct intramolecular arylations of various polyalkoxy flavone derivatives and the preparation of the starting materials that were required to carry out these intramolecular couplings.

We envisioned a palladium-catalyzed synthetic route for the preparation of polyannulated fused tetracyclic flavone derivatives including a dibenzopyran motif, starting from the appropriate flavones bearing a (2-bromobenzyl)oxy group at position 5 or 7. Therefore, as a model compound, chrysin (**1**) was reacted with 2-bromobenzyl bromide to provide compound **2** in excellent yield (Scheme 1).



Scheme 1 Synthesis of 2-bromobenzylated chrysin derivative **2**

Although two potentially reactive phenolic hydroxyl groups are represented, only the 7-hydroxy was found to react due to the strong chelating effect between the 5-hydroxy group and the oxo group at position 4. As a model for the ring closure reaction, compound **2** was then used to study the time and temperature dependence as described later.

Moreover, based on these observations, a number of polymethylated flavones **8** containing a free hydroxyl group at position 5 were prepared. First, phloroacetophenone (**3**) was methylated with dimethyl sulfate to obtain **4**, which was then reacted with the corresponding benzaldehyde derivatives **5a–d** under basic conditions to give the appropriate chalcones **6a–d** in Claisen–Schmidt type condensation reactions (Table 1).

Generally, the yields of these reactions were good, except for the preparation of chalcone **6d**, which was obtained only in low yield even when a large excess of **5d** was used. Chalcones **6a–d** were then converted to flavones **7a–d** in good yields (Table 1) by refluxing with a catalytic amount of iodine in DMSO.

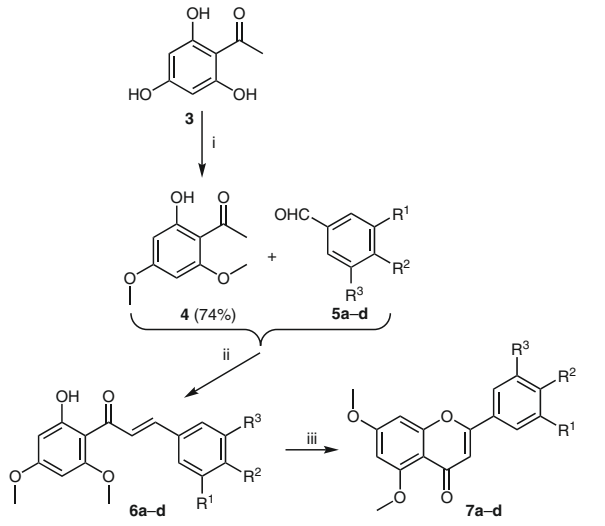
Having obtained flavones **7a–d** containing two to five methoxy groups, a method had to be found to remove the

Biographical Sketches

Krisztina Kónya earned her M.Sc. in 2000 and her Ph.D. in 2005 from the University of Debrecen supervised by Professor Sándor Antus. In her thesis, she dealt with the synthesis of neolignanes with antioxidant properties. Then, she joined Professor Patonay's group in 2005 as an Assistant Lecturer. Since October 2009 she is an Assistant Professor. In 2006, she was a postdoctoral fellow at Professor Prokai's group at the University of North Texas HSC, Fort Worth, Texas. Since 2007 she has focused on studying the formation of the carbon–nitrogen bond in oxygen containing heterocyclic compounds by transition-metal-catalyzed coupling reaction and the use of high-throughput synthetic methods. In the last few years, the utilization of C–H activation is in her focus for the synthesis of new oxygen containing scaffolds.

Zoltán Sipos was born in Vásárosnamény in 1988. He obtained a B.Sc. in chemical engineering in 2012 and an M.Sc. in synthetic chemistry in 2014 at the University of Debrecen (Hungary). He was a Ph.D. student under the supervision of Dr. Krisztina Kónya at the University of Debrecen (Hungary), where he is an assistant lecturer currently. His main research interests include palladium-catalyzed transformations of halochromenoids (halocoumarins, chromones, and flavones, in particular) and application of microwave-assisted organic synthesis in palladium catalysis.

Table 1 Chalcones **6a–d** and Flavones **7a–d** Prepared[a]



R^1	R^2	R^3	Product	Yield (%)[b]	Product	Yield (%)[b]
H	H	H	**6a**	71	**7a**	81
H	OMe	H	**6b**	99	**7b**	77
OMe	OMe	H	**6c**	84	**7c**	76
OMe	OMe	OMe	**6d**	52	**7d**	65

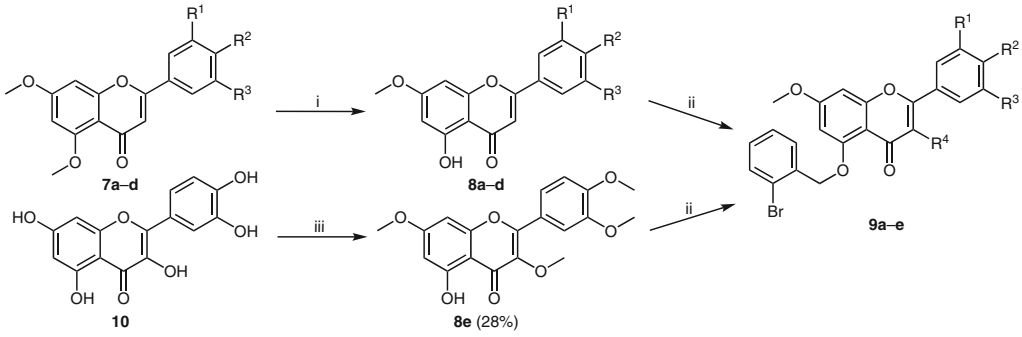
[a] Reagents and conditions: (i) **3** (1.0 equiv), Me_2SO_4 (1.9 equiv), K_2CO_3 (2.0 equiv), acetone; (ii) **4** (1.0 equiv), **5** (1.5 equiv), aq 60% KOH, EtOH, r.t.; (iii) **6a–d** (1.0 equiv), I_2 (0.08 equiv), DMSO, reflux.
[b] Isolated yields.

methyl protecting group from position 5 selectively to obtain compounds **8a–d**. After failing to remove the 5-methyl group with BBr_3 using a method described in the literature,[21] $AlCl_3$ was chosen for the cleavage of the methyl group. The demethylating agent was added to the reaction mixture and the suspension was refluxed in acetonitrile to give the expected 5-hydroxy derivatives **8a–d** in good to excellent yields (Table 2).[22] To our surprise, the TLC spot of the starting materials displayed a lower R_f value (very close to the starting point) compared to the R_f values of the demethylated products even though the latter ones contained polar hydroxyl groups, indicating the formation of hydroxyl groups chelated to the 4-oxo groups.

Quercetin (**10**), obtained as a commercially available starting material, was methylated with methyl iodide, resulting in a mixture of **8e** and the permethylated quercetin. The by-product permethylated quercetin was then washed out with acetone to yield the pure **8e** in 28% yield. Flavones **9a–e** were then prepared by the reaction of **8a–e** and 2-bromobenzyl bromide in the presence of K_2CO_3 at room temperature using DMF as the solvent in good to excellent yields (Table 2).

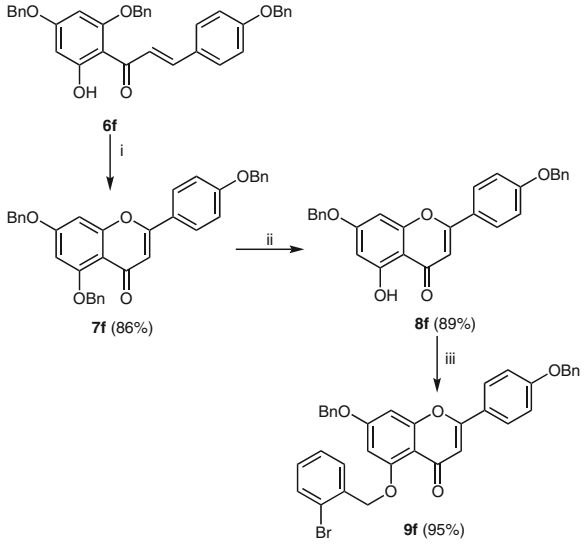
Alternatively, the benzylated analogue of **9b**, that is **9f**, was prepared to compare the reactivity of derivatives bearing different protecting groups. Chalcone **6f** was converted to flavone **7f** by the usual method using 8 mol% iodine and refluxing gently in DMSO (Scheme 2, step 1). Afterwards, **7f** was refluxed in a mixture of acetic acid and water (4:1) to

Table 2 Demethylation of Flavones **7** and Preparation of Flavones **9**[a,b]



R^1	R^2	R^3	R^4	Product	Yield (%)[c]	Product	Yield (%)[c]
H	H	H	H	**8a**	84	**9a**	70
H	OMe	H	H	**8b**	83	**9b**	69
OMe	OMe	H	H	**8c**	90	**9c**	94
OMe	OMe	OMe	H	**8d**	77	**9d**	88
OMe	OMe	H	OMe	**8e**	28	**9e**	95

[a] Reagents and conditions: (i) **7a–d** (1.0 equiv), $AlCl_3$ (2 × 2.5 equiv), MeCN, reflux; (ii) **8a–e** (1.0 equiv), 2-bromobenzyl bromide (1.2 equiv), K_2CO_3 (1.2 equiv), DMF, r.t.; (iii) **10** (1.0 equiv), MeI (4.5 equiv), K_2CO_3 (4.5 equiv), DMF, r.t.
[b] Additional portions of 2-bromobenzyl bromide (0.6 or 1.2 equiv) and K_2CO_3(0.6 or 1.2 equiv) were added if the starting material was not consumed overnight.
[c] Isolated yields.

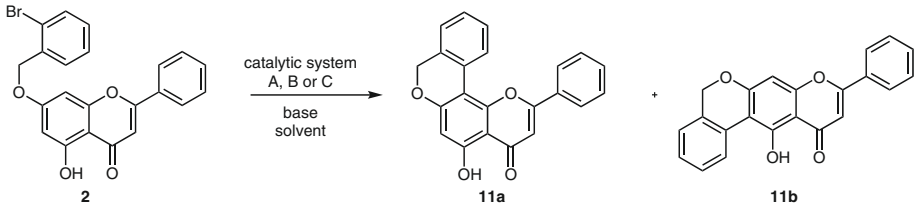


Scheme 2 *Reagents and conditions*: (i) **6f** (1.0 equiv), I_2 (0.08 equiv), DMSO, reflux; (ii) **7f** (1.0 equiv), AcOH/H_2O (4:1), reflux; (iii) **8f** (1.0 equiv), 2-bromobenzyl bromide (1.2 equiv), K_2CO_3(1.2 equiv), DMF, r.t.

afford 7-(benzyloxy)-2-[4-(benzyloxy)phenyl]-5-hydroxy-4*H*-chromen-4-one (**8f**) (Scheme 2, step 2).[23] 2-Bromobenzylated derivative **9f** was then synthesized by the method described above (Scheme 2, step 3). The overall yield for the three steps was 73%.

Our initial experiments toward the synthesis of polyannulated flavones were carried out with chrysin derivative **2** (Table 3). We began the optimization of the reaction conditions with the application of Rawal's method (Table 3, entry 1),[16d] but the desired product was not isolated. Use of pivalic acid as the solvent instead of DMA at 120 °C (entry 2) did not result in any conversion; neither did the reaction in glacial acetic acid, when palladium acetate was used as palladium source instead of $Pd(PPh_3)_4$ (entry 3). Pivalic acid, used as a co-catalyst, might act as a 'proton shuttle' in the concerted metalation-deprotonation (CMD) pathway, thus facilitating the cleavage of the C–H bond.[16f,24] It has previously been effectively used also as the solvent in oxidative inter- or intramolecular C–H arylation reactions.[25] After failing to isolate any product, a different approach was established to carry out the intermolecular ring-closure reaction by using a CEM Discover microwave reactor. The utility of microwave irradiation in organic synthesis is well documented.[26,27] Therefore, the modified conditions of Miura et al.[28] were used, resulting in a complex reaction mixture with modest conversion of the starting material, but the formation of a product was observed by TLC (entry 4), which was then confirmed to be **11b** by NMR spectroscopy. Using a 1:1 mixture of DMF and pivalic acid as solvent at 150 °C resulted in the formation of the same product in 43% yield (entry 5) and the formation of another product was also discovered, but we could not separate it from the starting material. When copper(II) acetate was added to the

Table 3 Screening of Intramolecular Direct Arylation Reaction Conditions



Entry	Catalyst[a]	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	A	KO*t*-Bu (3.0 equiv)	DMA	95[c]	48	–
2	A	KOAc (3.0 equiv)	PivOH	120[c]	24	–
3	B	–	AcOH	130[c]	48	–
4	C	Cs_2CO_3 (2.0 equiv)	DMF	160[d]	1	–
5	C	Cs_2CO_3 (2.0 equiv)	DMF/PivOH (2:1)	150[d]	1	43 **11b**[f]
6[e]	C	Cs_2CO_3 (2.0 equiv)	DMF/PivOH (2:1)	150[d]	1	–
7	C	KOAc (3.0 equiv)	DMF/PivOH (1:1)	150[d]	1	8.2 **11b**[f]
8	C	K_3PO_4 (3.0 equiv)	DMF/PivOH (1:1)	150[d]	2	73[g]

[a] Catalyst A: $Pd(PPh_3)_4$; Catalyst B: $Pd(OAc)_2$ (10 mol%); Catalyst C: $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%).
[b] Isolated yields.
[c] Heated in an oil bath.
[d] Microwave irradiation was used for heating.
[e] $Cu(OAc)_2$ (3.0 equiv) was added; very high reaction pressure observed.
[f] A mixture of the starting material and **11a** was also detected by TLC.
[g] Mixture of 31% **11a** and 42% **11b**, respectively.

same reaction as oxidant the pressure increased dangerously in the reaction vessel and the equipment was forced to halt (entry 6). Changing the base to KOAc led to lower yields (8.2% of **11b**, as well as a mixture of the starting material **2** and the other product **11a** (entry 7)). When K_3PO_4 was applied as base, the reaction reached full conversion, while it yielded the two possible regioisomer annulated products **11a** and **11b** in 73% overall yield (31% and 42%, respectively) (entry 8).

To elucidate the exact structures of the two regioisomers, 2D NMR experiments were carried out on **11b** (see Supporting information). The ^{1}H-^{13}C HMBC spectrum confirmed the presumed structure.

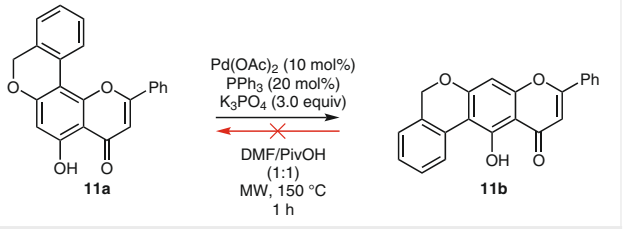
Moreover, the time dependence of the reaction was also studied (Table 4). The reaction time was altered between 5 and 60 minutes in the microwave reactor using the conditions given in entry 8 of Table 3 and the reaction mixtures were analyzed by GC-MS. During the reactions, all of the starting material was consumed in each case and both products were detected, with **11a** as the major product, whereas **11b** was the minor product of the reactions.

Table 4 The Effect of Reaction Time on the Intramolecular Arylation of **2**

Entry	Time (min)	**11a** (%)[a]	**11b** (%)[a]	Product ratio (**11a**/**11b**)
1	5	79	12	6.6:1
2	10	84	10	8.4:1
3	20	81	10	8.1:1
4	30	81	14	5.8:1
5	40	80	16	5.0:1
6	50	74	20	3.7:1
7	60	62	35	1.8:1

[a] Determined by GC-MS.

Surprisingly, although the reaction was complete within 5 minutes, increased reaction times resulted in the decrease of the product ratios of **11a**/**11b** from ~8:1 to ~2:1 (Table 4, entries 1–7). Previously, when both products were isolated, a larger amount of **11b** was obtained (31% of **11a** and 42% of **11b**, respectively; Table 3, entry 8), while according to the GC-MS measurements, **11a** was supposed to be the major product (Table 4). The apparent contradiction between the ratio of the isolated products and the observed product ratios of the time dependence studies can be explained by a Wessely–Moser type rearrangement of the 5,7,8-trisubstituted flavone derivative **11a** to afford 5,6,7-trisubstituted **11b**.[29] In order to examine this phenomenon, we attempted to convert the two products into each other by exposing **11a** and **11b** to the reaction conditions shown in entry 8 of Table 3 (Scheme 3). In the case of **11a**, the formation of **11b** was observed by TLC, while in the other case no conversion was found. This is in accordance with the observations of Hlubucek and co-workers, who experienced similar results with fused chrysin derivatives.[29b]



Scheme 3 Experiments for the interconversion of **11a** and **11b**

The effect of the reaction temperature was also investigated through a series of experiments, which ran under the same conditions with the exception of the temperature; the reaction time was 10 minutes in each case and the reaction mixtures were also analyzed by GC-MS. According to these experiments, the starting material was consumed completely when the temperature was set to 110 °C or above (Table 5, entries 1–5) and the product ratios were similar in each case, while there was a significant decrease in the conversion if the reaction temperature was below 90 °C (Table 5). As a consequence of these studies, we can conclude that the best regioselectivity was achieved when the reaction is carried out at 150 °C within 10 minutes; nevertheless, complete conversion also could be achieved at 120 °C with good regioselectivity towards **11a** using a short reaction time.

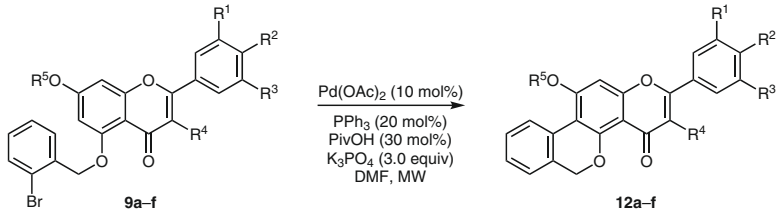
Table 5 The Effect of the Reaction Temperature on the Model Reaction

Entry	Temp (°C)	**11a**(%)[a]	**11b**(%)[a]	Conversion[a]
1	150	84	10	100
2	140	79	12	100
3	130	80	11	100
4	120	79	15	100
5	110	79	12	99
6	90	79	10	94
7	80	6	1	7

[a] Determined by GC-MS.

In order to ensure the formation of one singular direct arylation product, compounds **9a–f** containing a (2-bromobenzyl)oxy group at position 5 were utilized as substrates using the above described palladium-catalyzed intramolecular direct arylation reaction conditions applying only a substoichometric amount of pivalic acid (30 mol%)[16f] instead of using it as a co-solvent in order to simplify the workup of the reaction mixture. Taking into consideration that in the case of chrysin derivative **2** the coupling at position 8 was the preferred pathway initially and our aim was

Table 6 Microwave-Assisted Direct Intramolecular Arylation of the Prepared Flavone Derivatives



Entry	9	R^1	R^2	R^3	R^4	R^5	12	Yield (%)[a]
1	**a**	H	H	H	H	Me	**a**	34
2	**b**	H	OMe	H	H	Me	**b**	55
3	**c**	OMe	OMe	H	H	Me	**c**	43
4	**d**	OMe	OMe	OMe	H	Me	**d**	16
5	**e**	OMe	OMe	H	OMe	Me	**e**	40
6	**f**	H	OBn	H	H	Bn	**f**	42

[a] Isolated yields.

to furnish the reaction at position 6 which seemed to have lower reactivity, we supposed that its reaction might require longer reaction times. These experiments were then carried out with 1 hour reaction time and 120 °C was preferred as the reaction temperature to avoid the formation of different by-products. Nevertheless, the formation of the debrominated and debenzylated derivatives was still observed, these undesired side-products contributed to the decreased yields of the direct arylation reactions. Although full conversion was not achieved under the above specified reaction time in some cases, longer reaction times (2 h) did not lead to improved product yields. Compounds **12a–f** were isolated in poor to moderate yields (16–55%) using these conditions (Table 6); the structures of the compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy, as well as LC-MS and FT-IR measurements.

The best isolated yield was obtained in the case of apigenin derivative **12b** (Table 6, entry 2), while in the case of **12d** (entry 4), containing three methoxy groups on the B ring**,** only 16% yield was achieved. Interestingly, the preparation of this starting material proved to be the most difficult during the Claisen–Schmidt condensation, as well as the flavone ring-closure yielded the corresponding product in the lowest yield. In terms of the difference in reactivity between the apigenin derivatives **9b** and **9f** bearing different protecting groups, the methoxy containing **9b** proved to be slightly more reactive than the benzylated analogue **9f** (entries 2 and 6).

After chromatography, some of the obtained substances still contained Ph_3PO as a contaminant. However, products **12** occasionally dissolved poorly in acetone, providing a convenient way to obtain them in appropriate purity to carry out the required measurements for structural elucidation.

In conclusion, we have developed a microwave assisted method for the synthesis of tetracyclic fused flavone derivatives using substoichiometric amount of pivalic acid and palladium acetate as the catalyst. The application of microwave irradiation allowed the utilization of shorter reaction times compared to the generally available methods. The fused benzopyran moiety can be found in bioactive natural products, thus our results open a new pathway towards the synthesis of such analogues. The syntheses of the necessary intermediates were also carried out to produce the corresponding starting materials bearing a (2-bromobenzyl)oxy group either at position 7 or position 5 in good to excellent yields. The effects of the reaction time and temperature were studied on 7-[(2-bromobenzyl)oxy]-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**2**), to reveal a Wessely–Moser type rearrangement that resulted in the conversion of product **11a** to the regioisomer product **11b** to some extent.

The reagents and solvents were purchased from Sigma-Aldrich, TCI, or Molar Ltd. and used without further purification. The synthesized compounds were purified via column chromatography on silica gel (Merck 60, 0.063–0.200 nm). TLC analyses were performed on precoated aluminum-backed (Merck Kieselgel 60 F_{245}) plates.^{1}H NMR and ^{13}C NMR spectra were recorded either on a 360 MHz Bruker AM-360 instrument (^{1}H 360.13 MHz, ^{13}C 90.56 MHz) or on a 400 MHz Bruker DRX-400 instrument (^{1}H 400.13 MHz, ^{13}C 100.03 MHz). Chemical shifts (δ) are expressed in ppm downfield from TMS as the internal standard (δ = 0.00) in $CDCl_3$ or DMSO-d_6 (δ = 2.50) for ^{1}H NMR and $CDCl_3$ ($CDCl_3$, δ = 77.00) or DMSO-d_6 (δ = 39.52) for ^{13}C NMR. Standard abbreviations are used in reporting the NMR splitting patterns. Coupling constants are calculated in Hz. Melting points were obtained on a Büchi B-540 melting point apparatus in open capillary tubes; the values are provided in °C without correction. LC-MS measurements were carried out on a Thermo LTQ XL mass spectrometer equipped

with an Accela HPLC system. Elemental analyses (CHNS) were conducted using an Elementar Vario MicroCube instrument. IR spectra were recorded as KBr disc on a Jasco FT-IR 4100A equipment.

Microwave irradiation experiments were performed using single-mode CEM Discover© Systems (CEM Corporation, USA). Experiments were performed in dynamic mode. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. Stirring speed was set to 'High' (ca. 700 rpm). Standard 10 mL volume cylindrical Pyrex® reaction vessels (inner diameter 12 mm; obtained from CEM Corporation, USA) were used, equipped with small cylindrical magnetic stirring bars. The vessels were sealed with PEEK snap caps and standard PTFE-coated silicone septa. The external IR thermometer of the equipment was used to monitor the reaction temperatures. Pressure sensing is achieved by a hydraulic sensor. Reaction cooling is performed by compressed air automatically after the heating period has elapsed.

The synthesis of 5-hydroxyflavones **8a–f** and the numbering of carbon atoms for NMR spectra are provided in the Supporting Information.

7-[(2-Bromobenzyl)oxy]-5-hydroxy-2-phenyl-4*H*-chromen-4-one (2)

Chrysin (**1**; 1.5 g, 5.91 mmol, 1 equiv) was suspended in anhyd acetone (40 mL), then anhyd K_2CO_3 (0.98 g, 7.09 mmol, 1.2 equiv) was added to the suspension under vigorous stirring. 2-Bromobenzyl bromide (1.77 g, 7.09 mmol, 1.2 equiv) was dissolved in anhyd acetone (20 mL) and was added portion wise to the stirred suspension. The reaction mixture was stirred overnight at r.t. until the completion of the reaction (TLC: hexane/EtOAc 1:1). The precipitate was filtered, washed with H_2O, and then with acetone to give the pure product as an off-white solid; yield: 2.36 g (94%); mp 179–180 °C.

IR (KBr): 3071, 2911, 2853, 2689, 1667, 1622, 1589, 1564, 1504, 1491, 1472, 1447, 1420, 1351, 1303, 1288, 1273, 1210, 1197, 1169, 1123, 1076, 1044, 1027, 861, 808, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.74 (s, 1 H, 5-OH), 7.93–7.86 (m, 2 H, 2′,6′-H), 7.61 (d, *J* = 6.8 Hz, 1 H, 3″H), 7.52 (m, 4 H, 3′,4′,5′-H, 6″-H), 7.36 (t, *J* = 6.8 Hz, 1 H, 5″-H), 7.22 (t, *J* = 7.2 Hz, 1 H, 4″-H), 6.66 (s, 1 H, 3-H), 6.58 (s, 1 H, 8-H), 6.46 (s, 1 H, 6-H), 5.20 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.4 (C-4), 164.3 (C-7), 164.0 (C-2), 162.2 (C-5), 157.7 (C-8a), 135.0 (C-1″), 132.8 (C-6″), 131.8 (C-4′), 131.2 (C-1′), 129.6 (C-4″), 129.0 (C-3′,5′), 128.8 (C-3″), 127.7 (C-5″), 126.3 (C-2′,6′), 122.4 (C-2″), 106.0 (C-4a), 105.9 (C-3), 99.0 (C-6), 93.4 (C-8), 68.8 (CH_2).

MS: *m*/*z* = 424.0 [M^+ + 2], 422.0 [M^+], 393.1, 369.1, 343.1 [100%], 314.9, 287.1, 241.1, 225.0, 168.9, 170.9, 123.0, 107.0, 90.0.

Anal. Calcd for $C_{22}H_{15}BrO_4$: C, 62.43; H, 3.57. Found: C, 62.45; H, 3.60.

5-[2-Bromobenzyl(oxy)]flavone Derivatives 9; General Procedure

To a solution of the appropriate starting material **8a–f** (1 equiv) in anhyd DMF (5 mL per 0.5 mmol) was added anhyd K_2CO_3 (1.2 equiv). The resulting suspension was stirred at r.t. for 0.5 h and 2-bromobenzyl bromide (1.2 equiv) was added dropwise and the reaction mixture was stirred overnight at r.t. If the reaction was not complete (TLC; the disappearance of the phenolic hydroxyl group was indicated by aq $FeCl_3$ solution), additional portion(s) of K_2CO_3 (0.6 equiv or 1.2 equiv) and 2-bromobenzyl bromide (0.6 equiv or 1.2 equiv) were added to the reaction mixture and stirred until completion. The reaction mixture was poured onto ice-water, the precipitate was filtered, and washed with H_2O and with hexane to yield the pure product. Alternatively, if the precipitate was non-filterable, the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic phases were dried ($MgSO_4$), and filtered. The solvent was evaporated under vacuum, the residue was treated with hexane, and filtered to yield the pure compounds.

5-[(2-Bromobenzyl)oxy]-7-methoxy-2-phenyl-4*H*-chromen-4-one (9a)

Prepared from 5-hydroxyflavone **8a** (0.268 g, 1.0 mmol, 1 equiv); eluent: hexane/EtOAc (2:1); yield: 0.305 g (70%); white solid; mp 176–178 °C.

IR (KBr): 3456, 3062, 3026, 3005, 2922, 2853, 1648, 1609, 1577, 1489, 1450, 1433, 1349, 1214, 1202, 1186, 1163, 1129, 1022, 845, 814 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 7.6 Hz, 1 H, 3″-H), 7.89 (m, 2 H, 2′,6′-H), 7.55 (d, *J* = 8.0 Hz, 1 H, 6″-H), 7.53–7.49 (m, 3 H, 3′,4′,5′-H), 7.45 (t, *J* = 7.6 Hz, 1 H, 5″-H), 7.18 (dt, *J* = 7.8, 1.1 Hz, 1 H, 4″-H),6.68 (s, 1 H, 3-H), 6.60 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.48 (d, *J* = 2.2 Hz, 1 H, 6-H), 5.21 (s, 2 H, CH_2), 3.91 (s, 3 H, 7-OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 (C-4), 164.0 (C-7), 160.8 (C-2), 159.9 (C-5), 159.2 (C-8a), 135.7 (C-1″), 132.0 (C-6″), 131.6 (C-1′), 131.2 (C-4′), 128.9 (C-3′,5′), 128.9, 128.8 (C-3″,4″), 128.0 (C-5″), 126.0 (C-2′,6′), 120.7 (C-2″), 110.0 (C-4a), 109.1 (C-3), 97.5 (C-6), 93.3 (C-8), 70.1 (CH_2), 55.8 (7-OCH_3).

MS: *m*/*z* = 461.17 [M + Na^+ + 2], 459.17 [M + Na^+], 439.25 [M + H^+ + 2], 440.17, 437.25 [M + H^+, 100%], 210.00, 211.92, 330.50, 290.17.

Anal. Calcd for $C_{23}H_{17}BrO_4$: C, 63.17; H, 3.92. Found: C, 63.20; H, 3.94.

5-[(2-Bromobenzyl)oxy]-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (9b)

Prepared from 5-hydroxyflavone **8b** (0.30 g, 1.0 mmol, 1.0 equiv); eluent: hexane/EtOAc (2:1); yield: 0.322 g (69%); off-white solid; mp 206–208 °C.

IR (KBr): 3461, 3053, 3009, 2940, 2912, 2844, 1894, 1747, 1644, 1606, 1573, 1512, 1488, 1433, 1349, 1313, 1270, 1249, 1213, 1186, 1162, 1131, 1024, 834, 815, 753 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.5 Hz, 1 H, 3″-H), 7.81 (d, *J* = 8.6 Hz, 2 H, 2′,5′-H), 7.54 (d, *J* = 7.8 Hz, 1 H, 6″-H), 7.45 (t, *J* = 7.4 Hz, 1 H, 5″-H), 7.17 (t, *J* = 7.3 Hz, 1 H, 4″-H), 6.98 (d, *J* = 8.6 Hz, 2 H, 3′,5′-H), 6.57 (s, 1 H, 3-H), 6.56 (s, 1 H, 8-H), 6.44 (s, 1 H, 6-H), 5.18 (s, 2 H, CH_2), 3.89, 3.87 (s, 6 H, 2 × OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3 (C-4), 163.8 (C-7), 162.0 (C-2), 160.7 (C-4′), 159.7 (C-5), 159.1 (C-8a), 135.8 (C-1″), 131.9 (C-6″), 128.8 (C-3″,4″), 128.0 (C-5″), 127.6 (C-3′,5′), 123.8 (C-2″), 120.7 (C-1′), 114.3 (C-2′,6′), 109.4 (C-4a), 107.6 (C-3), 97.4 (C-6), 93.3 (C-8), 70.0 (CH_2), 55.7, 55.4 (2 × OCH_3).

MS: *m*/*z* = 491.17 [M + Na^+], 470.25, 469.08 [M + H^+ + 2, 100%], 467.25 [M + H^+], 298.17, 210.08, 212.00.

Anal. Calcd for $C_{24}H_{19}BrO_5$: C, 61.69; H, 4.10. Found: C, 61.72; H, 4.07.

5-[(2-Bromobenzyl)oxy]-2-(3,4-dimethoxyphenyl)-7-methoxy-4*H*-chromen-4-one (9c)

Prepared from 5-hydroxyflavone **8c** (0.20 g, 0.61 mmol, 1.0 equiv); eluent: hexane/EtOAc (2:1); yield: 0.286 g (94%); light brown solid; mp 204–206 °C.

IR (KBr): 3087, 3062, 2999, 2938, 2838, 1644, 1607, 1517, 1489, 1453, 1435, 1355, 1322, 1285, 1258, 1201, 1163, 1124, 1024, 840, 815, 745 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.6 Hz, 1 H, 3″-H), 7.54 (d, *J* = 7.9 Hz, 1 H, 6″), 7.48 (d, *J* = 9.1 Hz, 1 H, 6′-H), 7.45–7.42 (m, 1 H, 5″-H), 7.31 (s, 1 H, 2′-H), 7.19 (t, *J* = 7.5 Hz, 1 H, 4″-H), 6.94 (d, *J* = 8.5 Hz, 1 H, 5′-H), 6.58 (s, 1 H, 3-H), 6.56 (s, 1 H, 8-H), 6.43 (s, 1 H, 6-H), 5.19 (s, 2 H, CH_2), 3.97, 3.94, 3.89 (3 s, 3 H each, 3 × OCH_3).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 177.3 (C-4), 163.8 (C-7), 160.7 (C-2), 159.7 (C-5), 159.1 (C-8a), 151.7 (C-4′), 149.1 (C-3′), 135.7 (C-1″), 131.9 (C-6″), 128.8, 128.8 (C-3″,C-4″), 127.9 (C-5″), 123.9 (C-2″), 119.5 (C-1′), 119.5 (C-6′), 110.0 (C-5′) 109.3 (C-4a), 108.5 (C-2′), 107.8 (C-3), 97.4 (C-6), 93.3 (C-8), 70.0 (CH_2), 56.0, 56.0, 55.8 (3 × OCH_3).

MS: *m*/*z* = 521.17 [M + Na^+ + 2], 519.25 [M + Na^+], 501.17, 500.25, 499.08 [M + H^+ + 2], 497.25 [M + H^+, 100%], 328.17, 329.25, 209.92, 212.00.

Anal. Calcd for $C_{25}H_{21}BrO_6$: C, 60.38; H, 4.26. Found: C, 60.31; H, 4.23.

5-[(2-Bromobenzyl)oxy]-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-4-one (9d)

Prepared from 5-hydroxyflavone **8d** (0.203 g, 0.57 mmol, 1.0 equiv); eluent: hexane/EtOAc (2:1); yield: 0.262 g (88%); yellowish solid; mp 170–173 °C.

IR (KBr): 3428, 3099, 3066, 2926, 2850, 1715, 1642, 1608, 1506, 1492, 1456, 1420, 1350, 1250, 1221, 1166, 1127, 1069, 1025, 836, 819, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.6 Hz, 1 H, 3″-H), 7.55 (d, *J* = 7.9 Hz, 1 H, 6″-H), 7.43 (t, *J* = 7.5 Hz, 1 H, 5″-H), 7.19 (t, *J* = 7.5 Hz, 1 H, 4″-H), 7.09 (s, 2 H, 2′,6′-H), 6.66 (s, 1 H, 3-H), 6.59 (s, 1 H, 8-H), 6.46 (s, 1 H, 6-H), 5.23 (s, 2 H, CH_2), 3.96 (s, 6 H, 2 × OCH_3), 3.93, 3.92 (2 s, 3 H each, 2 × OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6 (C-4), 164.1 (C-7), 160.8 (C-2), 159.8 (C-5), 159.2 (C-8a), 153.5 (C-3′,5′), 140.9 (C-4′), 135.6 (C-1″), 132.0 (C-6″), 128.9, 128.8 (C-3″,4″), 128.0 (C-5″), 126.7 (C-2″), 120.8 (C-1′), 109.3 (C-4a), 108.7 (C-3), 103.5 (C-2′,6′), 97.6 (C-6), 93.4 (C-8), 70.1 (CH_2), 61.0 (4′-OCH_3), 56.4 (2 × OCH_3, 3′,5′-OCH_3), 55.8 (7-OCH_3).

MS: *m*/*z* = 551.33 [M + 2 + Na^+], 549.33 [M + Na^+], 529.33 [M + 2 + H^+, 100%], 527.33 [M + H^+], 380.25, 212.00.

Anal. Calcd for $C_{26}H_{23}BrO_7$: C, 59.22; H, 4.40. Found: C, 59.17; H, 4.36.

5-[(2-Bromobenzyl)oxy]-2-(3,4-dimethoxyphenyl)-3,7-dimethoxy-4*H*-chromen-4-one (9e)

Prepared from 5-hydroxyflavone **8e** (0.179 g, 0.5 mmol, 1.0 equiv); eluent: hexane/EtOAc (1:1); yield: 0.250 g (95%); greyish solid; mp 184–186 °C.

IR (KBr): 3087, 3063, 3025, 2974, 2937, 2911, 2837, 1747, 1631, 1606, 1517, 1486, 1438, 1358, 1267, 1252, 1220, 1197, 1175, 1162, 1141, 1022, 817, 771 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.1 Hz, 1 H, 3″-H), 7.73 (m, 2 H, 2′,6′-H), 7.55 (dd, *J* = 7.9, 0.8 Hz, 1 H, 6″-H), 7.47 (td, *J* = 7.6, 0.8 Hz, 1 H, 5″-H), 7.19 (td, *J* = 7.9, 1.4 Hz, 1 H, 4″-H), 6.99 (d, *J* = 8.4 Hz, 1 H, 5″-H), 6.54 (d, *J* = 2.2 Hz, 1 H, 8-H), 6.46 (d, *J* = 2.2 Hz, 1 H, 6-H), 5.23 (s, 2 H, CH_2), 3.98, 3.97 (2 s, 3 H each, 3′-OCH_3, 4′-OCH_3), 3.91, 3.87 (2 s, 3 H each, 3-OCH_3, 7-OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (C-4), 163.8 (C-7), 159.3 (C-5), 158.8 (C-8a), 152.9 (C-2), 150.9 (C-4′), 148.7 (C-3′), 141.3 (C-3), 135.7 (C-1″), 131.9 (C-6″), 128.9 (C-3″,4″), 128.1 (C-5″), 123.3 (C-2″), 121.7 (C-6′), 120.7 (C-1′), 111.2 (C-5′), 110.8 (C-2′), 109.7 (C-4a), 97.1 (C-6), 93.0 (C-8), 70.1 (CH_2), 60.0 (3-OCH_3), 56.0, 55.9, 55.8 (3 × OCH_3, 3′-OCH_3, 4′-OCH_3, 7-OCH_3).

MS: *m*/*z* = 551.25 [M + 2 + Na^+], 530.17, 529.17 [M + H^+ + 2], 527.33 [M + H^+, 100%], 358.17, 343.17, 340.17, 315.17, 212.00.

Anal. Calcd for $C_{26}H_{23}BrO_7$: C, 59.22; H, 4.40. Found: C, 59.24, H, 4.44.

7-(Benzyloxy)-2-[4-(benzyloxy)phenyl]-5-[(2-bromobenzyl)oxy]-4*H*-chromen-4-one (9f)

Prepared from 5-hydroxyflavone **8f** (0.225 g, 0.5 mmol, 1.0 equiv); eluent: hexane/EtOAc (1:1); yield: 0.295 g (95%); off-white solid; mp 188–190 °C.

IR (KBr): 3060, 3031, 2921, 2853, 1642, 1606, 1508, 1485, 1344, 1296, 1256, 1170, 1113, 1021, 833 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.4 Hz, 1 H, 3″-H), 7.82 (d, *J* = 8.2 Hz, 2 H, 2′,6′-H), 7.54 (d, *J* = 7.8 Hz, 1 H, 6″-H), 7.49–7.33 (m, 11 H, 5″-H, 2 × C_6H_5), 7.17 (t, *J* = 7.4 Hz, 1 H, 4″-H), 7.07 (d, *J* = 8.2 Hz, 2 H, 3′, 5′-H), 6.67 (s, 1 H, 3-H), 6.59 (s, 1 H, 8-H), 6.55 (s, 1 H, 6-H), 5.18 (s, 2 H, 5-OCH_2), 5.14 (s, 4 H, 4′,7-OCH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 (C-4), 162.9 (C-7), 161.2 (C-2), 160.8 (C-4′), 159.7 (C-5), 159.3 (C-8a), 136.3 (C-1″), 135.8, 135.6 ($OCH_2C_6H_5$, 2 × C-1), 131.9 (C-6″), 128.8 ($OCH_2C_6H_5$, 2 × C-3,5), 128.7 ($OCH_2C_6H_5$, 2 × C-4), 128.5 (C-4″), 128.2 (C-3″), 128.0 (C-5″), 127.7, 127.7 ($OCH_2C_6H_5$, 2 × C-2,6), 127.5 (C-3′,5′), 124.0 (C-2″), 120.6 (C-1′), 115.2 (C-2′,6′), 109.9 (C-4a), 107.8 (C-3), 97.9 (C-6), 94.3 (C-8), 70.6 (5-OCH_2), 70.2 (4′,7-OCH_2).

MS: *m*/*z* = 643.25 [M + 2 + Na^+], 641.33 [M + Na^+], 621.33 [M + 2 + H^+], 619.33 [M + H^+, 100%].

Anal. Calcd for $C_{37}H_{27}BrO_4$: C, 69.80; H, 4.39. Found: C, 69.73; H, 4.32.

Microwave-Assisted Intramolecular Direct Arylation; General Procedure

A 10 mL Pyrex® microwave vial equipped with a small magnetic stirring bar was charged with 5- or 7-(2-bromobenzyloxy)flavone **9** or **2** (1.0 equiv), K_3PO_4 (3.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and PivOH (30 mol%). Anhyd DMF (1 mL) was added, the reaction vessel was purged with N_2, and the vial was sealed with a PEEK snap cap. The sealed reaction vial was then placed in the microwave reactor, heated to the desired temperature, and stirred at the given temperature over the indicated time (1 h). The solution was then cooled to r.t., diluted with CH_2Cl_2 (25 mL), and evaporated onto silica gel. The crude product was purified by silica gel column chromatography to afford the corresponding product.

5-Hydroxy-2-phenyl-4*H*,8*H*-benzo[*c*]pyrano[2,3-*f*]chromen-4-one (11a)

Prepared from **2** (0.50 mmol, 0.212 g, 1.0 equiv) with $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), PPh_3 (26.6 mg, 0.10 mmol), pivalic acid (2 mL), and K_3PO_4 (0.318 g, 1.50 mmol) in anhyd DMF (2 mL) at 130 °C; eluent: toluene; yield: 105 mg (31%); yellow solid; mp 236–237 °C.

IR (KBr): 3076, 3037, 2998, 2921, 2852, 1661. 1591, 1449, 1428, 1376, 1294, 1162 1115, 1087, 1056, 833, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.15 (s, 1 H, 5-OH), 8.23 (d, *J* = 7.9 Hz, 1 H, 12-H), 7.98–7.92 (m, 2 H, 2′,6′-H), 7.62–7.52 (m, 3 H, 3′,4′,5′-H), 7.42 (t, *J* = 7.3 Hz, 1 H, 11-H), 7.33 (t, *J* = 7.4 Hz, 1 H, 10-H), 7.25 (d, *J* = 6.0 Hz, 1 H, 9-H), 6.78 (s, 1 H, 3-H), 6.53 (s, 1 H, 6-H), 5.12 (s, 2 H, 8-CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.9 (C-4), 164.3 (C-6a), 162.2 (C-5), 161.9 (C-2), 154.3 (C-12c), 132.0 (C-4′), 131.4 (C-1′), 130.6 (C-8a), 129.3 (C-3′,5′), 128.6 (C-11), 127.3 (C-12a), 127.2 (C-10), 126.6 (C-2′,6′), 125.2 (C-9), 125.0 (C-12), 107.1 (C-12b), 106.4 (C-3), 104.0 (C-4a), 101.2 (C-6), 69.3 (C-8).

MS: *m*/*z* = 342.1 [M$^+$, 100%], 313.1, 281.1, 239.0, 208.0, 184.1, 155.0.

Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 77.25; H, 4.15.

12-Hydroxy-9-phenyl-5*H*,11*H*-benzo[*c*]pyrano[3,2-*g*]chromen-11-one (11b)

Prepared from **2** (0.50 mmol, 0.212 g, 1.0 equiv) with $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), PPh_3 (26.6 mg, 0.10 mmol), pivalic acid (2 mL), and K_3PO_4 (0.318 g, 1.50 mmol) in anhyd DMF (2 mL) at 130 °C; eluent: toluene; yield: 144 mg (42%); yellow solid; mp 203–205 °C.

IR (KBr): 3072, 3018, 2921, 2850, 2827, 2769, 2712, 1644, 1587, 1564, 1485, 1446, 1420, 1390, 1342, 1255, 1214, 1162, 1133, 1059 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.11 (s, 1 H, 5-OH), 8.55 (d, *J* = 7.9 Hz, 1 H, 1-H), 7.87–7.82 (m, 2 H, 2′,6′-H), 7.54–7.46 (m, 3 H, 3′,4′,5′-H), 7.38 (t, *J* = 7.6 Hz, 1 H, 2-H), 7.25 (t, *J* = 7.4 Hz, 1 H, 3-H), 7.12 (d, *J* = 7.4 Hz, 1 H, 4-H), 6.64 (s, 1 H, 3-H), 6.59 (s, 1 H, 8-H), 5.09 (s, 2 H, 5-CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.9 (C-11), 163.8 (C-9), 161.8 (C-6a), 159.8 (C-12), 156.5 (C-7a), 131.8 (C-4′), 131.0 (C-1′), 130.0 (C-4a), 129.0 (C-3′,5′), 128.5 (C-2), 127.7 (C-12b), 127.2 (C-3), 126.3 (C-1), 126.2 (C-2′,6′), 124.1 (C-4), 107.4 (C-12a), 106.3 (C-11a), 105.6 (C-10), 95.8 (C-7), 69.1 (C-5).

MS: *m*/*z* = 342.1 [M$^+$, 100%], 313.1, 281.0, 258.1, 239.1, 207.0, 171.1, 139.1, 115.1.

Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 77.23; H, 4.14.

11-Methoxy-2-phenyl-4*H*,6*H*-benzo[*c*]pyrano[2,3-*h*]chromen-4-one (12a)

Prepared from **9a** (0.144 g, 0.33 mmol, 1.0 equiv) with $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), PPh_3 (17.3 mg, 0.066 mmol), pivalic acid (10 mg, 0.099 mmol), and K_3PO_4 (0.210 g, 0.99 mmol) in anhyd DMF (1 mL) at 120 °C, conversion = 89%; eluent: hexane/EtOAc (2:1); yield: 40 mg (34%); brown solid; mp 176–178 °C.

IR (KBr): 3061, 3034, 2924, 2852, 1726, 1656, 1601, 1577, 1492, 1451, 1434, 1419, 1352, 1233, 1195, 1130, 1105 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 6.6 Hz, 1 H, 10-H), 7.89 (m, 2 H, 2′,6′-H), 7.51 (m, 3 H, 3′,4′,5′-H), 7.40–7.33 (m, 1 H, 9-H), 7.32–7.26 (m, 1 H, 8-H), 7.20 (s, 1 H, 7-H), 6.89 (s, 1 H, 3-H), 6.76 (s, 1 H, 12-H), 5.18 (s, 2 H, 6-CH_2), 4.07 (s, 3 H, 11-OCH_3).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 177.3 (C-4), 161.7 (C-11), 161.6 (C-2), 158.3 (C-4b), 156.7 (C-12a), 131.6 (C-4′), 131.1 (C-1′), 130.7 (C-6a), 129.0 (C-3′,5′), 128.1 (C-8), 127.6 (C-9), 127.4 (C-10a), 126.2 (C-2′,6′), 126.0 (C-7), 124.4 (C-10), 110.7 (C-10b), 108.9 (C-4a), 108.2 (C-3), 93.5 (C-12), 69.4 (C-6), 56.3 (11-OCH_3).

MS: *m*/*z* = 379.17 [M + Na$^+$], 358.17, 357.17 [M + H$^+$, 100%], 343.33, 342.17, 340.17, 326.17, 325.25.

Anal. Calcd for $C_{23}H_{16}O_4$: C, 77.52; H, 4.53. Found: C, 77.55; H, 4.56.

11-Methoxy-2-(4-methoxyphenyl)-4*H*,6*H*-benzo[*c*]pyrano[2,3-*h*]chromen-4-one (12b)

Prepared from **9b** (0.154 g, 0.33 mmol, 1.0 equiv) with $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), PPh_3 (17.3 mg, 0.066 mmol), pivalic acid (10 mg, 0.099 mmol), and K_3PO_4 (0.210 g, 0.99 mmol) in anhyd DMF (1 mL) at 120 °C; conversion = 71%; eluent: hexane/EtOAc (2:1); yield: 70 mg (55%); white solid; mp 182–184 °C.

IR (KBr): 3038, 3003, 2828, 2835, 1639, 1599, 1574, 1512, 1493, 1462, 1425, 1354, 1301, 1260, 1179, 1130, 1033 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 7.3 Hz, 1 H, 10-H), 7.83 (d, *J* = 7.8 Hz, 2 H, 2′,6′-H), 7.35 (t, *J* = 7.0 Hz, 1 H, 9-H), 7.32–7.25 (m, 1 H, 8-H), 7.21 (d, *J* = 6.3 Hz, 1 H, 7-H), 7.00 (d, *J* = 7.8 Hz, 2 H, 3′,5′-H), 6.72 (s, 1 H, 3-H), 6.61 (s, 1 H, 12-H), 5.19 (s, 2 H, 6-CH_2), 4.05 (s, 3 H, 11-OCH_3), 3.88 (s, 3 H, 4′-OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2 (C-4), 162.1 (C-11), 161.1 (C-2), 160.8 (C-4′), 158.2 (C-4b), 156.7 (C-12a), 130.8 (C-6a), 128.1 (C-8), 127.7 (C-10a), 127.7 (C-4′), 127.6 (C-3′,5′), 127.4 (C-9), 126.0 (C-7), 124.3 (C-10), 123.8 (C-1′), 114.4 (C-2′,6′), 110.3 (C-10b), 109.5 (C-4a), 107.6 (C-3), 93.4 (C-12), 69.4 (C-6), 56.0 (11-OCH_3), 55.5 (4′-OCH_3).

MS: *m*/*z* = 409.33 [M + Na$^+$], 388.25, 387.33 [M + H$^+$, 100%], 372.25, 356.25.

Anal. Calcd for $C_{24}H_{18}O_5$: C, 74.60; H, 4.70. Found: C, 74.67; H, 4.78.

2-(3,4-Dimethoxyphenyl)-11-methoxy-4*H*,6*H*-benzo[*c*]pyrano[2,3-*h*]chromen-4-one (12c)

Prepared from **9c** (0.149 g, 0.3 mmol, 1.0 equiv) with $Pd(OAc)_2$ (6.7 mg, 0.030 mmol), PPh_3 (15.7 mg, 0.060 mmol), pivalic acid (9 mg, 0.090 mmol), and K_3PO_4 (0.191 g, 0.90 mmol) in anhyd DMF (1 mL) at 140 °C; conversion = 91%; eluent: hexane/acetone (2:1); yield: 54 mg (43%); off-white solid; mp 217–220 °C.

IR (KBr): 2956, 2923, 2853, 1731, 1638, 1598, 1573, 1518, 1494, 1465, 1440, 1423, 1361, 1271, 1250, 1109, 1021 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 6.1 Hz, 1 H, 10-H), 7.49 (d, *J* = 7.1 Hz, 1 H, 6′-H), 7.38–7.27 (m, 3 H, 2′-H, 8-H, 9-H), 7.20 (s, 1 H, 7-H), 6.94 (d, *J* = 7.1 Hz, 1 H, 5′-H), 6.70 (s, 1 H, 3-H), 6.61 (s, 1 H, 12-H), 5.18 (s, 2 H, 6-CH_2), 4.04 (s, 3 H, 11-OCH_3), 3.97, 3.94 (2 s, 3 H each, 3′-OCH_3, 4′-OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C-4), 161.1 (C-11), 160.8 (C-2), 158.2 (C-4b), 156.6 (C-12a), 151.7 (C-4′), 149.2 (C-3′), 130.7 (C-6a), 128.0 (C-8), 127.6 (C-10a), 127.4 (C-9), 126.0 (C-7), 124.3 (C-10), 123.8 (C-1′), 119.5 (C-6′), 111.0 (C-5′), 110.3 (C-10b), 109.4 (C-4a), 108.5 (C-2′), 107.8 (C-3), 93.4 (C-12), 69.4 (C-6), 56.0 (11-OCH_3), 55.9 (3′-OCH_3, 4′-OCH_3).

MS: *m*/*z* = 439.33 [M + Na$^+$], 418.33, 417.33 [M + H$^+$, 100%], 401.25, 400.33, 386.33, 373.25.

Anal. Calcd for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 72.02; H, 4.73.

11-Methoxy-2-(3,4,5-trimethoxyphenyl)-4*H*,6*H*-benzo[*c*]pyrano[2,3-*h*]chromen-4-one (12d)

Prepared from **9d** (0.125 g, 0.237 mmol, 1.0 equiv) with $Pd(OAc)_2$ (5.0 mg, 0.024 mmol), PPh_3 (12.4 mg, 0.047 mmol), pivalic acid (7.3 mg, 0.071 mmol), and K_3PO_4 (0.150 g, 0.711 mmol) in anhyd DMF (1 mL) at 120 °C; conversion = 92%; eluent: hexane/acetone (2:1); yield: 17 mg (16%); white solid; mp 245–247 °C.

IR (KBr): 3447, 3053, 2946, 2920, 2836, 1645, 1598, 1507, 1461, 1423, 1357, 1251, 1203, 1182, 1129, 1071 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 7.8 Hz, 1 H, 10-H), 7.38 (t, *J* = 7.4 Hz, 1 H, 9-H), 7.31 (t, *J* = 7.3 Hz, 1 H, 8-H), 7.22 (d, *J* = 7.2 Hz, 1 H, 7-H), 7.09 (s, 2 H, 2′,6′-H), 6.74 (s, 1 H, 3-H), 6.66 (s, 1 H, 12-H), 5.21 (s, 2 H, 6-CH_2), 4.09 (s, 3 H, 11-OCH_3), 3.97 (s, 6 H, 3′,5′-OCH_3), 3.93 (s, 3 H, 4′-OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C-4), 161.2 (C-11), 160.7 (C-2), 158.2 (C-4b), 156.7 (C-12a), 153.5 (C-3′,5′), 140.8 (C-4′), 130.7 (C-6a), 128.1 (C-8), 127.5 (C-9), 126.7 (C-10a), 126.0 (C-7), 124.4 (C-10), 110.5 (C-10b), 109.9 (C-1′), 109.5 (C-4a), 108.8 (C-3), 103.4 (C-2′,6′), 93.4 (C-12), 69.5 (C-6), 61.0 (4′-OCH_3), 56.4 (3′-OCH_3, 5′-OCH_3), 56.1 (11-OCH_3).

MS: *m*/*z* = 470.33, 448.42, 447.33 [M + H$^+$, 100%], 417.33.

Anal. Calcd for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97. Found: C, 69.87; H, 4.92.

2-(3,4-Dimethoxyphenyl)-3,11-dimethoxy-4*H*,6*H*-benzo[*c*]pyrano[2,3-*h*]chromen-4-one (12e)

Prepared from **9e** (0.125 g, 0.237 mmol, 1.0 equiv) with $Pd(OAc)_2$ (5.0 mg, 0.024 mmol), PPh_3 (12.4 mg, 0.047 mmol), pivalic acid (7.3 mg, 0.071 mmol), and K_3PO_4 (0.150 g, 0.711 mmol) in anhyd DMF (1 mL) at 120 °C; eluent: hexane/acetone (1:1); yield: 42 mg (40%); white solid; mp 212–215 °C.

IR (KBr): 3007, 2962, 2933, 2837, 1723, 1637, 1600, 1576, 1516, 1495, 1460, 1439, 1420, 1358, 1323, 1268, 1242, 1217, 1163, 1144, 1127 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.8 Hz, 1 H, 10-H), 7.70 (m, 2 H, 2′,6′-H), 7.35 (t, *J* = 7.2 Hz, 1 H, 9-H), 7.29 (t, *J* = 7.2 Hz, 1 H, 8-H), 7.21 (d, *J* = 7.1 Hz, 1 H, 7-H), 6.97 (d, *J* = 8.6 Hz, 1 H, 5′-H), 6.66 (s, 1 H, 12-H), 5.19 (s, 2 H, 6-OCH_2), 4.05 (s, 3 H, 11-OCH_3), 3.96 (2 s, 3 H each, 3′-OCH_3, 4′-OCH_3), 3.89 (s, 3 H, 3-OCH_3).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 173.5 (C-4), 161.1 (C-11), 157.2 (C-4b), 156.8 (C-12a), 152.7 (C-2), 150.8 (C-4′), 148.6 (C-3′), 141.1 (C-3), 130.7 (C-6a), 128.1 (C-8), 127.6 (C-10a), 127.3 (C-9), 125.9 (C-7), 124.3 (C-10), 123.3 (C-1′), 121.6 (C-6′), 111.3 (C-5′), 110.8 (C-2′), 109.9 (C-10b), 106.7 (C-4a), 93.0 (C-12), 69.4 (C-6), 59.9 (3-OCH_3), 56.04, 55.98, 55.91 (7-OCH_3, 3′-OCH_3, 4′-OCH_3).

MS: *m*/*z* = 469.33 [M + Na$^+$], 448.33, 447.33 [M + H$^+$, 100%], 432.17, 389.25.

Anal. Calcd for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97. Found: C, 69.98; H, 5.01.

11-(Benzyloxy)-2-[4-(benzyloxy)phenyl]-4*H*,6*H*-benzo[*c*]pyrano[2,3-*h*]chromen-4-one (12f)

Prepared from **9f** (0.204 g, 0.33 mmol, 1.0 equiv) with $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), PPh_3 (17.3 mg, 0.066 mmol), pivalic acid (10.2 mg, 0.100 mmol), and K_3PO_4 (0.210 g, 0.99 mmol) in anhyd DMF (1 mL) at 120 °C; conversion: 93%; eluent: hexane/EtOAc (1:1); yield: 74 mg (42%); yellow solid; mp 233–236 °C.

IR (KBr): 3057, 3028, 2922, 2876, 1729, 1636, 1597, 1575, 1511, 1494, 1460, 1453, 1427, 1353, 1314, 1297, 1264, 1244, 1181, 1132, 1099, 1037, 1025, 827, 808, 764, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.21 (m, 1 H, 10-H), 7.78 (d, *J* = 8.7 Hz, 2 H, 2′,6′-H), 7.50 (d, *J* = 7.2 Hz, 2 H, 2,6-H in C_6H_5), 7.46–7.36 (m, 6 H, 2 × 3,4,5-H in C_6H_5), 7.35 (t, *J* = 7.2 Hz, 1 H, 9 H), 7.32–7.21 (m, 3 H, 2,6-H in C_6H_5, 8-H), 7.20–7.16 (m, 1 H, 7-H), 7.04 (d, *J* = 8.7 Hz, 2 H, 3′,5′-H), 6.76 (s, 1 H, 3-H), 6.59 (s, 1 H, 12-H), 5.28 (s, 2 H, 6-CH_2), 5.18, 5.11 (2 s, 4 H, 2 × OCH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C-4), 161.2 (C-11), 160.8 (C-2), 160.0 (C-4b), 158.1 (C-4′), 156.8 (C-12a), 136.2 (C-6a), 135.5 (C_6H_5, 2 × C-1), 130.8 (C-10a), 128.8, 128.6 (2 × $OCH_2C_6H_5$, C-3,5), 128.3, 128.2 (2 × $OCH_2C_6H_5$, C-4), 128.1 (C-8), 127.6 (C-9), 127.4 (C-3′,5′), 127.4 (2 × $OCH_2C_6H_5$, C-2′,6′), 126.1 (C-7), 124.3 (C-10), 123.8 (C-1′), 115.2 (C-2′,6′), 110.5 (C-10b), 109.6 (C-4a), 107.6 (C-3), 94.5 (C-12), 71.1 (11-OCH_2), 70.1 (4′-OCH_2), 69.4 (C-6).

MS: *m*/*z* = 561.42 [M + Na$^+$], 540.50, 539.50 [M + H$^+$, 100%], 448.42.

Anal. Calcd for $C_{36}H_{26}O_5$: C, 80.28; H. 4.87. Found: C, 80.30, H, 4.89.

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Supporting Information

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