Selective Syntheses of Coumarin and Benzofuran Derivatives Using Phenols and α-Methoxy-β-ketoesters

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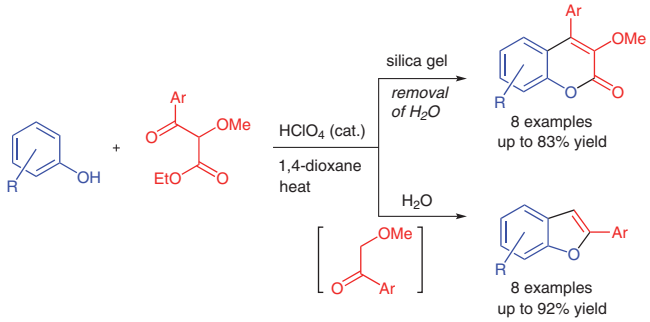


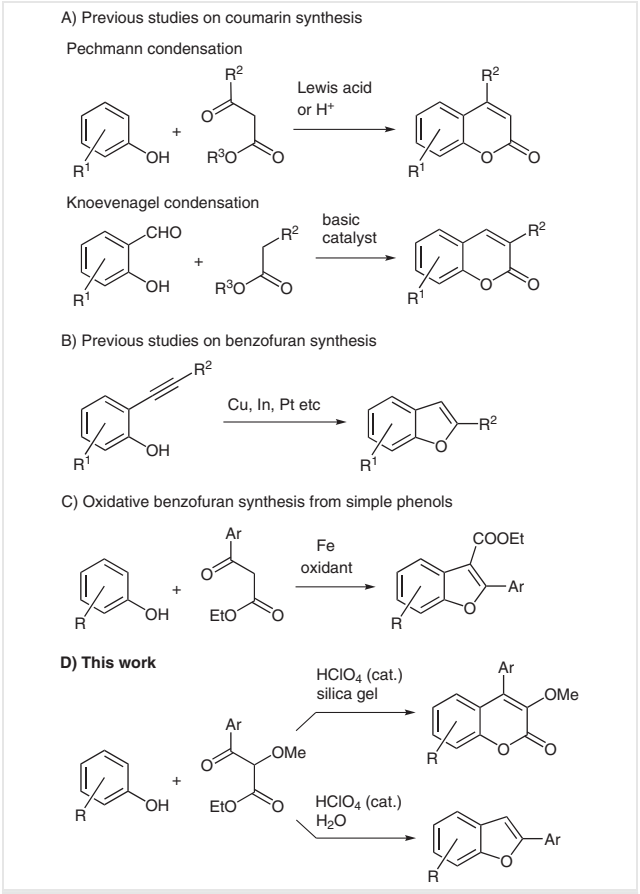
Received: 11.12.2022
Accepted: 13.12.2022
Published online: 26.01.2023 (Version of Record)
DOI: 10.1055/s-0042-1751408; Art ID: SO-2022-12-0073-OP

Abstract Selective syntheses of coumarin and benzofuran derivatives were achieved via $HClO_4$-mediated intermolecular annulation using phenols and α-methoxy-β-ketoesters. Coumarins are formed under dehydrated conditions, whereas benzofurans are formed in the presence of water. In the synthetic process of benzofurans, α-methoxy-β-ketoesters are converted into α-methoxyacetophenones, and the methoxy group is an important element in the intermolecular annulation.

Key words coumarin, benzofuran, selective syntheses, phenol, α-methoxy-β-ketoester, α-methoxyacetophenone

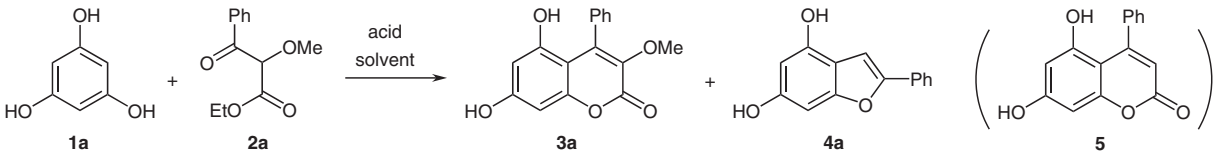
Coumarins and benzofurans are widely distributed in nature and are important heterocyclic compounds in medicinal and materials chemistry.[1] Coumarins exhibit various biological activities, including antioxidant,[2] antiprotozoal,[3] and anti-HIV activities.[4] Their derivatives are used as cosmetic ingredients[5] and dispersed fluorescent dyes.[6] Benzofurans also exhibit interesting activities, including as antitumors,[7] lipid peroxidation inhibitors,[8] and non-nucleoside adenosine A_1 antagonists.[9] They are widely used as fluorescent materials, such as fluorescent organic nanoparticles.[10] Therefore, many researchers are investigating the development of efficient synthetic methods for both coumarins and benzofurans.

Pechmann and Knoevenagel condensations are typical methods used for the synthesis of coumarin derivatives (Scheme 1A).[11,12] In recent years, new methodologies using transition metal catalysts have been developed, such as the hydroarylation of alkynes and the carbonylation of *ortho*-vinylphenols.[13] However, only a few studies have reported on the synthesis of 3-heteroatom-substituted coumarins.[14] The introduction of functional groups at the C3-position



Scheme 1 Various synthetic methods for coumarin and benzofuran derivatives

Table 1 Preliminary Survey for the Synthesis of Coumarin **3a** Starting from **1a** and **2a**



Entry	**1a** (equiv)	Acid (equiv)	Solvent	Temp. (°C)	Time (h)	NMR yield of **3a** (%)[a]	**3a**/**4a** ratio[a]
1	1.1	HCl (6.0)	EtOH	rt	72	57	1:0
2	1.1	H_2SO_4 (6.0)	EtOH	rt	72	24	1:0
3	1.1	TfOH (6.0)	EtOH	rt	72	70	1:0
4	1.1	TfOH (0.1)	EtOH	90	24	22	4.4:1
5	3.0	TfOH (0.1)	EtOH	90	24	32	3.4:1
6	3.0	TfOH (0.1)	*i*-PrOH	90	24	28	5.8:1
7	3.0	TfOH (0.1)	DMSO	90	24	trace	–
8	3.0	TfOH (0.1)	DCE	90	24	<56	1:0
9	3.0	TfOH (0.1)	1,4-dioxane	90	24	66	3.2:1
10	3.0	$HClO_4$ (0.1)	1,4-dioxane	90	24	68	3.2:1

[a] Determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard.

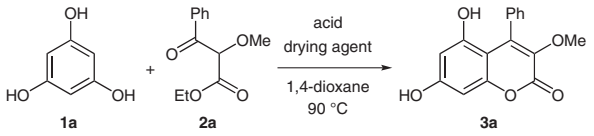
has attracted much attention for improving the physical properties of coumarin-based molecules and enriching the library of their derivatives.[15] Therefore, a convenient synthetic approach to 3-heteroatom-substituted coumarins is required.

Benzofurans are often constructed by the cyclization of *ortho*-functionalized phenols, including phenols bearing carbon–carbon multiple bonds and salicylaldehyde derivatives.[16] For example, transition-metal-catalyzed hydroalkoxylation of *ortho*-alkynylphenols has been used successfully to synthesize 2-substituted benzofurans (Scheme 1B).[17] Considering the wide availability of substrates, it is desirable to develop the reactions using simple phenols.[18] Li *et al.* presented the iron-catalyzed oxidative reaction of phenols with β-ketoesters to form ethyl 2-arylbenzofuran-3-carboxylates (Scheme 1C).[19] Cossío *et al.* demonstrated the synthesis of 2- and 3-substituted benzofurans from phenols and α-bromoacetophenones, respectively.[20] Nonetheless, practical methods using readily available substrates are still limited. Herein, we describe the novel selective syntheses of 3-methoxy-4-arylcoumarins and 2-arylbenzofurans using phenols **1** and α-methoxy-β-ketoesters **2** (Scheme 1D).

Using phloroglucinol (**1a**) and ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**) as substrates, the reaction conditions for the synthesis of 3-methoxy-4-phenylcoumarin **3a** were investigated. First, **2a** was synthesized by the reaction of β-ketoester with MeOH using iodobenzene diacetate.[21] The reaction of **1a** with **2a** was carried out in the presence of Brønsted acids, which are commonly employed in the Pechmann reaction,[22] and the desired 3-methoxycoumarin **3a** was successfully obtained (Table 1, entries 1–3). Among these acids, trifluoromethanesulfonic acid (TfOH) gave the best results, affording **3a** in 70% NMR yield. We aimed to use catalytic amounts of TfOH, but the yield of **3a** was low, even under heating conditions (entry 4). Unexpectedly, 2-phenylbenzofuran (**4a**) was obtained as a byproduct.[23] While it has been reported that acid treatment of α-methoxy-β-ketoester at high temperature leads to demethoxylation to β-ketoester,[24] the reaction of **1a** with **2a** did not give 4-phenylcoumarin **5**. To proceed with the reaction, substrate **1a** was increased to 3.0 equiv and the use of various solvents was examined (entries 5–9). Polar solvents, such as *i*-PrOH and DMSO, did not affect the yield (entries 6 and 7). 1,2-Dichloroethane (DCE) was a potential solvent that produced **3a** in good yields, along with side reactions (entry 8). The screening of solvents revealed that 1,4-dioxane was a suitable solvent (entry 9). Furthermore, the reaction in 1,4-dioxane was found to have an effect comparable with that observed using $HClO_4$ as an acid (entries 9 and 10).[25]

H_2O was released during the formation of **3a**. It was assumed that H_2O inhibits the transesterification of **1a** and **2a**. Therefore, the effects of drying agents were investigated (Table 2). In the case of molecular sieves (4Å) or trimethyl orthoformate, no reaction occurred (entries 2 and 3). When 2,2-dimethoxypropane was used, **3a** was obtained in 71% NMR yield. However, it could not be separated from the byproducts by column chromatography (entry 4). Silica gel was more effective, generating **3a** in 70% isolated yield (entry 5).[26] In contrast, the combination of TfOH and silica gel resulted in lower yields (entry 5 vs entry 6).

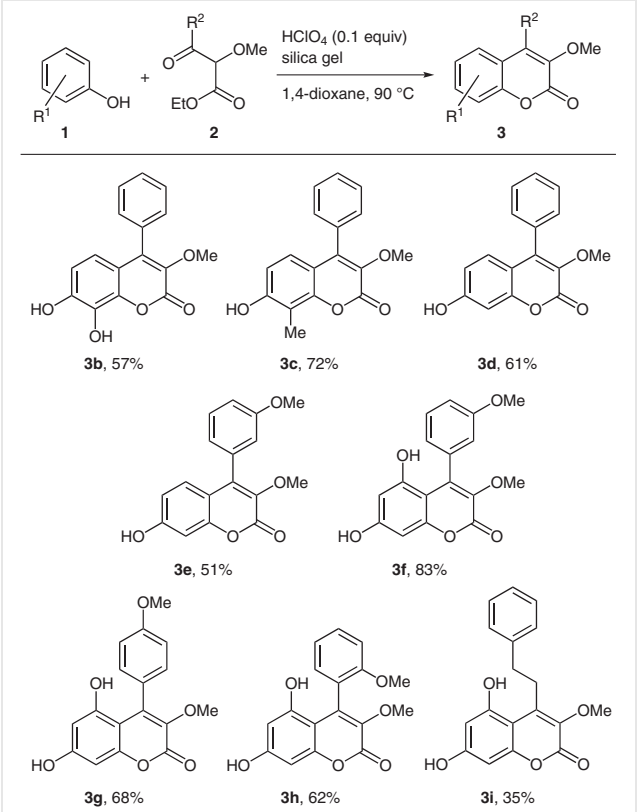
Table 2 Effects of Drying Agents on the Formation of **3a**



Entry	Acid (equiv)	Drying agent	Isolated yield (%)
1	$HClO_4$ (0.1)	–	60
2	$HClO_4$ (0.1)	molecular sieves 4Å	no reaction
3	$HClO_4$ (0.1)	$HC(OMe)_3$	no reaction
4	$HClO_4$ (0.1)	$Me_2C(OMe)_2$	71[a]
5	$HClO_4$ (0.1)	silica gel	70
6	TfOH (0.1)	silica gel	58

[a] Determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard.

With the optimized conditions in hand, the substrate scope was evaluated. The results are shown in Scheme 2. This method allowed for the isolation of 3-methoxy-4-arylcoumarins in good yields. Phenols **1** with varying numbers of substituents at different positions afforded the corresponding products **3b–d** in 57–72% yields. In particular, resorcinol was converted into 7-hydroxycoumarins **3d** and **3e** without the formation of 5-hydroxy compounds. α-Methoxy-β-ketoesters **2** with different substituent patterns were applied for the synthesis of coumarins **3f–h**. Furthermore, 4-alkylcoumarin **3i** could be also synthesized in 35% yield.

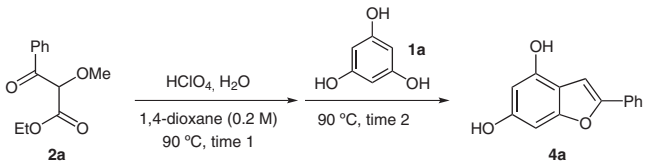


Scheme 2 $HClO_4$-mediated intermolecular annulation of **1** and **2** into coumarins **3**. *Reaction conditions*: **1** (3.0 mmol), **2** (1.0 mmol), silica gel (~1.3 g), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL), 1,4-dioxane (4.0 mL), 90 °C, 24 h. Isolated yields based on **2**.

Next, focusing on the observation of benzofuran **4a** during coumarin synthesis, we investigated whether water was involved in the formation of benzofuran **4** (Table 3). In the presence of excess H_2O, the $HClO_4$-mediated reaction between **1a** and **2a** did not proceed at all (entry 1). In contrast, the reaction using 3 equiv of H_2O gave benzofuran **4a** in higher yield than coumarin **3a** (entry 2). Simultaneously, α-methoxyacetophenone (**9**) was also observed. It was assumed that α-methoxy-β-ketoester **2a** was hydrolyzed and decarboxylated to **9**, which then underwent intermolecular annulation with phenol **1a** to afford benzofuran **4a**. On the other hand, Yonezawa *et al.* have reported the reaction of α-methoxy-carboxylic acids with aromatic compounds under acidic conditions, in which case the carboxyl and methoxy groups are replaced by two aryl groups.[27] In order to proceed with decarboxylation, the reaction procedure was modified as follows: to a solution of **2a** in 1,4-dioxane were added H_2O and catalytic $HClO_4$, and after stirring at 90 °C for 7 h, **1a** was added. As shown in entry 3, the reaction gave **4a** in 53% NMR yield, with a **4a**/**3a** ratio of 3.8:1. The change to 0.3 equiv of $HClO_4$ afforded good product selectivity, but excess use of H_2O reduced the yield of **4a** (entries 4–6). Finally, increasing the amount of **1a** and the reactant concentration afforded only **4a** in 73% isolated yield (entries 7 and 8, see the Supporting Information for details).

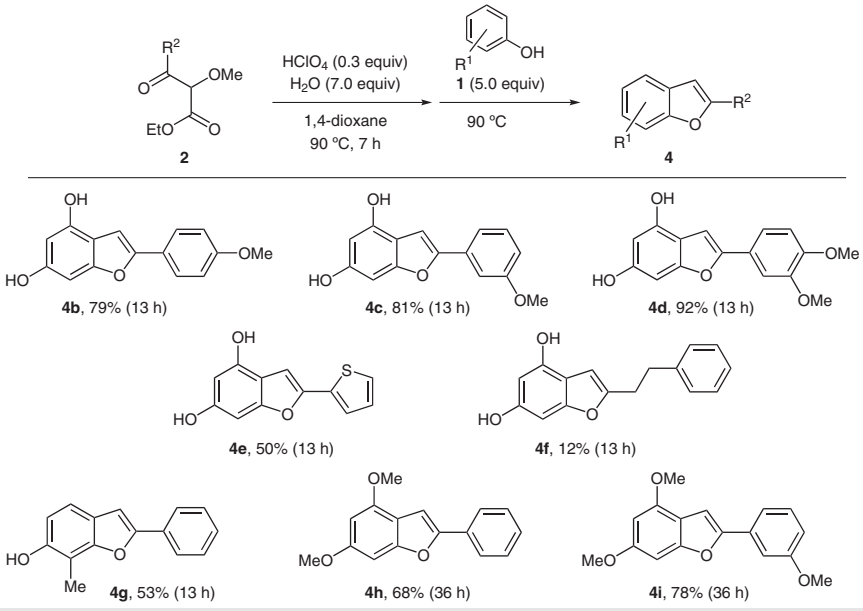
The developed protocol was applied to phenols **1** and α-methoxy-β-ketoesters **2** (Scheme 3). Treatment of **2** with $HClO_4$ and H_2O, followed by the addition of **1**, produced the desired benzofurans **4** in good to excellent yields. Additional substituents on the aromatic ring of **2** increased the yields. Benzofurans with heterocyclic as well as aryl groups in the C2-position could be synthesized in good yields, while 2-alkylbenzofuran **4f** was synthesized in a low yield. The use of 3,5-dimethoxyphenol instead of phloroglucinol required a long reaction time; however, products **4h** and **4i** were obtained in good yields.

Table 3 Optimizing the Conditions for the Synthesis of Benzofuran **4a**



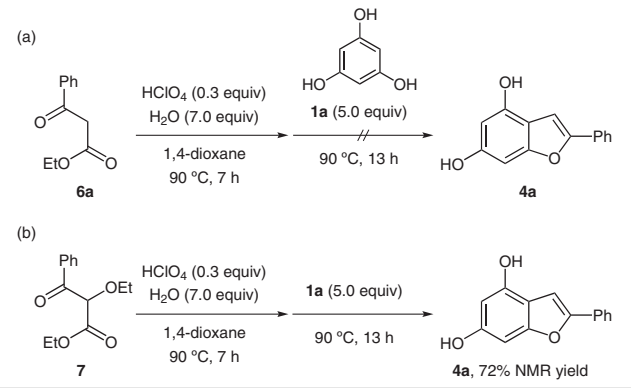
Entry	$HClO_4$ (equiv)	H_2O (equiv)	Time 1 (h)	**1a** (equiv)	Time 2 (h)	NMR yield of **4a** (%)[a]	**4a**/**3a** ratio[a]
1	0.1	excess	–	3.0	24	no reaction	–
2	0.1	3.0	–	3.0	24	33	1.5:1
3	0.1	3.0	7	3.0	17	53	3.8:1
4	0.3	3.0	7	3.0	17	60	15:1
5	0.3	7.0	7	3.0	17	69	12:1
6	0.3	15.0	7	3.0	17	54	1:0
7	0.3	7.0	7	5.0	13	75	1:0
8[b,c]	0.3	7.0	7	5.0	13	80 (73)[d]	1:0

[a] Determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard.
[b] 0.33 M solution of **2a** in 1,4-dioxane.
[c] Ar gas was bubbled through the solvent.
[d] Isolated yield in parenthesis.



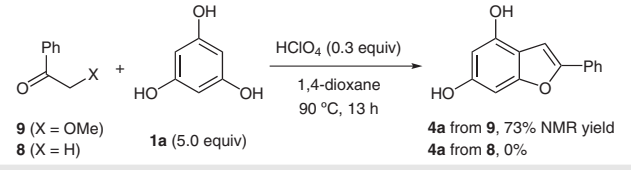
Scheme 3 $HClO_4$-mediated intermolecular annulation of **1** and **2** into benzofurans **4**. *Reaction conditions*: **2** (0.33 mmol), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL), H_2O (2.3 mmol), 90 °C, 7 h, then **1** (1.7 mmol), 90 °C for the time indicated in parentheses. Isolated yields based on **2**.

Control experiments were performed to elucidate the reaction mechanism. Using β-ketoester **6a** without the α-substituent, the reaction with **1a** gave acetophenone (**8**) as the main product, instead of benzofuran **4a** (Scheme 4a). α-Ethoxy-β-ketoester **7** exhibited a reactivity comparable to that of α-methoxy derivative **2a**, although with a slightly low yield of **4a** (Scheme 4b). This phenomenon indicates that the α-alkoxy group in β-ketoester **2** is essential for benzofuran formation.



Scheme 4

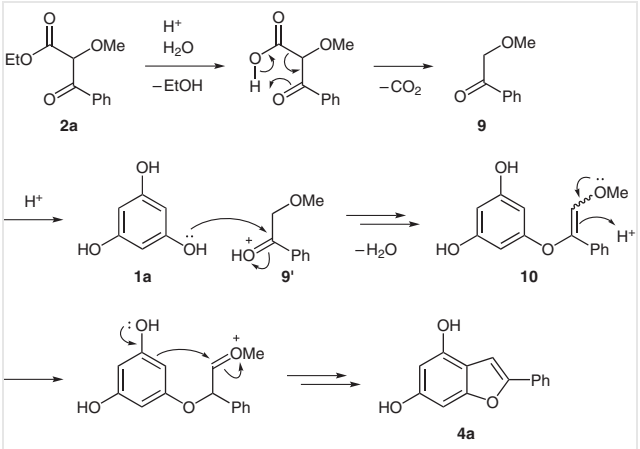
Therefore, we were interested in at what step of the intermolecular annulation process the ester group was decarboxylated. α-Methoxyacetophenone (**9**) was reacted with **1a** under the optimal condition, without water. The reaction proceeded smoothly to form benzofuran **4a** in 73% NMR yield (Scheme 5). Even in acetophenone, the absence of the methoxy group did not lead to the formation of benzofuran **4a**. It was found that the ester group was initially decarboxylated and the resulting α-methoxyacetophenone underwent intermolecular annulation.



Scheme 5 Conversion of acetophenones **8** and **9** into benzofuran **4a**

Based on our experimental findings, we propose the following mechanism for benzofuran formation (Scheme 6). First, α-methoxy-β-ketoester is hydrolyzed by $HClO_4$ and H_2O, followed by decarboxylation to form α-methoxyacetophenone (**9**). The hydroxy group of phenol **1a** undergoes nucleophilic addition to the carbonyl carbon of protonated **9**, resulting in the formation of intermediate **10**. Finally, the intramolecular cyclization of **10** gives the corresponding benzofuran **4a**.

In conclusion, we have developed a method for selective syntheses of coumarin and benzofuran derivatives starting from common substrates **1** and **2**. Both reactions are facilitated by $HClO_4$, and the choice of route depends on the water content. During the synthesis of benzofurans, H_2O induces the decarboxylation of α-methoxy-β-ketoester. The resulting α-methoxyacetophenone undergoes intermolecular annulation with phenols. To the best of our knowledge, this is the first successful conversion of phenols and α-methoxyacetophenones into benzofurans.[28] Further investigation of the practical extension and elucidation of this mechanism is currently in progress in our laboratory.



Scheme 6 Proposed mechanism for the formation of benzofuran

Melting points were determined on a Yanaco Micro Melting Point Apparatus and are uncorrected. Infrared (IR) absorption spectra were obtained using a Jasco FT/IR-4200 or FT/IR-4700 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker BioSpin AVANCE III 400 or a JEOL JNM-ECZ500R spectrometer. NMR spectra were referenced to residual solvent peaks (acetone-d_6: ^1H NMR δ = 2.05, ^{13}C NMR δ = 29.84). Mass spectra were determined with a Thermo Fisher Scientific Q-Exactive HR-ESI-Orbitrap-MS mass spectrometer. For preparative HPLC, a Jasco PU-1586 Intelligent HPLC Pump, a Tosoh UV-8010 detector, a Shiseido Capcell Pak UG 120 C18 column (5 µm, 20 × 250 mm), and HPLC grade solvents were used.

Kanto Chemical silica gel (silica gel 60N, spherical neutral, particle size 40–50 µm) was directly used for column chromatography. Silica gel was activated by heating with a heat gun when used as a drying agent. 0.1 M $HClO_4$ in 1,4-dioxane (CAS: 7601-90-3) was purchased from Hayashi Pure Chemicals Ind., Ltd. Other commercial reagents were directly used without further purification.

General Procedure for the Synthesis of Coumarin Derivatives 3

To the solution of phenol **1** (3.0 mmol, 3.0 equiv) and α-methoxy-β-ketoester **2** (1.0 mmol, 1.0 equiv) in 1,4-dioxane (4.0 mL, 0.2 M) was added silica gel (~1.3 g) under a N_2 atmosphere. $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 equiv) was dropwise added to the mixture at rt. The reaction mixture was heated at 90 °C (oil bath) for 24 h. The resulting mixture was filtered through Celite. The filtrate was quenched with sat. aq $NaHCO_3$ and extracted with EtOAc (100 mL × 3). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography or reverse phase preparative HPLC to give the corresponding coumarin **3**.

5,7-Dihydroxy-3-methoxy-4-phenylcoumarin (3a)

Phloroglucinol (**1a**; 380 mg, 3.0 mmol, 3.0 equiv), ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**; 230 mg, 1.0 mmol, 1.0 equiv), silica gel (1.1 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) in 1,4-dioxane (4.0 mL) were heated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1:1) to afford **3a** (200 mg, 70%) as a white solid; mp 245–248 °C.

IR (KBr): 3497, 3262, 1705, 1623, 1596, 1573, 1461, 1380, 1300, 1243, 1201 cm^{-1}.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 7.42–7.27 (m, 5 H), 6.36 (d, *J* = 2.3 Hz, 1 H), 6.25 (d, *J* = 2.3 Hz, 1 H), 3.57 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 160.7, 158.6, 157.2, 154.9, 142.1, 138.4, 136.7, 128.9, 128.2, 128.1, 102.4, 100.5, 95.8, 60.1.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{11}O_5$: 283.0612; found: 283.0616.

7,8-Dihydroxy-3-methoxy-4-phenylcoumarin (3b)

Pyrogallol (**1b**; 430 mg, 3.4 mmol, 3.0 equiv), ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**; 250 mg, 1.1 mmol, 1.0 equiv), silica gel (1.1 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) in 1,4-dioxane (4.0 mL) were heated. The residue was purified by reverse phase preparative HPLC (H_2O/MeCN = 1:1, 0.1% TFA) to afford **3b** (180 mg, 57%) as a brown solid; mp 93–95 °C.

IR (KBr): 3557, 3485, 3179, 1710, 1702, 1600, 1469, 1340, 1275 cm^{-1}.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 7.59–7.46 (m, 3 H), 7.38 (d, *J* = 7.6 Hz, 2 H), 6.78 (d, *J* = 8.7 Hz, 1 H), 6.46 (d, *J* = 8.7 Hz, 1 H), 3.69 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 158.5, 148.3, 142.1, 141.6, 138.7, 133.5, 133.0, 129.9, 129.4, 129.2, 118.2, 114.6, 113.2, 60.3.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{11}O_5$: 283.0612; found: 283.0615.

7-Hydroxy-3-methoxy-8-methyl-4-phenylcoumarin (3c)

2-Methylresorcinol (**1c**; 380 mg, 3.1 mmol, 3.0 equiv), ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**; 220 mg, 1.0 mmol, 1.0 equiv), silica gel (1.1 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) in 1,4-dioxane (4.0 mL) were heated. The residue was purified by reverse phase preparative HPLC (H_2O/MeCN = 1:1, 0.1% TFA) to afford **3c** (200 mg, 72%) as a white solid; mp 214–217 °C.

IR (ATR): 3283, 2928, 1672, 1611, 1571, 1458, 1356, 1256 cm^{-1}.

^{1}H NMR (acetone-d_6, 500 MHz): δ = 9.15 (s, 1 H), 7.59–7.47 (m, 3 H), 7.43–7.37 (m, 2 H), 6.81 (d, *J* = 9.0 Hz, 1 H), 6.76 (d, *J* = 9.0 Hz, 1 H), 3.70 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (acetone-d_6, 125 MHz): δ = 158.9, 158.1, 151.6, 141.9, 138.6, 133.5, 129.9, 129.4, 129.3, 125.4, 113.8, 112.8, 112.2, 60.2, 8.3.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{13}O_4$: 281.0819; found: 281.0816.

7-Hydroxy-3-methoxy-4-phenylcoumarin (3d)

Resorcinol (**1d**; 410 mg, 3.7 mmol, 3.0 equiv), ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**; 270 mg, 1.2 mmol, 1.0 equiv), silica gel (1.2 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) in 1,4-dioxane (4.0 mL) were heated. The residue was purified by flash column chromatography (CH_2Cl_2/EtOAc = 10:1 to 5:1) to afford **3d** (200 mg, 61%) as a white solid; mp 196–200 °C.

IR (KBr): 3340, 1699, 1616, 1557, 1511, 1464, 1350, 1321, 1257 cm^{-1}.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 9.26 (brs, 1 H), 7.60–7.48 (m, 3 H), 7.39 (d, *J* = 6.6 Hz, 2 H), 6.95 (d, *J* = 8.7 Hz, 1 H), 6.82 (d, *J* = 2.4 Hz, 1 H), 6.77 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.70 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 160.4, 158.8, 153.6, 141.5, 138.9, 133.3, 129.9, 129.5, 129.3, 128.7, 113.83, 113.81, 103.3, 60.3.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{11}O_4$: 267.0663; found: 267.0666.

7-Hydroxy-3-methoxy-4-(3-methoxyphenyl)coumarin (3e)

Resorcinol (**1d**; 340 mg, 3.1 mmol, 3.0 equiv), ethyl 2-methoxy-3-(3-methoxyphenyl)-3-oxopropanoate (**2c**; 250 mg, 0.99 mmol, 1.0 equiv), silica gel (1.3 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) in 1,4-dioxane (4.0 mL) were heated. The residue was purified by reverse phase preparative HPLC (H_2O/MeCN = 2:3, 0.1% TFA) to afford **3e** (150 mg, 51%) as a white solid; mp 179–182 °C.

IR (ATR): 3272, 1684, 1610, 1451, 1362, 1238 cm^{-1}.

^{1}H NMR (acetone-d_6, 500 MHz): δ = 9.33 (s, 1 H), 7.47 (t, *J* = 8.2 Hz, 1 H), 7.09–7.04 (m, 1 H), 6.97 (d, *J* = 8.7 Hz, 1 H), 7.01–6.93 (m, 2 H), 6.81 (d, *J* = 2.4 Hz, 1 H), 6.78 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.71 (s, 3 H).

^{13}C NMR (acetone-d_6, 125 MHz): δ = 160.7, 160.4, 158.8, 153.5, 141.5, 138.8, 134.6, 130.5, 128.8, 121.9, 115.4, 114.9, 113.8, 113.7, 103.2, 60.3, 55.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{13}O_5$: 297.0768; found: 297.0765.

5,7-Dihydroxy-3-methoxy-4-(3-methoxyphenyl)coumarin (3f)

Phloroglucinol (**1a**; 380 mg, 3.0 mmol, 3.0 equiv), ethyl 2-methoxy-3-(3-methoxyphenyl)-3-oxopropanoate (**2c**; 260 mg, 1.0 mmol, 1.0 equiv), silica gel (1.3 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) in 1,4-dioxane (4.0 mL) were heated. The residue was purified by reverse phase preparative HPLC (H_2O/MeCN = 3:2, 0.1% TFA) to afford **3f** (260 mg, 83%) as an orange solid; mp 198–200 °C.

IR (KBr): 3509, 3223, 1684, 1627, 1599, 1558, 1468, 1395, 1371, 1296, 1249, 1200 cm^{-1}.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 9.17 (brs, 1 H), 8.45 (brs, 1 H), 7.30 (t, *J* = 7.4 Hz, 1 H), 6.95–6.84 (m, 3 H), 6.35 (d, *J* = 2.4 Hz, 1 H), 6.25 (d, *J* = 2.4 Hz, 1 H), 3.80 (s, 3 H), 3.59 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 160.7, 160.2, 158.6, 157.1, 154.9, 141.9, 138.3, 137.9, 129.4, 121.1, 114.5, 113.7, 102.4, 100.5, 95.8, 60.2, 55.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{13}O_6$: 313.0718; found: 313.0719.

5,7-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)coumarin (3g)

Phloroglucinol (**1a**; 420 mg, 3.3 mmol, 3.0 equiv), ethyl 2-methoxy-3-(4-methoxyphenyl)-3-oxopropanoate (**2b**; 280 mg, 1.1 mmol, 1.0 equiv), silica gel (1.1 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) were heated in 1,4-dioxane (4.0 mL). The residue was purified by reverse phase preparative HPLC (H_2O/MeCN = 1:1, 0.1% TFA) to afford **3g** (240 mg, 68%) as an orange solid; mp 268–270 °C.

IR (KBr): 3233, 1687, 1612, 1556, 1513, 1471, 1372, 1297, 1234 cm^{-1}.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 8.29 (brs, 1 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.35 (d, *J* = 2.4 Hz, 1 H), 6.25 (d, *J* = 2.4 Hz, 1 H), 3.84 (s, 3 H), 3.57 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 160.6, 160.2, 158.6, 157.3, 154.9, 141.8, 138.7, 130.3, 128.2, 113.8, 102.6, 100.6, 95.9, 60.0, 55.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{13}O_6$: 313.0718; found: 313.0722.

5,7-Dihydroxy-3-methoxy-4-(2-methoxyphenyl)coumarin (3h)

Phloroglucinol (**1a**; 380 mg, 3.0 mmol, 3.0 equiv), ethyl 2-methoxy-3-(2-methoxyphenyl)-3-oxopropanoate (**2d**; 260 mg, 1.0 mmol, 1.0 equiv), silica gel (1.3 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1

mmol, 0.1 equiv) were heated in 1,4-dioxane (4.0 mL). The residue was purified by reverse phase preparative HPLC (H_2O/MeCN = 3:2, 0.1% TFA) to afford **3h** (200 mg, 62%) as a brown solid; mp 207–210 °C.

IR (KBr): 3466, 3400, 1703, 1624, 1566, 1493, 1464, 1432, 1351, 1292, 1238 cm^{-1}.

^1H NMR (acetone-d_6, 400 MHz): δ = 9.13 (brs, 1 H), 8.50 (brs, 1 H), 7.32 (t, *J* = 8.2 Hz, 1 H), 7.15 (d, *J* = 7.5 Hz, 1 H), 7.01 (d, *J* = 8.2 Hz, 1 H), 6.96 (t, *J* = 7.5 Hz, 1 H), 6.34 (d, *J* = 2.3 Hz, 1 H), 6.23 (d, *J* = 2.3 Hz, 1 H), 3.73 (s, 3 H), 3.57 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 160.3, 158.7, 157.6, 157.3, 154.8, 139.5, 138.4, 129.8, 129.7, 125.9, 120.6, 111.3, 102.9, 100.2, 95.6, 59.8, 55.8.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{13}O_6$: 313.0718; found: 313.0721.

5,7-Dihydroxy-3-methoxy-4-phenethylcoumarin (3i)

Phloroglucinol (**1a**; 350 mg, 2.8 mmol, 3.0 equiv), ethyl 2-methoxy-3-oxo-5-phenylpentanoate (**2g**; 230 mg, 0.92 mmol, 1.0 equiv), silica gel (1.3 g), and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.1 equiv) were heated in 1,4-dioxane (4.0 mL). The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1:1) to afford **3i** (100 mg, 35%) as a brown solid; mp 216–219 °C.

IR (ATR): 3437, 3154, 1659, 1610, 1460, 1362, 1282, 1241 cm^{-1}.

^1H NMR (acetone-d_6, 500 MHz): δ = 9.66 (s, 1 H), 9.16 (s, 1 H), 7.32–7.25 (m, 4 H), 7.23–7.15 (m, 1 H), 6.46 (d, *J* = 2.6 Hz, 1 H), 6.33 (d, *J* = 2.6 Hz, 1 H), 3.74 (s, 3 H), 3.40–3.33 (m, 2 H), 3.30–2.83 (m, 2 H).

^{13}C NMR (acetone-d_6, 125 MHz): δ = 160.3, 157.9, 157.4, 155.2, 143.2, 143.0, 138.5, 129.22, 129.18, 126.8, 102.5, 100.7, 96.1, 60.0, 36.8, 30.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{18}H_{15}O_5$: 311.0925; found: 311.0924.

General Procedure for the Synthesis of Benzofuran Derivatives 4

α-Methoxy-β-ketoester **2** (0.33 mmol, 1.0 equiv) was placed in a glass vessel, and $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv) and H_2O (42 µL, 2.3 mmol, 7.0 equiv) were added. The mixture was stirred at rt for 5 min while bubbling with argon. After stirring at 90 °C (oil bath) for 7 h, phenol **1** (1.7 mmol, 5.0 equiv) was added at rt. The reaction mixture was stirred at 90 °C (oil bath) for 13–36 h, quenched with H_2O, and extracted with EtOAc (50 mL × 2). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography. Further purification of the desired combined fractions was performed by reverse phase preparative HPLC to give the corresponding benzofuran **4**.

4,6-Dihydroxy-2-phenylbenzofuran (4a)

Ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**; 74 mg, 0.33 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (42 µL, 2.3 mmol, 7.0 equiv) were heated. Phloroglucinol (**1a**; 210 mg, 1.7 mmol, 5.0 equiv) was added and the reaction mixture was heated for 13 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 2:1 to 3:2) followed by reverse phase preparative HPLC (H_2O/MeCN = 1:1, 0.1% TFA) to afford benzofuran **4a** (55 mg, 73%) as a white solid; mp 168–170 °C.

IR (KBr): 3317, 1698, 1610, 1507, 1488, 1442, 1345, 1254 cm^{-1}.

^1H NMR (acetone-d_6, 400 MHz): δ = 8.83 (brs, 1 H), 8.41 (brs, 1 H), 7.83 (d, *J* = 7.8 Hz, 2 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 7.31 (t, *J* = 7.8 Hz, 1 H), 7.21 (s, 1 H), 6.56 (s, 1 H), 6.32 (s, 1 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 158.2, 157.8, 153.5, 152.1, 131.8, 129.7, 128.5, 124.8, 112.3, 99.9, 98.7, 90.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9O_3$: 225.0557; found: 225.0555.

4,6-Dihydroxy-2-(4-methoxyphenyl)benzofuran (4b)

Ethyl 2-methoxy-3-(4-methoxyphenyl)-3-oxopropanoate (**2b**; 82 mg, 0.33 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (41 µL, 2.3 mmol, 7.0 equiv) were heated. Phloroglucinol (**1a**; 210 mg, 1.7 mmol, 5.0 equiv) was added and the reaction mixture was heated for 13 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 3:2) followed by reverse phase preparative HPLC (H_2O/MeCN = 1:1, 0.1% TFA) to afford benzofuran **4b** (66 mg, 79%) as an orange solid; mp 185–188 °C.

IR (KBr): 3329, 1645, 1612, 1501, 1450, 1398, 1343, 1301, 1253 cm^{-1}.

^1H NMR (acetone-d_6, 400 MHz): δ = 8.74 (brs, 1 H), 8.33 (brs, 1 H), 7.75 (d, *J* = 8.5 Hz, 2 H), 7.04 (s, 1 H), 7.01 (d, *J* = 8.5 Hz, 2 H), 6.54 (s, 1 H), 6.30 (s, 1 H), 3.84 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 160.5, 157.9, 157.3, 153.8, 151.9, 126.3, 124.6, 115.1, 112.5, 98.7, 98.0, 90.7, 55.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{11}O_4$: 255.0663; found: 255.0664.

4,6-Dihydroxy-2-(3-methoxyphenyl)benzofuran (4c)

Ethyl 2-methoxy-3-(3-methoxyphenyl)-3-oxopropanoate (**2c**; 85 mg, 0.34 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (42 µL, 2.3 mmol, 7.0 equiv) were heated. Phloroglucinol (**1a**; 210 mg, 1.7 mmol, 5.0 equiv) was added and the reaction mixture was heated for 13 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 2:1 to 3:2) followed by reverse phase preparative HPLC (H_2O/MeCN = 1:1, 0.1% TFA) to afford benzofuran **4c** (70 mg, 81%) as a red amorphous solid.

IR (KBr): 3377, 1686, 1611, 1489, 1340, 1258, 1213 cm^{-1}.

^1H NMR (acetone-d_6, 400 MHz): δ = 7.45–7.32 (m, 3 H), 7.23 (s, 1 H), 6.88 (dd, *J* = 8.1, 2.4 Hz, 1 H), 6.57 (s, 1 H), 6.33 (s, 1 H), 3.87 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 161.1, 158.1, 157.7, 153.4, 152.1, 133.0, 130.8, 117.2, 114.3, 112.2, 109.9, 100.2, 98.6, 90.6, 55.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{11}O_4$: 255.0663; found: 255.0664.

4,6-Dihydroxy-2-(3,4-dimethoxyphenyl)benzofuran (4d)

Ethyl 2-methoxy-3-(3,4-dimethoxyphenyl)-3-oxopropanoate (**2e**; 95 mg, 0.34 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (42 µL, 2.3 mmol, 7.0 equiv) were heated. Phloroglucinol (**1a**; 210 mg, 1.7 mmol, 5.0 equiv) was added and the reaction mixture was heated for 13 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 3:2 to 1:1) to afford benzofuran **4d** (89 mg, 92%) as a colorless amorphous solid.

IR (ATR): 3369, 1687, 1610, 1503, 1447, 1338, 1241 cm^{-1}.

^1H NMR (acetone-d_6, 400 MHz): δ = 8.75 (brs, 1 H), 8.35 (brs, 1 H), 7.40–7.35 (m, 2 H), 7.07 (s, 1 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 6.54 (s, 1 H), 6.31 (s, 1 H), 3.91 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 157.9, 157.4, 153.8, 151.9, 150.7, 150.4, 124.9, 117.6, 113.0, 112.5, 108.8, 98.7, 98.4, 90.6, 56.17, 56.16.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{13}O_5$: 285.0768; found: 285.0769.

4,6-Dihydroxy-2-(thiophen-2-yl)benzofuran (4e)

Ethyl 2-methoxy-3-oxo-3-(thiophen-2-yl)propanoate (**2f**; 72 mg, 0.32 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (40 µL, 2.2 mmol, 7.0 equiv) were heated. Phloroglucinol (**1a**; 220 mg, 1.7 mmol, 5.0 equiv) was added and the reaction mixture was heated for 13 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1:1) followed by reverse phase preparative HPLC (H_2O/MeCN = 3:2, 0.1% TFA) to afford benzofuran **4e** (37 mg, 50%) as a white solid; mp 155–158 °C.

IR (ATR): 3327, 2482, 1685, 1604, 1497, 1439, 1331, 1250 cm^{-1}.

^1H NMR (acetone-d_6, 500 MHz): δ = 7.47 (d, *J* = 4.3 Hz, 1 H), 7.45 (d, *J* = 4.3 Hz, 1 H), 7.13 (t, *J* = 4.3 Hz, 1 H), 7.02 (d, *J* = 2.0 Hz, 1 H), 6.53 (d, *J* = 2.5 Hz, 1 H), 6.32 (d, *J* = 2.5 Hz, 1 H).

^{13}C NMR (acetone-d_6, 125 MHz): δ = 157.8, 157.7, 152.0, 149.1, 134.3, 128.8, 125.8, 124.2, 112.0, 99.5, 98.9, 90.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{12}H_7O_3S$: 231.0121; found: 231.0117.

4,6-Dihydroxy-2-phenethylbenzofuran (4f)

Ethyl 2-methoxy-3-oxo-5-phenylpentanoate (**2g**; 80 mg, 0.32 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (40 µL, 2.2 mmol, 7.0 equiv) were heated. Phloroglucinol (**1a**; 200 mg, 1.6 mmol, 5.0 equiv) was added and the reaction mixture was heated for 13 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1:1) followed by reverse phase preparative HPLC (H_2O/MeCN = 1:1, 0.1% TFA) to afford benzofuran **4f** (10 mg, 12%) as a white solid; mp 132–134 °C.

IR (ATR): 3331, 2914, 1679, 1637, 1509, 1448, 1410, 1341, 1260 cm^{-1}.

^1H NMR (acetone-d_6, 500 MHz): δ = 8.60 (s, 1 H), 8.23 (s, 1 H), 7.34–7.14 (m, 5 H), 6.45 (d, *J* = 1.3 Hz, 1 H), 6.41 (s, 1 H), 6.25 (d, *J* = 1.3 Hz, 1 H), 3.12–2.80 (m, 4 H).

^{13}C NMR (acetone-d_6, 125 MHz): δ = 157.9, 156.7, 155.7, 151.3, 142.1, 129.22, 129.18, 126.9, 111.4, 100.2, 98.3, 90.5, 34.6, 30.8.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{13}O_3$: 253.0870; found: 253.0866.

6-Hydroxy-7-methyl-2-phenylbenzofuran (4g)

Ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**; 74 mg, 0.33 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (42 µL, 2.3 mmol, 7.0 equiv) were heated. 2-Methylresorcinol (**1c**; 210 mg, 1.7 mmol, 5.0 equiv) was added and the reaction mixture was heated for 13 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 6:1 to 3:1) followed by reverse phase preparative HPLC (H_2O/MeCN = 2:3, 0.1% TFA) to afford benzofuran **4g** (39 mg, 53%) as a white solid; mp 102–105 °C.

IR (ATR): 3266, 2923, 1603, 1417, 1313, 1216 cm^{-1}.

^1H NMR (acetone-d_6, 500 MHz): δ = 8.46 (s, 1 H), 8.00 (s, 1 H), 7.71 (d, *J* = 7.7 Hz, 2 H), 7.52 (d, *J* = 8.6 Hz, 1 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 6.94 (d, *J* = 8.6 Hz, 1 H), 2.37 (s, 3 H).

^{13}C NMR (acetone-d_6, 125 MHz): δ = 157.0, 154.1, 141.4, 133.4, 129.8, 128.0, 127.9, 123.0, 119.2, 118.0, 112.9, 108.5, 8.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}O_2$: 225.0910; found: 225.0909.

4,6-Dimethoxy-2-phenylbenzofuran (4h)

Ethyl 2-methoxy-3-oxo-3-phenylpropanoate (**2a**; 72 mg, 0.32 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (41 µL, 2.3 mmol, 7.0 equiv) were heated. 3,5-Dimethoxyphenol (**1e**; 250 mg, 1.6 mmol, 5.0 equiv) was added and the reaction mixture was heated for 36 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 10:1) to afford benzofuran **4h** (56 mg, 68%) as a white solid; mp 62–64 °C.

IR (ATR): 3376, 1687, 1610, 1500, 1446, 1329, 1220 cm^{-1}.

^1H NMR (acetone-d_6, 400 MHz): δ = 7.86 (d, *J* = 7.3 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.20 (s, 1 H), 6.78 (s, 1 H), 6.41 (s, 1 H), 3.93 (s, 3 H), 3.86 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 160.6, 157.5, 154.6, 154.3, 131.6, 129.7, 128.7, 124.9, 113.8, 99.8, 95.3, 89.0, 56.1, 56.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}O_3$: 255.1016; found: 255.1015.

4,6-Dimethoxy-2-(3-methoxyphenyl)benzofuran (4i)

Ethyl 2-methoxy-3-(3-methoxyphenyl)-3-oxopropanoate (**2c**; 82 mg, 0.33 mmol, 1.0 equiv), $HClO_4$ (0.1 M in 1,4-dioxane; 1.0 mL, 0.1 mmol, 0.3 equiv), and H_2O (41 µL, 2.3 mmol, 7.0 equiv) were heated. 3,5-Dimethoxyphenol (**1e**; 250 mg, 1.6 mmol, 5.0 equiv) was added and the reaction mixture was heated for 36 h. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 9:1) to afford benzofuran **4i** (72 mg, 78%) as a white solid; mp 78–80 °C.

IR (ATR): 1602, 1560, 1495, 1478, 1461, 1425, 1324, 1273, 1204 cm^{-1}.

^1H NMR (acetone-d_6, 400 MHz): δ = 7.47–7.33 (m, 3 H), 7.22 (s, 1 H), 6.90 (d, *J* = 8.1 Hz, 1 H), 6.78 (s, 1 H), 6.41 (s, 1 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 161.1, 160.7, 157.5, 154.6, 154.2, 132.9, 130.8, 117.4, 114.7, 113.8, 110.1, 100.2, 95.3, 89.0, 56.1, 56.0, 55.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_4$: 285.1121; found: 285.1119.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

This research was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant JP20J23632.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1751408.

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