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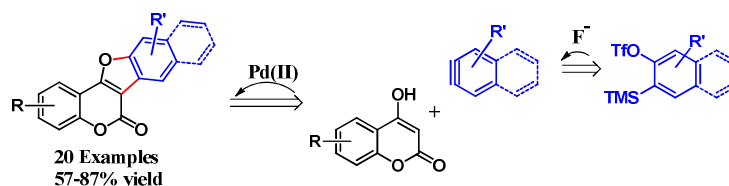
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Palladium(II)-Catalyzed C-H Bond Activation/C-C and C-O Bond Formation Reaction Cascade: Direct Synthesis of Coumestans

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ABSTRACT: A palladium catalyzed cascade reaction of 4-hydroxycoumarins and *in situ* generated arynes has been developed for the direct synthesis of coumestans. This cascade strategy proceeds *via* C-H bond activation/C-O and C-C bond formations in a single reaction vessel. This methodology affords moderate to good yields of coumestans and is tolerant of a variety of functional groups including halide. The methodology was applied to the synthesis of natural product flemichapparin C.

Coumestan constitutes the central core unit of a variety of natural polycyclic lactones¹ with important biological activities² including anticancer, antibacterial, antifungal, antimyotoxic, and phytoalexine effects. Most importantly, they are known as non-steroidal "dietary estrogens". Some of the coumestans have the same binding affinity for the ER- β estrogen receptor as 17 β -estradiol.³ Figure 1 shows some of the naturally occurring biologically active coumestans such as coumestrol, wedelolactone, medicagol and psoralidin. Due to wide range of biological properties make coumestans an interesting synthetic target for chemist.

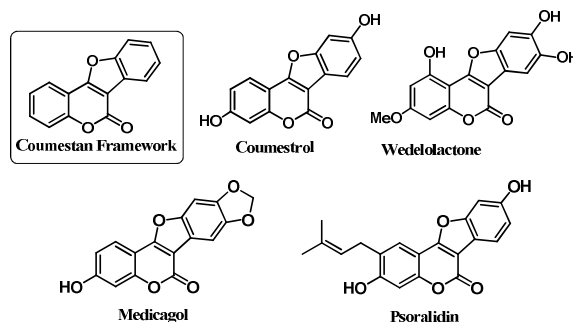


Figure 1. Examples of some naturally occurring coumestans

The total syntheses of coumestans particularly coumestrol, wedelolactone, psoralidin, and flemichapparin have been reported by several groups using quite different approaches with modest overall yields.^{1d,4} Because of impressive biological activities, particularly

estrogenic, it is highly desirable to develop more efficient and general synthetic methods for the synthesis of coumestans and their derivatives. In this regard, a number of synthetic methods have been developed for the construction of this privileged structural unit. For example, Pd-catalyzed C-S activation followed by intramolecular transesterification of 2-(methylthio)benzofuran-3-carboxylates and 2-hydroxyphenylboronic acid,^{5a} iodocyclization and Pd-catalyzed intramolecular lactonization of acetoxy-containing 2-(1-alkynyl)anisoles,^{5b} base-catalyzed condensation of phenyl acetic acid methyl ester with benzoylchloride followed by intramolecular cyclization,^{5c} LDA-induced migration of heterobiaryl *O*-carbamates,^{5d} Ag₂CO₃/Celite mediated construction of furan ring from 1,3-dicarbonyl compounds and vinyl sulfides followed by dehydrogenation,^{5e} aerobic iron-based cross-dehydrogenative coupling of β -ketoesters and phenols have been reported for the syntheses of coumestan derivatives.^{5f} In addition to these, derivatives of 4-hydroxycoumarins have also been extensively used to lead to diversified coumestan derivatives. In this regard, FeCl₃-mediated intramolecular oxidative annulation of 4-hydroxy-3-phenyl-2*H*-chromen-2-one derivatives,^{6a} Pd-catalyzed intramolecular arylation of 4-(aryloxy)-3-halocoumarins,^{6b} double C-H activations of 4-phenoxy-2-coumarins,^{6c} and intramolecular C-H bond functionalization^{6d,e} are the notable examples (Figure 2). However, in all the cases, pre-functionalizations of 4-hydroxycoumarins are required to get the starting materials. Detsi *et al.* has reported the use of enzyme peroxidase from onion solid waste for the synthesis of coumestans from catechols and 4-hydroxycoumarins in satisfactory yields.⁷ While there are presently a number of useful synthetic procedures to prepare these compounds, there remain several limitations as well. (i) Most of the reported procedures involve multiple steps with moderate overall yield. (ii) The starting materials are often not very readily available. (iii) Harsh reaction conditions are usually required. In view of these limitations, the development of efficient strategy for the synthesis of coumestan is highly desirable.

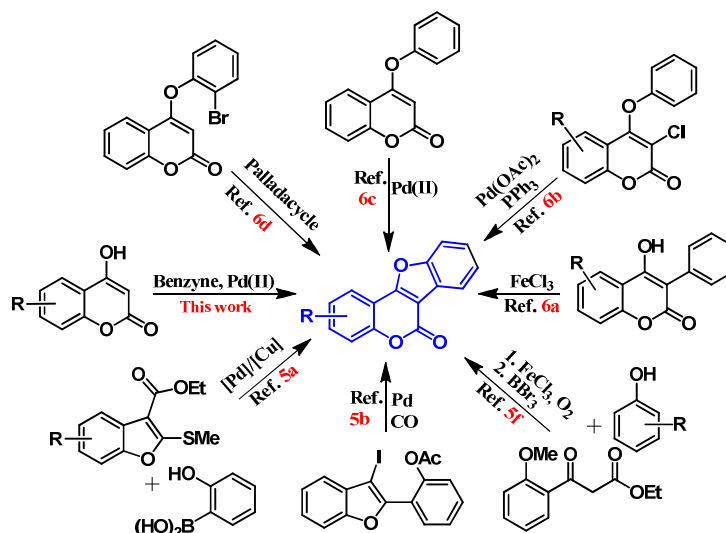
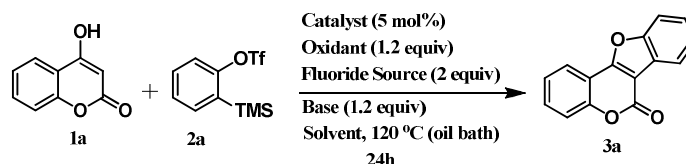


Figure 2. Some synthetic approaches to coumestans

Arynes have been successfully used for the development of several useful synthetic methodologies⁸ and demonstrated as versatile intermediate for the synthesis of natural products.⁹ There are several methods for the generation of aryne,¹⁰ however Kobayashi's protocol^{10a} using *o*-silyl aryl triflate and a fluoride source provides an excellent opportunity to demonstrate the application of arynes in various useful synthetic methodologies. In addition, palladium-catalyzed C–H activation/C–C bond formation has emerged as a powerful tool for chemical synthesis.¹¹ This synthetic strategy is attractive from the viewpoint of synthetic simplicity and step economy. Recently, Xu¹² *et al.* reported a palladium-catalyzed oxidative annulation of acrylamides with benzyne precursors for the synthesis of quinolinones *via* N–H activation/Heck reaction strategy. Much progress has been achieved in terms of synthesis efficiency and atom economy in the highly selective functionalization of C–H bonds involving directing substituents. In this regard, we envisaged here the Pd-catalyzed C–H activation of 4-hydroxycoumarins followed by C–C and C–O bond formations with reactive intermediate arynes to access synthetically useful and biologically important coumestan derivatives.

To achieve this challenging transformation, we optimized our reaction conditions employing 4-hydroxycoumarin **1a** and benzyne precursor **2a** as model substrates (Table 1). After a detailed investigation, the oxidative annulation of **1a** with **2a** gave coumestan **3a** in 81% yield under the optimized conditions (Table 1, entry 4).

Table 1. Optimization Studies^a



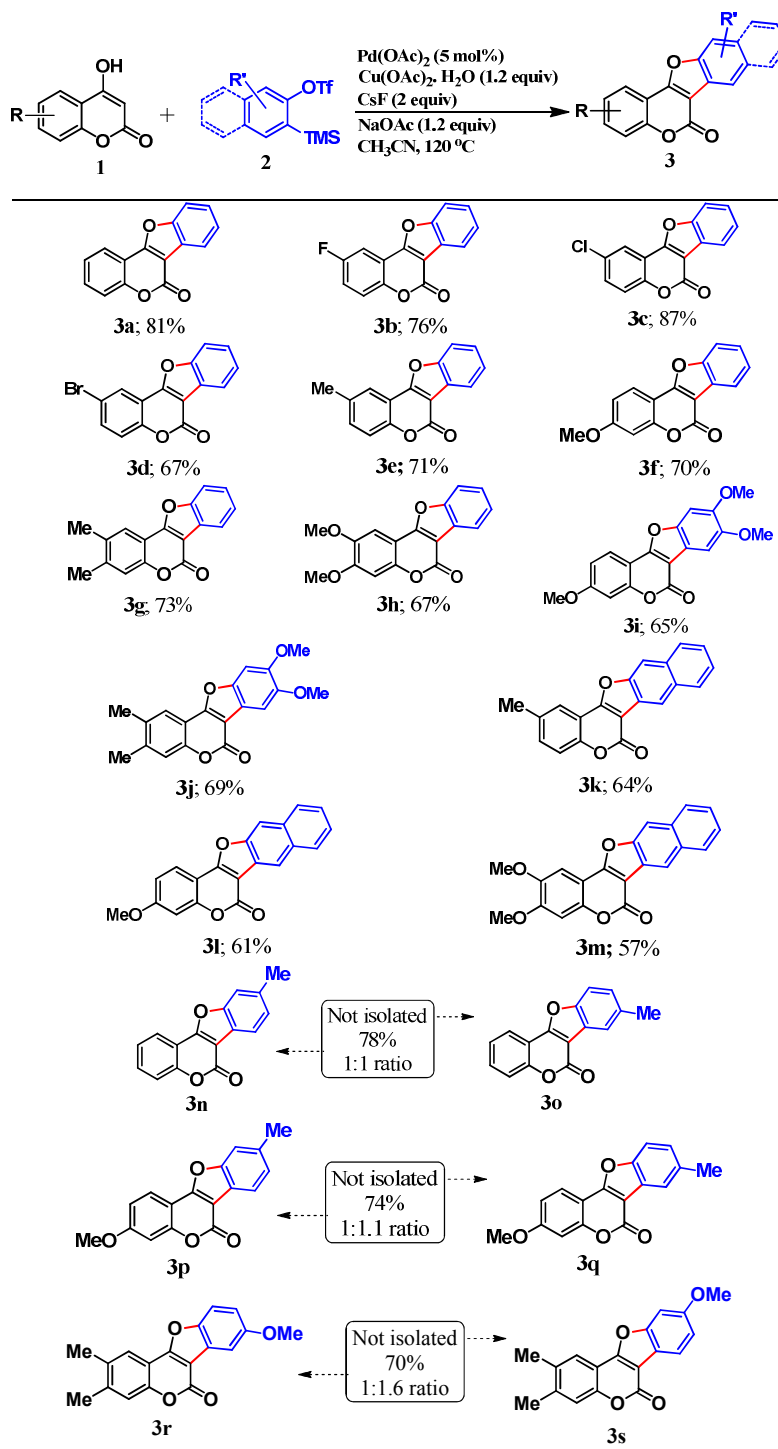
Entry	Catalyst	Oxidant	Fluoride Source	Base	Solvent	Isolated Yield 3a (%) ^b
1	Pd(OAc) ₂	Cu(OAc) ₂	CsF	K ₂ CO ₃	CH ₃ CN	47
2	Pd(OAc) ₂	Air	CsF	K ₂ CO ₃	CH ₃ CN	trace
3	Pd(OAc) ₂	Cu(OAc) ₂	CsF	--	CH ₃ CN	trace
4	Pd(OAc)₂	Cu(OAc)₂	CsF	NaOAc	CH₃CN	81
5	--	Cu(OAc) ₂	CsF	NaOAc	CH ₃ CN	ND
6	Pd(PPh ₃) ₄	Cu(OAc) ₂	CsF	NaOAc	CH ₃ CN	59
7	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	CsF	NaOAc	CH ₃ CN	39
8	[RuCl ₂ (<i>p</i> -Cymene)] ₂	Cu(OAc) ₂	CsF	NaOAc	CH ₃ CN	47
9	Pd(OAc) ₂	K ₂ S ₂ O ₈	CsF	NaOAc	CH ₃ CN	15
10	Pd(OAc) ₂	Ag ₂ O	CsF	NaOAc	CH ₃ CN	39
11	Pd(OAc) ₂	Cu(OAc) ₂	CsF	NaOAc	DMSO	61
12	Pd(OAc) ₂	Cu(OAc) ₂	CsF	NaOAc	DMF	59
13	Pd(OAc) ₂	Cu(OAc) ₂	CsF	NaOAc	Dioxane	60
14	Pd(OAc) ₂	Cu(OAc) ₂	TBAF	NaOAc	CH ₃ CN	39
15	Pd(OAc) ₂	Cu(OAc) ₂	KF	NaOAc	CH ₃ CN	22
16	--	--	CsF	--	CH ₃ CN	ND

^a Conditions: 4-Hydroxy coumarin (1.0 mmol), *o*-Silyl aryl triflate (1.5 mmol), Catalyst (5 mol%), Oxidant (1.2 mmol); Fluoride source (2 mmol); Base (1.2 mmol), CH₃CN (5 mL) stirred in Ace pressure tube at 120 °C; ^b isolated yield; ND: Not detected.

The structure of **3a** was confirmed by ^1H NMR, ^{13}C NMR, HRMS analysis and finally compared with the reported data.¹³ The choice of Pd(II) catalyst was crucial for our strategy as when it was replaced with Pd(0) or Rh(III) or Ru(II) catalyst, the desired product was obtained with low yield (Table 1; entries 6, 7 and 8). In our optimization studies, various oxidants such as air, Cu(II), $\text{K}_2\text{S}_2\text{O}_8$ and Ag_2O were screened, where air did not work in our catalytic process. On the other hand, $\text{K}_2\text{S}_2\text{O}_8$ and Ag_2O gave only 15% and 39% of **3a** respectively (entry 2, 9 and 10; Table 1). As a control experiment, the reaction was performed in the absence of catalyst and oxidant, no desired product **3a** was observed (Table 1; entry 16).

After having the optimized reaction conditions in our hand, we next generalized the Pd(II)-catalyzed C-H bond activation/C-C and C-O bond formation reaction cascade for the synthesis of our targeted coumestans. This cascade oxidative annulation of benzyne with a range of 4-hydroxycoumarins for the one-pot synthesis of coumestans are demonstrated in Table 2. As shown in Table 2, *o*-silyl aryl triflates reacted with a variety of 4-hydroxycoumarins bearing fluoro, chloro, bromo, methyl, methoxy substituents, leading to our desired coumestans in good yields (Table 2; **3a-3h**). Most interestingly, coupling-prone functional groups like chloro and bromo are remaining intact during our Pd-catalyzed cascade process, which could be used for further functionalization of our synthesized coumestans (Table 2; **3c** and **3d**). Electron withdrawing groups on 4-hydroxycoumarins gave high yields of coumestans in comparison to neutral or electron donating groups substituted on 4-hydroxycoumarins in our cascade reaction. Silyl triflate having symmetrical substituents *i.e.* 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2b** participated in our cascade process with 6- and 7-substituted 4-hydroxycoumarins providing targeted coumestans with excellent regioselectivity (Table 2; **3i** and **3j**). 3-(Trimethylsilyl)-2-naphthyl trifluoromethanesulfonate, **2c** also participated in our cascade for the synthesis of some structurally novel coumestan derivatives (Table 2; **3k**, **3l**, **3m**). However the extended π conjugation of naphthalene silyl triflate afforded relatively lower yields of coumestans. Additionally, mono substituted silyl triflates *i.e.* 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2d** and 4-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2e** were also used as aryne precursors for our reaction. Benzyne from silyl triflate **2d** fused with 4-hydroxycoumarin and 7-methoxy-4-hydroxycoumarin providing coumestans **3n/3o** and **3p/3q** as regioisomers with 1:1 and 1:1.6 ratios respectively. On the other hand, when 6,7-dimethoxy-4-hydroxycoumarin is treated with **2e**, the coumestans **3r** and **3s** were formed as regioisomers with 1:1.6 ratio. The regioisomers are not separated and their ratios are calculated from ^1H NMR.

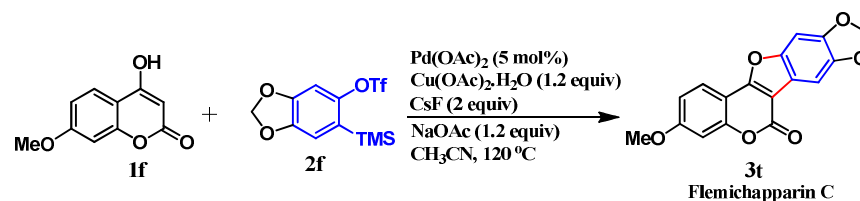
Table 2. Cascade synthesis of coumestans from 4-hydroxycoumarins and benzyne precursors



^a Conditions: 4-Hydroxy coumarin (1.0 mmol), *o*-Silyl aryl triflate (1.5 mmol), Pd(OAc)₂ (5 mol%), Cu(OAc)₂, H₂O (1.2 mmol); CsF (2 mmol); NaOAc (1.2 mmol), CH₃CN (5 mL) stirred in Ace pressure tube at 120 °C for 24h

In order to explore the synthetic application of our Pd(II)-catalyzed cascade strategy, it was planned to access the coumestan group of natural product flemichapparin C. Commercially available 4-hydroxy-7-methoxycoumarin **1f** was coupled with benzyne precursor 5-(trimethylsilyl)benzo[d][1,3]dioxol-6-yl trifluoromethanesulfonate **2f** under the

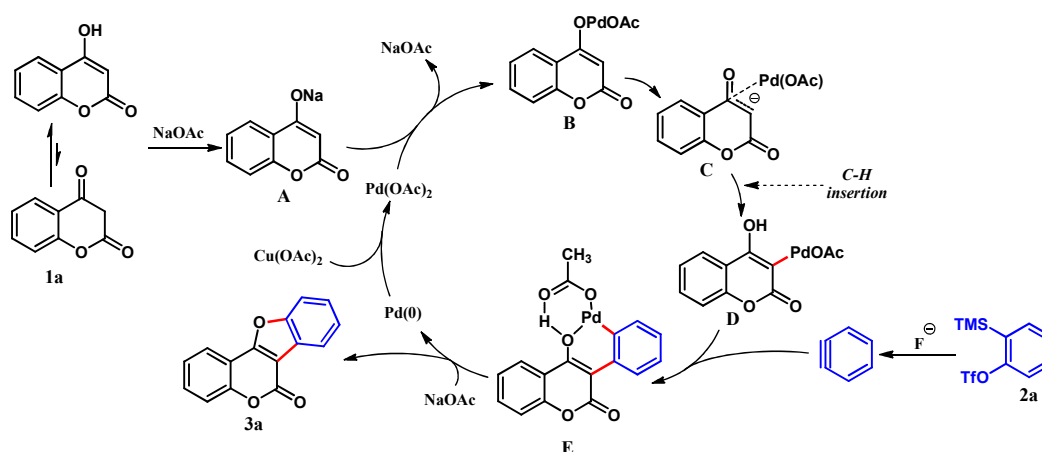
optimized reaction conditions. The product flemichapparin C **3t** was formed in 67% yield with excellent regioselectivity (Scheme 1). The requisite aryne precursor **2f** was efficiently synthesized from sesamol according to the known literature procedure.¹⁴ Notably, the present cascade strategy proves a single-step route to this natural product, in comparison to long and complex chemical^{6b,6c,15} or enzyme-mediated routes.¹⁶



Scheme 1. Synthesis of flemichapparin C

At present, the exact mechanism of Pd(II)-catalyzed method for the synthesis of coumestans is not clear; however, a plausible reaction mechanism for this reaction is shown in scheme 2 based on our experiments and reported mechanisms.¹⁷ We assume that the sodium salt of 4-hydroxycoumarin and palladium(II)acetate exchanges their alkoxide anions to form Pd-salt of 4-hydroxycoumarin **B**, which then forms the anion species **C**. Concurrently, the C3-Pd species **D** is formed *via* the C-H activation at 3-position carbon of **C**, which further undergoes carbopalladation¹⁸ of aryne generated *in situ* from aryne precursor giving species **E**. Finally, in the presence of base the intermediate **E** underwent to our desired product **4a** and Pd(0), which is reoxidized to Pd(II) by Cu(OAc)₂ to complete the catalytic cycle.

Scheme 2. Proposed mechanism for the synthesis of coumestan



In conclusion, we have developed a novel Pd-catalyzed aryne annulation by 4-hydroxycoumarins, which affords moderate to good yields of coumestans. This strategy involves C-H activation, C-C and C-O bond formation successively in a single reaction vessel. Additionally this method has advantages over the reported methods as it does not required pre-functionalization of 4-hydroxycoumarin to have the targeted coumestans. Most interestingly, coupling-prone functional groups like chloro and bromo are remaining intact during our cascade process.

EXPERIMENTAL SECTION

General Information. All reactions involving oxygen- or moisture-sensitive compounds were carried out under argon atmosphere using oven-dried or flame-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in solutions of *p*-anisaldehyde followed by heating. Flash column chromatography was performed with silica gel 60 (100-200 mesh). HRMS data were recorded by electrospray ionization with a Q-TOF mass analyzer.

Extreme caution should be taken when heating a sealed tube. Do not fill the reaction vessel beyond half volume. High pressures and temperatures are generated which have led to explosions. Thus, all reactions must be run in a fume hood with appropriate blast shielding in place. Pressure Ace pressure tubes were purchased from *SIGMA-ALDRICH* (catalog No. Z181064-1EA).

General procedure for the synthesis of coumestans. An oven-dried Ace pressure tube (15 mL capacity) equipped with a magnetic stir bar was evacuated and filled with argon. 4-Hydroxycoumarine (0.162g, 1 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulphonate (0.364 mL, 1.5 mmol), Pd(OAc)₂ (0.011 g, 5 mol%), Cu(OAc)₂·H₂O (0.240 g, 1.2 mmol), NaOAc (0.098g, 1.2 mmol), CsF (0.304 g, 2 mmol) and acetonitrile (5 mL) were added successively at room temperature. The reaction tube again filled with argon and closed with O-ring and PTFE plug by hand tightening. The reaction mixture was heated at 120 °C (preheated oil-bath) with stirring for 24 h and then allowed to cool to room temperature. Water (10 mL) was added to the reaction mixture and the organic layer was extracted with ethyl acetate (2×20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (10%) as eluent.

6*H*-Benzofuro[3,2-*c*]chromen-6-one (3a).¹³

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3a** (0.192 g, 81% yield) as a white solid, *R*_f = 0.6 (10% ethyl acetate/hexanes), mp 180 °C (lit.¹³ mp 181-

182 °C); ¹H NMR (500 MHz, CDCl₃): δ 8.15 (dd, *J*₁= 2.4 Hz, *J*₂= 6.6 Hz, 1H), 8.05 (dd, *J*₁= 1.5 Hz, *J*₂= 7.8 Hz, 1H), 7.68 (dd, *J*₁=1.7 Hz, *J*₂=6.9 Hz, 1H), 7.60-7.64 (m, 1H), 7.41-7.52 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 160.0, 158.1, 155.6, 153.7, 131.9, 126.8, 125.2, 124.7, 123.5, 121.9, 117.5, 112.7, 111.8, 105.9 (one peak is missing due to overlap); IR (CHCl₃): 2918, 2849, 1736, 1628, 1498, 1452, 1371, 1320, 1192, 1096, 1083, 1032, 972, 912, 889, 780, 744 cm⁻¹; HRMS (+ESI) Calcd for C₁₅H₉O₃ [M+H]⁺ : 237.0552; found: 237.0557.

2-Fluoro-6H-benzofuro[3,2-c]chromen-6-one (3b).

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3b** (0.193 g, 76% yield) as light yellow solid; R_f = 0.59 (10% ethyl acetate/hexanes), mp 198-201 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.15 (d, *J*=7.4 Hz, 1H), 7.62-7.74 (m, 2H), 7.45-7.55 (m, 3H), 7.29-7.34 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 159.0 (d, *J*=2.8 Hz), 158.9 (d, *J*=245.7 Hz), 157.6, 155.7, 149.8 (d, *J*=1.6 Hz), 127.2, 126.4, 123.2, 122.0, 119.4 (d, *J*=34.7 Hz), 119.3, 113.4 (d, *J*=9.8 Hz), 111.8, 107.4 (d, *J*=25.8 Hz), 106.6; IR (CHCl₃): 2920, 2850, 1763, 1734, 1567, 1451, 1401, 1257, 1157, 1094, 1066, 996, 861, 821, 774, 748, 667 cm⁻¹; HRMS (+ESI) Calcd for C₁₅H₈FO₃ [M+H]⁺ : 255.0457; found: 255.0455.

2-Chloro-6H-benzofuro[3,2-c]chromen-6-one (3c).^{5e}

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3c** (0.235 g, 87% yield) as light yellow solid; R_f = 0.59 (10% ethyl acetate/hexanes), mp 219 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.14 (dd, *J*₁=1.2 Hz, *J*₂=7.9 Hz, 1H), 8.01 (d, *J*=2.5 Hz, 1H), 7.68 (d, *J*=7.6 Hz, 1H), 7.55 (dd, *J*₁=2.5 Hz, *J*₂=8.9 Hz, 1H), 7.47-7.52 (m, 2H), 7.45 (d, *J*=8.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 158.5, 157.4, 155.6, 151.8, 131.8, 130.2, 127.1, 125.4, 123.1, 121.9, 121.2, 118.8, 113.6, 111.8, 106.5; IR (CHCl₃): 2919, 2850, 1760, 1732, 1556, 1447, 1416, 1162, 1094, 1068, 981, 870, 822, 774, 750, 662 cm⁻¹; HRMS (+ESI) Calcd for C₁₅H₈ClO₃ [M+H]⁺: 271.0162; found: 271.0166

2-Bromo-6H-benzofuro[3,2-c]chromen-6-one (3d).

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3d** (0.211 g, 67% yield) as white solid; R_f = 0.53 (10% ethyl acetate/hexanes), mp 215-217 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.18 (d, *J*=2.3 Hz, 1H), 8.13-8.16 (m, 1H), 7.67-7.71 (m, 2H), 7.46-7.55 (m, 2H), 7.40 (d, *J*=8.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 158.4, 157.3, 155.6, 152.3, 134.6, 127.2, 125.4, 124.3, 123.1, 121.9, 119.1, 117.4, 114.1, 111.8, 106.5; IR (CHCl₃): 2921, 2851, 1757, 1734, 1447, 1162, 979, 872, 820, 775, 750, 665 cm⁻¹; HRMS (+ESI) Calcd for C₁₅H₈BrO₃ [M+H]⁺ : 314.9657; found: 314.9651.

2-Methyl-6H-benzofuro[3,2-c]chromen-6-one (3e).

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3e** (0.177 g, 71% yield) as white solid; R_f=0.58 (10% ethyl acetate/hexanes), mp 151-153 °C; ¹H NMR (500

MHz, CDCl₃): δ 8.07-8.18 (m, 1H), 7.80 (br s, 1H), 7.59-7.70 (m, 1H), 7.32-7.51 (m, 4H), 2.48 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 160.0, 158.2, 155.5, 151.9, 134.5, 133.0, 126.6, 125.1, 123.5, 121.8, 121.5, 117.2, 112.3, 111.7, 105.8, 20.9; IR (CHCl₃): 2920, 2850, 1713, 1635, 1570, 1447, 1358, 1320, 1161, 1097, 1077, 1009, 982, 817, 776, 748, 737, 669, 656 cm⁻¹; HRMS (+ESI) Calcd for C₁₆H₁₁O₃ [M+H]⁺: 251.0708; found: 251.0706

3-Methoxy-6H-benzofuro[3,2-c]chromen-6-one (3f)^{6a}

Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3f** (0.186 g, 70% yield) as light yellow solid, R_f = 0.6 (20% ethyl acetate/hexanes, mp 188 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.04-8.14 (m, 1H), 7.91 (dd, *J*₁ = 1.9 Hz, *J*₂ = 7.3 Hz, 1H), 7.57-7.67 (m, 1H), 7.39-7.47 (m, 2H), 6.94-7.02 (m, 2H), 3.91 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 163.0, 160.6, 158.3, 155.5, 155.2, 126.0, 125.0, 123.5, 122.8, 121.4, 113.0, 111.4, 105.8, 103.3, 101.3, 55.7; IR (CHCl₃): 2921, 2851, 1729, 1613, 1600, 1447, 1427, 1367, 1275, 1254, 1095, 1023, 986, 945, 855, 774, 753, 746 cm⁻¹; HRMS (+ESI) calcd for C₁₆H₁₁O₄ [M+H]⁺: 267.0657; found: 267.0652.

2,3-Dimethyl-6H-benzofuro[3,2-c]chromen-6-one (3g)^{5e}

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3g** (0.193 g, 73% yield) as light yellow solid, R_f = 0.58 (10% ethyl acetate/hexanes), mp: 208-210 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.03-8.14 (m, 1H), 7.67 (s, 1H), 7.56-7.64 (m, 1H), 7.36-7.50 (m, 2H), 7.21 (s, 1H), 2.34 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 160.2, 158.3, 155.2, 152.1, 142.1, 133.5, 126.2, 124.9, 123.6, 121.6, 121.5, 117.8, 111.5, 109.9, 104.8, 20.4, 19.2; IR (CHCl₃): 2917, 2849, 1741, 1638, 1448, 1375, 1177, 1095, 1055, 866, 776, 749, 737 cm⁻¹; HRMS (+ESI) Calcd for C₁₇H₁₃O₃ [M+H]⁺: 265.0865; found: 265.0863.

2,3-Dimethoxy-6H-benzofuro[3,2-c]chromen-6-one (3h).

Flash column chromatography on silica gel (25% ethyl acetate/hexanes) gave **3h** (0.198 g, 67% yield) as light yellow solid, R_f = 0.56 (40% ethyl acetate/hexanes), mp: 227-230 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.09 (dd, *J*₁ = 3.4 Hz, *J*₂ = 5.7 Hz, 1H), 7.62 (dd, *J*₁ = 3.0 Hz, *J*₂ = 6.2 Hz, 1H), 7.44 (d, *J* = 3.3 Hz, 1H), 7.43 (d, *J* = 3.1 Hz, 1H), 7.35 (s, 1H), 6.99 (s, 1H), 4.02 (s, 3H), 3.97 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 160.5, 158.4, 155.1, 152.9, 149.6, 146.7, 126.1, 125.0, 123.6, 121.5, 111.3, 104.5, 103.6, 101.7, 100.5, 56.3x2; IR (CHCl₃): 2917, 2849, 1722, 1515, 1459, 1444, 1270 cm⁻¹; HRMS (+ESI) Calcd for C₁₇H₁₃O₅ [M+H]⁺: 297.0763; found: 297.0765.

3,8,9-Trimethoxy-6H-benzofuro[3,2-c]chromen-6-one (3i)^{6a}

Flash column chromatography on silica gel (35% ethyl acetate/hexanes) gave **3i** (0.212 g, 65% yield) as light yellow solid, R_f = 0.48 (40% ethyl acetate/hexane); mp 230-233 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.85 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.13 (s, 1H), 6.94-7.04 (m, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 162.4, 159.7,

158.8, 154.9, 149.9, 149.0, 147.9, 122.3, 115.5, 113.0, 106.3, 103.8, 102.2, 101.4, 95.5, 56.5, 56.4, 55.8; IR (CHCl₃): 2924, 2853, 1741, 1628, 1608, 1494, 1464, 1411, 1278, 1214, 1024, 837, 804, 765 cm⁻¹; HRMS (+ESI) Calcd for C₁₈H₁₅O₆ [M+H]⁺: 327.0869; found: 327.0871.

8,9-Dimethoxy-2,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (3j)

Flash column chromatography on silica gel (40% ethyl acetate/hexanes) gave **3j** (0.223g, 69% yield) as brown solid, R_f = 0.52 (40% ethyl acetate/hexanes), mp 163 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.64 (s, 1H), 7.49 (s, 1H), 7.22 (s, 1H), 7.15 (s, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 159.3, 158.8, 151.5, 150.1, 149.2, 147.9, 141.2, 135.5, 121.2, 117.8, 115.5, 110.4, 105.1, 102.2, 95.5, 56.5, 56.3, 20.4, 19.4; IR (CHCl₃): 2925, 2854, 1733, 1631, 1595, 1511, 1419, 1351, 1272, 1213, 1023, 819, 803, 756, 664, 638, 584 cm⁻¹; HRMS (+ESI) Calcd for C₁₉H₁₇O₅ [M+H]⁺: 325.1076; found: 325.1077.

2-Methyl-6H-naphtho[2',3':4,5]furo[3,2-c]chromen-6-one (3k)

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3k** (0.192 g, 64% yield) pale yellow sticky solid, R_f = 0.52 (10% ethyl acetate/ hexane); ¹H NMR (500 MHz, CDCl₃): 8.59 (s, 1H), 7.94-8.06 (m, 3H), 7.86 (s, 1H), 7.42-7.56 (m, 4H), 2.51 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 162.4, 158.3, 153.9, 152.4, 135.7, 134.7, 133.7, 132.1, 128.5, 127.9, 126.2, 125.3, 123.4, 121.8, 120.4, 117.3, 112.1, 107.7, 105.2, 20.9 ; IR (CHCl₃): 2923, 2853, 1729, 1714, 1613, 1594, 1506, 1464, 1456, 1367, 1261, 1210, 805, 771, 666, 645 cm⁻¹; HRMS (+ESI) Calcd for C₂₀H₁₃O₃ [M+H]⁺: 301.0865; found: 301.0867.

3-Methoxy-6H-naphtho[2',3':4,5]furo[3,2-c]chromen-6-one (3l).

Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3l** (0.193 g, 61% yield) as brown solid, R_f = 0.65 (20% ethyl acetate/ hexanes); mp: 197-200 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.55 (s, 1H), 7.87-8.12 (m, 4H), 7.43-7.60 (m, 2H), 6.92-7.10 (m, 2H), 3.93 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 163.5, 162.9, 158.2, 156.1, 153.8, 131.8, 131.4, 128.3, 127.9, 125.9, 125.2, 123.4, 123.2, 119.8, 113.2, 107.5, 105.6, 102.6, 101.4, 55.8 ; IR (CHCl₃): 3419, 2922, 2851, 1743, 1613, 1465, 1206, 1161, 1025, 937, 768, 746, 702 cm⁻¹; HRMS (+ESI) Calcd for C₂₀H₁₃O₄ [M+H]⁺: 317.0814; found: 317.0819.

2,3-Dimethoxy-6H-naphtho[2',3':4,5]furo[3,2-c]chromen-6-one (3m).

Flash column chromatography on silica gel (30% ethyl acetate/hexanes) gave **3m** (0.197 g, 57% yield) as pale yellow sticky solid, R_f = 0.48 (in 40% ethyl acetate/hexanes); ¹H NMR (500 MHz, CDCl₃): δ 8.54 (s, 1H), 7.94-8.05 (m, 3H), 7.50-7.55 (m, 2H), 7.39 (s, 1H), 7.00 (s, 1H), 4.04 (s, 3H), 3.99 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 162.9, 158.5, 153.8, 153.6, 150.4, 146.9, 131.8, 131.5, 128.4, 127.9, 126.0, 125.3, 123.6, 119.9, 114.1, 107.5, 104.4, 102.0, 100.6, 56.5x2; IR (CHCl₃): 2960, 2925, 2854, 138, 1732, 1519, 1456, 1276,

1261, 1095, 1020, 800, 675, 664 cm^{-1} ; HRMS (+ESI) Calcd for $\text{C}_{21}\text{H}_{15}\text{O}_5$ $[\text{M}+\text{H}]^+$: 347.0919; found: 347.0916.

**8-Methyl-6H-benzofuro[3,2-c]chromen-6-one (3n) and
9-Methyl-6H-benzofuro[3,2-c]chromen-6-one (3o) (~1:1 mixture)**^{6c}

Flash column chromatography on silica gel (5% ethyl acetate/hexanes) gave **3n** and **3o** (0.195 g, 78% yield) as yellow solid, R_f = 0.51 (in 10% ethyl acetate/ hexane); ^1H NMR (500 MHz, CDCl_3): 7.98 (m, 3H), 7.91 (s, 1H), 7.55-7.61 (m, 2H), 7.52 (d, J = 8.5 Hz, 1H), 7.49 (s, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 7.39 (m, 2H), 7.26 (d, J = 8.0 Hz, 2H), 2.52 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 159.9, 159.4, 158.1, 158.0, 155.8, 153.8, 153.4, 153.3, 137.4, 135.0, 131.6, 131.5, 127.8, 126.4, 124.5, 124.4, 121.7, 121.6, 121.5, 121.1, 117.3, 117.2, 112.7, 112.6, 111.8, 111.1, 105.8, 105.5, 21.8, 21.2; IR (CHCl_3): 2921, 2853, 1742, 1631, 1598, 1450, 1410, 1260, 1094, 1080, 1029, 975, 811, 801, 752, 727, 666, 593 cm^{-1} ; HRMS (+ESI) calcd for $\text{C}_{16}\text{H}_{11}\text{O}_3$ $[\text{M}+\text{H}]^+$: 251.0708; found: 251.0709.

**3-Methoxy-8-methyl-6H-benzofuro[3,2-c]chromen-6-one (3p) and
3-Methoxy-9-methyl-6H-benzofuro[3,2-c]chromen-6-one (3q) (~1:1.1 mixture)**

Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3p** and **3q** (0.207 g, 74% yield) as pale yellow solid, R_f = 0.6 (20% ethyl acetate/hexanes); ^1H NMR (500 MHz, CDCl_3): δ 7.91 (d, J =7.9 Hz, 1H), 7.82-7.86 (m, 3H), 7.46 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.21 (t, J = 8.5 Hz, 2H), 6.90-6.97 (m, 4H), 3.88 (s, 6H), 2.50 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 162.8, 162.7, 160.7, 160.2, 158.5, 158.4, 155.6, 155.4, 155.3, 153.6, 136.7, 134.9, 127.2, 126.3, 123.5, 122.7, 122.6, 121.3, 120.9, 120.8, 113.0, 112.9, 111.7, 110.9, 105.9, 105.8, 103.3, 103.1, 101.3, 101.2, 55.7x2, 21.8, 21.3 cm^{-1} ; IR (CHCl_3): 2925, 2854, 1733, 1632, 1511, 1493, 1418, 1350, 1272, 1213, 1101, 1056, 1022, 819, 803, 770, 666 cm^{-1} ; HRMS (+ESI) Calcd for $\text{C}_{17}\text{H}_{13}\text{O}_4$ $[\text{M}+\text{H}]^+$: 281.0814; found: 281.0816.

**8-methoxy-2,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (3r) and
9-methoxy-2,3-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (3s) (~1: 1.6)**

Flash column chromatography on silica gel (15% ethyl acetate/hexanes) gave **3r** and **3s** (0.206 g, 70% yield) as pale yellow solid, R_f = 0.6 (20% ethyl acetate/hexanes); ^1H NMR (500 MHz, CDCl_3): δ 7.97 (d, J =8.6 Hz, 1H), 7.72 (s, 1H), 7.70 (s, 1H), 7.56 (d, J =2.6 Hz, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.27 (s, 1H), 7.16 (d, J =2.2 Hz, 1H), 6.99-7.07 (m, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H), 2.37 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 160.7, 159.6, 159.3, 158.6, 158.5, 157.5, 156.5, 152.0, 151.7, 149.9, 141.9, 141.4, 133.5, 133.4, 128.5, 124.3, 121.7, 121.6, 121.2, 120.9, 117.9, 117.8, 115.4, 113.1, 112.1, 110.2, 110.1, 103.3, 96.7, 55.9, 55.7, 20.4, 20.3, 19.3x2 cm^{-1} (One peak is missing due to overlap); IR (CHCl_3): 2921, 2851, 1731, 1634, 1594, 1494, 1462, 1272, 1213, 1176 cm^{-1} ; HRMS (+ESI) Calcd for $\text{C}_{18}\text{H}_{15}\text{O}_4$ $[\text{M}+\text{H}]^+$: 295.0970; found: 295.0972.

**3-Methoxy-6H-[1,3]dioxolo[4',5':5,6]benzofuro[3,2-c]chromen-6-one
(Flemichapparin C; 3t)^{6b,6c}**

Flash column chromatography on silica gel (10% ethyl acetate/hexanes) gave **3t** (0.208 g, 67% yield) pale yellow solid, $R_f = 0.52$ (20% ethyl acetate/ hexane); mp 271 °C; ^1H NMR (500 MHz, CDCl_3): 7.85 (d, $J=8.1$ Hz, 1H), 7.46 (s, 1H), 7.12 (s, 1H), 6.99-6.94 (m, 2H), 6.07 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 162.4, 159.9, 158.4, 154.7, 150.5, 147.3, 146.0, 122.2, 116.9, 112.9, 106.1, 103.8, 101.8, 101.3, 100.1, 93.9, 55.7; IR (CHCl_3): 2953, 2919, 2851, 1742, 1633, 1471 cm^{-1} ; HRMS (+ESI) Calcd for $\text{C}_{17}\text{H}_{11}\text{O}_6$ $[\text{M}+\text{H}]^+$: 311.0556; found: 311.0559.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at www.pubs.acs.org. Copies of ^1H and ^{13}C NMR spectra of all products are available.

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