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A New Synthetic Route of 2-Aroyl- and 2-Benzyl-Benzofurans and their Application in the Total Synthesis of a Metabolite Isolated from *Dorstenia gigas*

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The Lewis acid-catalyzed cyclization of the (*Z*)-3-(dimethylamino)-2-aryloxy-1-arylprop-2-en-1-ones **4a**–**h** leads to a regioselective and short synthesis of 2-aroylbenzofurans **2a**–**h**. The Wolff–Kishner reduction of the latter yielded a series of substituted 2-benzylbenzofurans **3a**–**h**. This methodology was applied in the first total synthesis of the metabolite 2-(4-hydroxybenzyl)-6-methoxybenzofuran **1**, which was isolated from the tropical plant *Dorstenia gigas*, and obtained through a six-step route and in a 24% overall yield.

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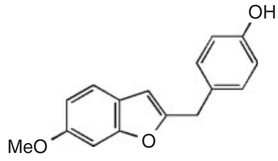
Introduction

The genus *Dorstenia* (Moraceae) has attracted special interest due to the isolation of a large variety of heterocyclic compounds such as furocoumarins, benzofurans, and flavonoids.[1–7] The presence of these metabolites has been associated with the biological properties exhibited by some species of this genus, when used in folk medicine, mainly for the treatment of skin diseases.[8–12] Among the metabolites isolated from *Dorstenia gigas*, a succulent shrub growing on Socotra Island whose extracts have shown anti-inflammatory and antibiotic activities,[13] one can find 2-(4-hydroxybenzyl)-6-methoxybenzofuran **1** (Scheme 1),[13] which is a natural product exhibiting antifungal activity in the *Cladosporium* bioassay, and which displays an uncommon 2-benzylbenzofuran framework.[14] Owing to the medicinal and horticultural interest of *D. gigas*, a micropropagation technique has been developed with the intention of reproducing this threatened species.[15]

However, 2-aroylbenzofurans and 2-benzylbenzofurans have been synthesized, and some of them have exhibited significant biological properties, such as estrogenic, spasmolytic, antiviral, antimicrobial, and anticancer activities.[16–20] In an intense effort to synthesize 2-substituted benzofurans,[21–24] many methodologies that lead to the preparation of 2-aroylbenzofurans have been reported,[16–20,23,25–29] whereas only a few approaches have been found for the synthesis of 2-benzylbenzofurans.[16,26,30–33]

Recently, we reported a new straightforward synthesis of 2-carbomethoxy- and 2-acetyl-benzofurans, through an intramolecular cyclization of enaminones promoted by Lewis acids.[34] This strategy allowed us to prepare a series of natural benzofurans in good overall yields.[35] Therefore, the ready access to the construction of the benzofuran scaffold by this methodology prompted us to extend it to the preparation of the substituted 2-aroyl- and 2-benzyl-benzofurans **2** and **3**, respectively, by using enaminones **4** as their precursors (Scheme 2), as well as to the development of the first total synthesis of natural compound **1**.



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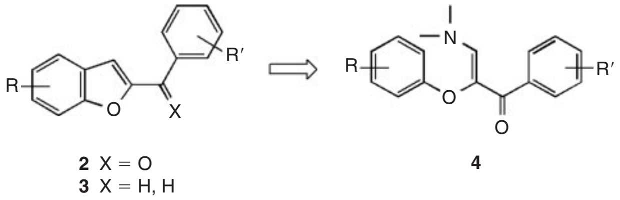
Scheme 1.



Scheme 2.

Results and Discussion

Phenoxyacetophenones **8a**–**h** were prepared in high yields (80–88%) by treating the corresponding 2-bromoacetophenones **6a**–**e** with phenols **7a**,**b** in the presence of potassium carbonate in acetone at reflux for 12 h (Scheme 3). 2-Bromoacetophenones

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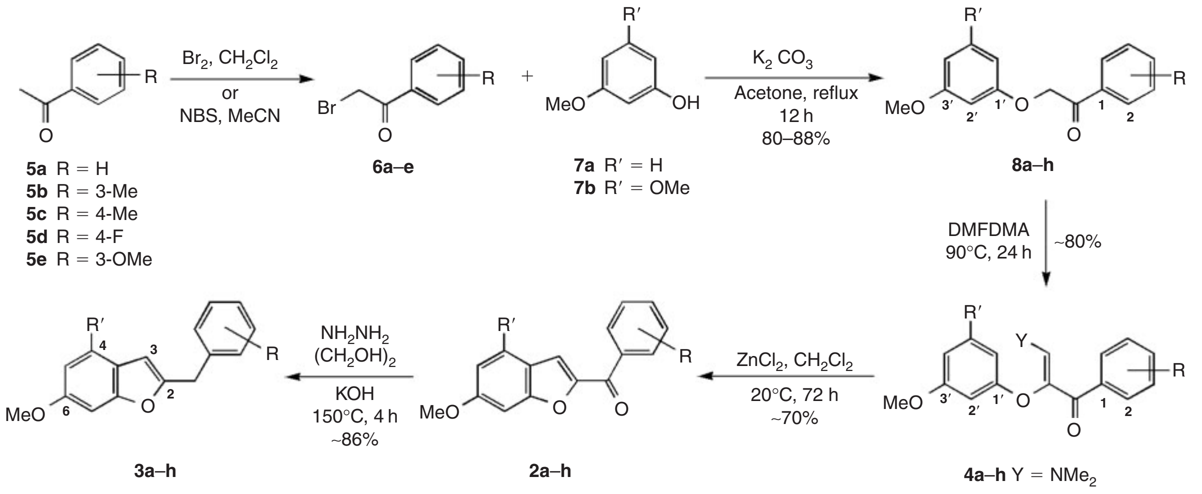


Scheme 3.

Table 1. Preparation of methyl 2-aryloxy-3-dimethylaminopropenoates 4a–h

Under a N_2 atmosphere, with 3.0 mol equiv. of DMFDMA at 90°C for 24 h

Entry	**8** (R)	(R′)	**4** [%][A]
1	**8a** (H)	H	**4a** (88)
2	**8b** (3-Me)	H	**4b** (86)
3	**8c** (4-Me)	H	**4c** (84)
4	**8d** (4-F)	H	**4d** (91)
5	**8e** (3-OMe)	H	**4e** (80)
6	**8f** (H)	OMe	**4f** (89)
7	**8g** (4-Me)	OMe	**4g** (82)
8	**8h** (4-F)	OMe	**4h** (93)

[A] After column chromatography and recrystallization.

Table 2. Preparation of 2-aroylbenzofurans 2a–h[A] and 2-benzylbenzofurans 3a–h[B]

Entry	(R)	(R′)	**2** [%][C]	**3** [%][C]
1	(H)	H	**2a** (72)	**3a** (89)
2	(3-Me)	H	**2b** (70)	**3b** (90)
3	(4-Me)	H	**2c** (63)	**3c** (91)
4	(4-F)	H	**2d** (76)	**3d** (78)
5	(3-OMe)	H	**2e** (55)	**3e** (90)
6	(H)	OMe	**2f** (78)	**3f** (88)
7	(4-Me)	OMe	**2g** (65)	**3g** (90)
8	(4-F)	OMe	**2h** (79)	**3h** (75)

[A] Under a N_2 atmosphere, with 5.0 mol equiv. of $ZnCl_2$ in CH_2Cl_2 as the solvent at 20°C for 72 h.

[B] Under a N_2 atmosphere, with 6.5 mol equiv. of NH_2NH_2, KOH in $(CH_2OH)_2$ as the solvent at 150°C for 4 h.

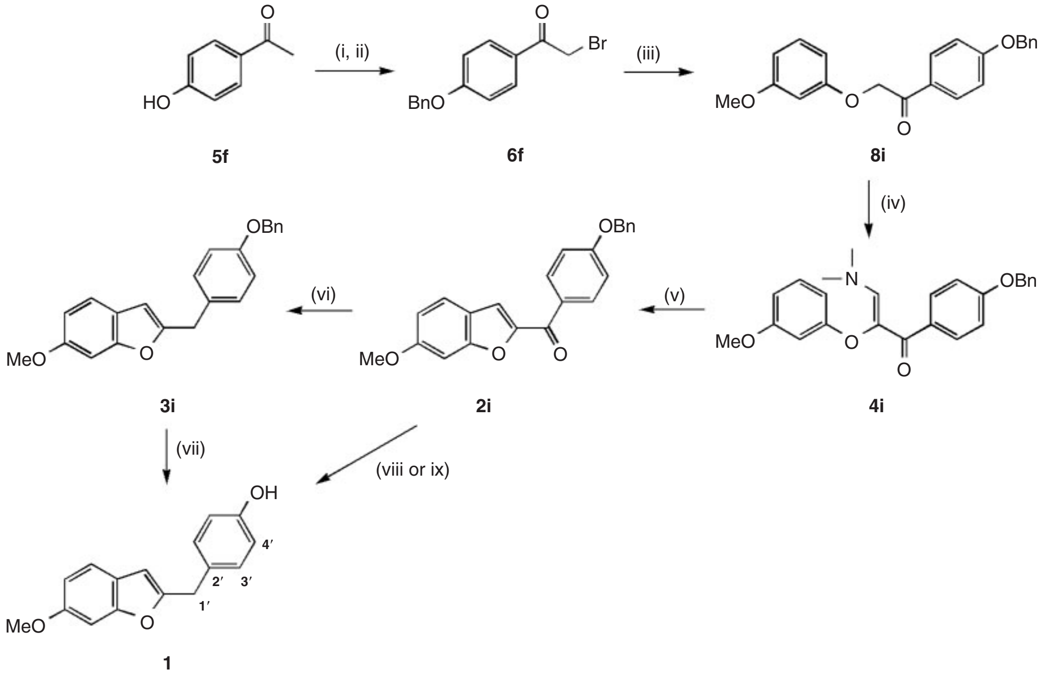
[C] After column chromatography or recrystallization.

6a–**e** are commercially available or can be prepared by bromination of the acetophenones **5a**–**e** with bromine in $CHCl_3$,[36] or in the presence of zinc dust in H_2O,[37] or with *N*-bromosuccinimide (NBS) in the presence of *p*-toluenesulfonic acid.[38] Treatment of **8a**–**h** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) at 90°C for 24 h provided the respective enaminones **4a**–**h**, also in high yields (Table 1). The latter were obtained as a single stereoisomer, whose geometry (*Z*) was established by nuclear Overhauser effect experiments: irradiation of the signal assigned to protons of the dimethylamino group of compound **4a** produced an enhancement of the signals corresponding to the aryloxy ring; the same was true for the irradiation of the vinyl proton with an enhancement of the acetophenone moiety.

Cyclization of enaminones **4a**–**h** promoted by $ZnCl_2$ as the Lewis acid furnished the desired 2-aroylbenzofurans **2a**–**h** (Scheme 3) in fairly good yields (55–79%) (Table 2). Owing to the low solubility of the catalyst in the solvent, we had to use a large excess (5.0 mol equiv.) to increase the conversion rate. Other Lewis acids were used such as $BF_3{\cdot}OEt_2$, $AlCl_3$, and $MgBr_2$ to improve the reaction yields, but they were less efficient. Also, low yields were obtained when we used microwave irradiation, in contrast with our previous results.[35] Reduction of the carbonyl group was carried out under Clemmensen conditions (Zn–Hg, HCl)[39,40] to give the corresponding 2-benzylbenzofurans **3a**–**h** (Scheme 3) in low yields. The reduction efficiency was significantly improved when Wolff–Kishner conditions (NH_2NH_2, $(CH_2OH)_2$, KOH)[26,41] were used (Table 2).

Once the reaction sequence conditions for the preparation of 2-benzylbenzofurans **3** were established, the synthesis of natural compound **1** was accomplished under analogous conditions. The substrate 2-bromoacetophenone **6f**[42,43] was prepared from phenol **5f** by protection with benzyl bromide in the presence of potassium carbonate as the base,[44] followed by a treatment with bromine in methylene chloride, to give **6f** in a 76% overall yield (Scheme 4). Substitution of the bromine atom by the phenoxy group was carried out by treatment of the latter with **7a**, to provide **8i** in high yield (86%). This product was treated with DMFDMA at 90°C for 24 h to give enaminone **4i** in good yield (81%). Treatment of the latter with the Lewis acid led to 2-aroylbenzofuran **2i** as a single regioisomer. It is worth noting that the cyclization of **4i** took place within 48 h by using only 3.0 mol equiv. of $ZnCl_2$, in contrast with the longer reaction time and larger amount of catalyst employed with the general method (Table 2).

Compound **2i** was transformed into the natural product **1** by two alternative pathways. The first consisted of a two-step



Scheme 4. Reagents and conditions: (i) BnBr, K_2CO_3, acetone, reflux, 6 h, 95%; (ii) Br_2, CH_2Cl_2, 20°C, 1 h, 80%; (iii) **7a**, K_2CO_3, acetone, reflux, 12 h, 86%; (iv) DMFDMA, 90°C, 24 h, 81%; (v) $ZnCl_2$, CH_2Cl_2, 20°C, 48 h, 68%; (vi) Zn–Hg, HCl, EtOH, 65°C, 8 h, 81%; (vii) H_2, Pd/C, EtOAc, 20°C, 12 h, 77%; (viii) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 20°C, 3 h, 40%; (ix) Zn–Hg, HCl, EtOH, 65°C, 12 h, 68%.

sequence, starting from a reduction with amalgam of zinc to give **3i**, and followed by a Pd-catalyzed hydrogenation to furnish **1** in a 62% overall yield for the two steps (Scheme 4). The second pathway was accomplished by reduction of the carbonyl group and debenzylation of **2i** in a single step. To carry out the latter, we tried two different sets of conditions: (1) treatment with triethylsilane in the presence of $BF_3{\cdot}OEt_2$ in methylene chloride at room temperature for 3 h,[45] to give **1** in 40% yield; (2) application of the same Clemmensen conditions (Zn–Hg, HCl, 65°C) used in the first pathway, but increasing the concentration of the reagents and the reaction time (12 h), afforded 68% of the desired product.[46] Therefore, the latter route was shorter and more efficient than the former one. The spectral data of the synthetic compound **1** were identical to those described for the natural metabolite.[13]

Conclusions

A new synthetic route for the preparation of the uncommon 2-benzylbenzofurans, **3a**–**h**, is described. It consists of a sequence of four steps, starting from the reaction between the series of 2-bromoacetophenones **6a**–**h** and the phenols **7a**,**b**, and includes an intramolecular cyclization of the corresponding enaminones **4a**–**h** to give the 2-aroylbenzofurans **2a**–**h**, as the key step. Reduction of the carbonyl group of the latter yielded the desired products **3a**–**h**. This methodology was applied to the first total synthesis of the naturally occurring metabolite **1**, through a six-step sequence, with a 24% overall yield.

Experimental

General

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin–Elmer (Spectrum 2000) Fourier transform (FT)-IR spectrometer. ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Varian Mercury-300 instrument, with TMS as internal standard. Mass spectra (MS) and high-resolution mass spectra (HR-MS) were obtained, in electron impact (EI) (70 eV) and fast-atom bombardment (FAB) modes, on a Thermo-Finnigan Polaris Q and on a Jeol JMS-AX 505 HA spectrometer, respectively. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ). Analytical TLC was carried out by using Merck silica gel 60 F_{254}-coated plates, visualized by long- and short-wavelength UV lamps. Flash column chromatography was performed on silica gel (230–400 mesh) from Natland International Co. All air moisture-sensitive reactions were carried out under nitrogen using oven-dried glassware. Methylene chloride, ethyl acetate, and acetonitrile were freshly distilled over calcium hydride, before use. Acetone was distilled after refluxing over $KMnO_4$ for 4 h. K_2CO_3 was dried overnight at 200°C before being used. All other reagents were used without further purification.

*General Method of Preparation of 2-Bromoacetophenones **6a**–**e**: 2-Bromoacetophenone **6a***

At room temperature and under a N_2 atmosphere, NBS (0.66 g, 3.72 mmol) was slowly added to a mixture of **5a** (0.50 g, 3.72 mmol) and *p*-TsOH (0.96 g, 5.58 mmol) in dry acetonitrile (150 mL). The mixture was heated to 70°C for 2 h, the solvent was removed under vacuum, the residue was dissolved with 100 mL of CH_2Cl_2, and then washed with H_2O (3×50 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (40 g, hexane/EtOAc, 98:2), to give **6a** as a white solid (0.63 g, 80%). Retention factor (R_f) 0.37 (hexane/EtOAc, 85:15). mp 45–46°C (lit.[47] 46–47°C).

2-Bromo-4′-benzyloxyacetophenone **6f**

A mixture of **5f** (2.0 g, 14.7 mmol) in 20 mL of dry acetone, and K_2CO_3 (4.06 g, 29.4 mmol) was heated to reflux for 30 min, and benzyl bromide (3.77 g, 22.0 mmol) was added dropwise. The mixture was stirred and heated to reflux for 6 h, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane/EtOAc, 85:15), to give **9** as a white solid (3.16 g, 95%). R_f 0.35 (hexane/EtOAc, 8:2). mp 93–94°C (lit.[44] 93°C). At room temperature and under a N_2 atmosphere, bromine (1.42 g, 8.85 mmol) in dry CH_2Cl_2 (5 mL) was slowly added to a solution of **9** (2.0 g, 8.85 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred to 20°C for 1 h, and washed with a cold saturated solution of $Na_2S_2O_4$ (3×5 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (40 g, hexane/EtOAc, 95:5), to give **6f** as a white solid (2.16 g, 80%). R_f 0.43 (hexane/EtOAc, 8:2). mp 89–90°C (lit.[42,43] 88–90°C).

Preparation of Acetophenones **8a–h**: 2-(3-Methoxyphenoxy)-1-phenylethanone **8a**

To a solution of **7a** (0.20 g, 1.61 mmol) in dry acetone (2 mL), at room temperature and under a N_2 atmosphere, anhydrous K_2CO_3 (0.33 g, 2.4 mmol) was added. The mixture was stirred at 60°C for 40 min, and a solution of **6a** (0.38 g, 1.91 mmol) in dry acetone (1 mL) was added dropwise. The mixture was maintained under the same conditions for 12 h, was filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane/EtOAc, 95:5), to give **8a** as a white solid (0.33 g, 84%). R_f 0.54 (hexane/EtOAc, 8:2). mp 85–86°C (lit.[48] 85–87°C).

2-(3-Methoxyphenoxy)-1-(3-tolyl)ethanone **8b**

Following the procedure as for **8a**, with **7a** (0.20 g, 1.61 mmol) in 2 mL of dry acetone, K_2CO_3 (0.33 g, 2.39 mmol), and **6b** (0.41 g, 1.93 mmol) in 1 mL of dry acetone afforded **8b** as a colourless solid (0.34 g, 84%). R_f 0.56 (hexane/EtOAc, 8:2). mp 43–44°C (Found: C 75.2, H 6.4. $C_{16}H_{16}O_3$ requires C 75.0, H 6.3%). ν_{max} (KBr)/cm^{-1} 1704, 1611, 1493, 1433, 1334, 1270, 1202, 1151, 1036, 932, 833, 788, 752, 687. δ_H ($CDCl_3$) 2.37 (3H, s, $ArCH_3$), 3.71 (3H, s, OCH_3), 5.19 (2H, s, OCH_2), 6.47–6.53 (3H, m, H2′, H4′, H6′), 7.09–7.17 (1H, m, H5′), 7.29–7.39 (2H, m, H4, H5), 7.72–7.77 (2H, m, H2, H6). δ_C ($CDCl_3$) 21.1, 55.0, 70.3, 101.2, 106.3, 107.0, 125.0, 128.2, 128.5, 129.7, 134.2, 134.4, 138.5, 159.0, 160.6, 194.1. *m*/*z* (EI) 256 (M$^+$, 10%), 239 (5), 119 (100), 91 (18).

2-(3-Methoxyphenoxy)-1-(4-tolyl)ethanone **8c**[49]

Following the procedure as for **8a**, with **7a** (0.20 g, 1.61 mmol) in 2 mL of dry acetone, K_2CO_3 (0.33 g, 2.39 mmol), and **6c** (0.41 g, 1.93 mmol) in 1 mL of dry acetone afforded **8c** as a white solid (0.343 g, 83%). R_f 0.62 (hexane/EtOAc, 8:2). mp 70–71°C.

1-(4-Fluorophenyl)-2-(3-methoxyphenoxy)ethanone **8d**[50]

Following the procedure as for **8a**, with **7a** (0.20 g, 1.61 mmol) in 2 mL of dry acetone, K_2CO_3 (0.33 g, 2.39 mmol), and **6d** (0.42 g, 1.93 mmol) in 1 mL of dry acetone afforded **8d** as a white solid (0.36 g, 86%). R_f 0.63 (hexane/EtOAc, 8:2). mp 61–62°C.

2-(3-Methoxyphenoxy)-1-(3-methoxyphenyl)ethanone **8e**

Following the procedure as for **8a**, with **7a** (0.20 g, 1.61 mmol) in 2 mL of dry acetone, K_2CO_3 (0.33 g, 2.39 mmol), and **6e** (0.44 g, 1.93 mmol) in 1 mL of dry acetone afforded **8e** as a pale yellow solid (0.354 g, 81%). R_f 0.33 (hexane/EtOAc, 8:2). mp 76–78°C (Found: (M)$^+$ 272.1048. $C_{16}H_{16}O_4$ requires 272.1049). ν_{max} (KBr)/cm^{-1} 1703, 1597, 1492, 1456, 1433, 1288, 1263, 1198, 1154, 1042, 766, 686. δ_H ($CDCl_3$) 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.24 (2H, s, OCH_2), 6.52–6.56 (3H, m, H2′, H4′, H6′), 7.12–7.18 (2H, m, H5′, H4), 7.39 (1H, t, *J* 7.8, H5), 7.51 (1H, dd, *J* 2.6, 1.3, H2), 7.55 (1H, ddd, *J* 7.5, 1.5, 1.2, H6). δ_C ($CDCl_3$) 55.2, 55.4, 70.7, 101.4, 106.5, 107.2, 112.3, 120.3, 120.4, 129.8, 129.9, 135.7, 159.2, 159.9, 160.8, 194.0. *m*/*z* 272 (M$^+$, 13%), 135 (100), 107 (21), 77 (12).

2-(3,5-Dimethoxyphenoxy)-1-phenylethanone **8f**

Following the procedure as for **8a**, with **7b** (0.20 g, 1.3 mmol) in 2 mL of dry acetone, K_2CO_3 (0.26 g, 1.88 mmol), and **6f** (0.31 g, 1.55 mmol) in 1 mL of dry acetone afforded **8f** as a white solid (0.30 g, 85%). R_f 0.40 (hexane/EtOAc, 8:2). mp 87–88°C (lit.[47] 87–88°C).

2-(3,5-Dimethoxyphenoxy)-1-(4-tolyl)ethanone **8g**

Following the procedure as for **8a**, with **7b** (0.20 g, 1.3 mmol) in 2 mL of dry acetone, K_2CO_3 (0.26 g, 1.88 mmol), and **6g** (0.33 g, 1.55 mmol) in 1 mL of dry acetone, afforded **8g** as a white solid (0.312 g, 84%). R_f 0.60 (hexane/EtOAc, 8:2). mp 94–95°C (lit.[51] 95–96°C).

2-(3,5-Dimethoxyphenoxy)-1-(4-fluorophenyl)ethanone **8h**

Following the procedure as for **8a**, with **7b** (0.2 g, 1.3 mmol) in 2 mL of dry acetone, K_2CO_3 (0.26 g, 1.88 mmol), and **6h** (0.34 g, 1.55 mmol) in 1 mL of dry acetone afforded **8h** as a white solid (0.33 g, 87%). R_f 0.50 (hexane/EtOAc, 8:2). mp 93–94°C (lit.[51] 92–93°C).

1-(4-Benzyloxy)-2-(3-methoxyphenoxy)ethanone **8i**

Following the procedure as for **8a**, with of **7a** (0.5 g, 4.03 mmol) in 5 mL of dry acetone, K_2CO_3 (0.83 g, 6.01 mmol), and **6f** (1.47 g, 4.82 mmol) in 1 mL of dry acetone afforded **8i** as a white solid (1.2 g, 86%). R_f 0.40 (hexane/EtOAc, 7:3). mp 96–97°C (Found: C 76.0, H 6.1. $C_{22}H_{20}O_4$ requires C 75.8, H 5.8%). ν_{max} (KBr)/cm^{-1} 1694, 1600, 1509, 1492, 1455, 1263, 1234, 1200, 1155, 1038, 975, 833, 740. δ_H ($CDCl_3$) 3.74 (3H, s, OMe), 5.10 (2H, s, OCH_2Ar), 5.16 (2H, s, H2), 6.46–6.54 (3H, m, H2′, H4′, H6′), 6.98–7.04 (2H, m, H3), 7.11–7.19 (1H, m, H5′), 7.30–7.46 (5H, m, BnH), 7.93–7.99 (2H, m, H2). δ_C ($CDCl_3$) 55.2, 70.0, 70.4, 101.3, 106.4, 107.1, 114.7, 127.4, 127.6, 128.2, 128.6, 129.9, 130.4, 135.9, 159.2, 160.7, 163.0, 192.8. *m*/*z* 348 (M$^+$, 8%), 212 (14), 211 (100), 137 (4), 91 (87).

Preparation of Enaminones **4a–i**: (Z)-3-Dimethylamino-2-(3-methoxyphenoxy)-1-phenylprop-2-en-1-one **4a**

Under a N_2 atmosphere, a mixture of of **8a** (0.30 g, 1.24 mmol) and DMFDMA (0.30 g, 2.48 mmol), in a threaded ACE glass pressure tube with a sealed Teflon screw cap, was heated to 90°C for 24 h. The crude product was purified by column chromatography over silica gel (35 g per g sample, hexane/EtOAc, 7:3) to give **4a** as a pale yellow solid (0.325 g, 88%). R_f 0.39 (hexane/EtOAc, 1:1). mp 98–99°C (Found: (M + H)$^+$ 298.1450. $C_{18}H_{20}NO_3$ requires 298.1443). ν_{max} (KBr)/cm^{-1} 1651, 1588, 1568, 1489, 1438, 1324, 1282, 1149, 1133, 1118, 1042, 975, 835, 716. δ_H ($CDCl_3$) 3.02 (6H, s, $N(CH_3)_2$), 3.76 (3H, s, OCH_3), 6.49 (1H, br d, J 8.1, H4′ or H6′), 6.52–6.62 (2H, m, H2′, H6′, or H4′), 7.06 (1H, br s, HC=), 7.13 (1H, t, J 8.1, H5′), 7.30–7.39 (3H, m, H3, H4, H5), 7.58–7.68 (2H, m, H2, H6). δ_C (CDCl$_3$) 44.0, 55.2, 101.4, 106.9, 107.3, 126.9, 127.9, 128.4, 129.9, 130.1, 139.8, 145.7, 160.0, 160.8, 189.1. *m/z* 297 (M$^+$, 15%), 280 (33), 250 (14), 193 (18), 192 (100), 176 (26), 174 (76), 164 (85), 157 (56), 148 (23), 121 (21), 105 (26), 96 (15).

*(Z)-3-Dimethylamino-2-(3-methoxyphenoxy)-1-(3-tolyl)prop-2-en-1-one **4b***

Following the procedure as for **4a**, with **8b** (0.30 g, 1.17 mmol) and DMFDMA (0.28 g, 2.34 mmol) afforded **4b** as a brown oil (0.31 g, 86%). R_f 0.51 (hexane/EtOAc, 1:1) (Found: $(M+H)^+$ 312.1602. $C_{19}H_{22}NO_3$ requires 312.1600). ν_{max} (KBr)/cm^{-1} 1651, 1590, 1489, 1436, 1358, 1319, 1281, 1200, 1143, 1117, 1042, 758. δ_H (CDCl$_3$) 2.35 (3H, br s, ArCH$_3$), 3.01 (6H, s, N(CH$_3$)$_2$), 3.76 (3H, s, OCH$_3$), 6.48 (1H, ddd, J 8.1, 2.1, 0.9, H4′ or H6′), 6.52–6.60 (2H, m, H2′, H6′, or H4′), 7.03 (1H, s, HC=), 7.13 (1H, t, J 8.1, H5′), 7.17–7.26 (2H, m, H5, H6), 7.38–7.42 (2H, m, H2, H4). δ_C (CDCl$_3$) 21.3, 42.5, 55.2, 101.4, 106.9, 107.3, 125.4, 126.9, 127.6, 128.9, 129.9, 130.8, 137.6, 139.8, 145.0, 160.1, 160.8, 189.2. *m/z* 311 (M$^+$, 37%), 294 (46), 192 (100), 188 (90), 171 (92), 164 (89), 162 (37), 121 (29), 119 (63), 91 (40).

*(Z)-3-Dimethylamino-2-(3-methoxyphenoxy)-1-(4-tolyl)prop-2-en-1-one **4c***

Following the procedure as for **4a**, with **8c** (0.30 g, 1.17 mmol) and DMFDMA (0.28 g, 2.34 mmol) afforded **4c** as a white solid (0.31 g, 84%). R_f 0.43 (hexane/EtOAc, 1:1). mp 99–100°C (Found: $(M+H)^+$ (FAB, *m*-nitrobenzyl alcohol (3NBA)) 312.1605. $C_{19}H_{22}NO_3$ requires 312.1600). ν_{max} (KBr)/cm^{-1} 1651, 1589, 1489, 1320, 1147, 1117, 1042, 975, 763. δ_H (CDCl$_3$) 2.35 (3H, s, ArCH$_3$), 3.02 (6H, s, N(CH$_3$)$_2$), 3.75 (3H, s, OCH$_3$), 6.45–6.59 (3H, m, H2′, H4′, H6′), 7.07 (1H, br s, HC=), 7.08–7.17 (3H, m, H5′, H3, H5), 7.52–7.59 (2H, m, H2, H6). δ_C (CDCl$_3$) 21.4, 42.0, 55.2, 101.3, 106.8, 107.3, 126.8, 128.51, 128.53, 129.9, 136.9, 140.4, 144.4, 160.1, 160.8, 188.9. *m/z* 311 (M$^+$, 13%), 294 (26), 192 (66), 188 (75), 171 (100), 164 (87), 162 (26), 133 (19), 119 (32), 91 (18).

*(Z)-3-Dimethylamino-1-(4-fluorophenyl)-2-(3-methoxyphenoxy)prop-2-en-1-one **4d***

Following the procedure as for **4a**, with **8d** (0.30 g, 1.15 mmol) and DMFDMA (0.27 g, 2.30 mmol) afforded **4d** as a pale brown solid (0.33 g, 91%). R_f 0.46 (hexane/EtOAc, 1:1). mp 84–85°C (Found: $(M+H)^+$ 316.1348. $C_{18}H_{19}NO_3F$ requires 316.1349). ν_{max} (KBr)/cm^{-1} 1651, 1601, 1489, 1432, 1321, 1283, 1229, 1149, 1119, 1042, 845, 765. δ_H (CDCl$_3$) 3.05 (6H, s, N(CH$_3$)$_2$), 3.75 (3H, s, OCH$_3$), 6.44–6.55 (3H, m, H2′, H4′, H6′), 6.94–7.04 (2H, m, H3), 7.12 (1H, t, J 7.8, H5′), 7.16 (1H, br s, HC=), 7.65–7.74 (2H, m, H2). δ_C (CDCl$_3$) 42.5, 55.1, 101.3, 106.8, 107.2, 114.7, 126.4, 129.9, 130.6, 135.6, 144.1, 159.9, 160.8, 163.8, 187.6. *m/z* 315 (M$^+$, 15%), 298 (18), 192 (100), 175 (40), 164 (66), 135 (36), 123 (48), 121 (26), 95 (15).

*(Z)-3-Dimethylamino-2-(3-methoxyphenoxy)-1-(3-methoxyphenyl)prop-2-en-1-one **4e***

Following the procedure as for **4a**, with **8e** (0.30 g, 1.10 mmol) and DMFDMA (0.26 g, 2.20 mmol) afforded **4e** as a brown oil (0.288 g, 80%). R_f 0.35 (hexane/EtOAc, 1:1) (Found: $(M+H)^+$ (FAB, 3NBA) 328.1547. $C_{19}H_{22}NO_4$ requires 328.1549). ν_{max} (KBr)/cm^{-1} 1651, 1589, 1488, 1430, 1320, 1283, 1255, 1143, 1119, 1042, 761. δ_H (CDCl$_3$) 3.03 (6H, s, N(CH$_3$)$_2$), 3.76 (3H, s, OCH$_3$), 3.80 (3H, s, OCH$_3$), 6.49 (1H, br dd, J 8.0, 2.3, H4′ or H6′), 6.52–6.60 (2H, m, H2′, H6′, or H4′), 6.93 (1H, dm, J 7.5, H4), 7.09 (1H, br s, HC=), 7.14 (1H, t, J 7.8, H5′), 7.15–7.29 (3H, m, H2, H5, H6). δ_C (CDCl$_3$) 42.9, 55.2, 55.3, 101.4, 106.9, 107.3, 113.3, 116.2, 120.8, 126.7, 128.8, 129.9, 141.2, 145.5, 159.1, 160.0, 160.8, 188.7. *m/z* 327 (M$^+$, 43%), 310 (34), 204 (51), 192 (100), 187 (60), 164 (63), 135 (66), 133 (37), 107 (36).

*(Z)-2-(3,5-Dimethoxyphenoxy)-3-dimethylamino-1-phenylprop-2-en-1-one **4f***

Following the procedure as for **4a**, with **8f** (0.30 g, 1.1 mmol) and DMFDMA (0.26 g, 2.2 mmol) afforded **4f** as a brown oil (0.32 g, 89%). R_f 0.31 (hexane/EtOAc, 1:1) (Found: $(M+H)^+$ (FAB, 3NBA) 328.1541. $C_{19}H_{22}NO_4$ requires 328.1549). ν_{max} (film)/cm^{-1} 1651, 1596, 1474, 1430, 1324, 1204, 1152, 1126, 1062, 1004, 823, 702. δ_H (CDCl$_3$) 3.03 (6H, s, N(CH$_3$)$_2$), 3.74 (6H, s, 2 OCH$_3$), 6.07 (1H, br t, J 2.1, H4′), 6.16 (2H, br d, J 2.1, H2′, H6′), 7.04 (1H, br s, HC=), 7.30–7.40 (3H, m, H3, H4, H5), 7.58–7.61 (2H, m, H2, H6). δ_C (CDCl$_3$) 42.9, 55.3, 93.6, 93.9, 126.7, 127.9, 128.3, 130.0, 139.8, 145.7, 160.8, 161.5, 189.0. *m/z* 327 (M$^+$, 20%), 310 (28), 280 (18), 222 (100), 194 (82), 174 (33), 157 (26), 152 (20), 105 (39), 91 (13).

*(Z)-2-(3,5-Dimethoxyphenoxy)-3-dimethylamino-1-(4-tolyl)prop-2-en-1-one **4g***

Following the procedure as for **4a**, with **8g** (0.30 g, 1.05 mmol) and DMFDMA (0.25 g, 2.1 mmol) afforded **4g** as a brown solid (0.29 g, 82%). R_f 0.41 (hexane/EtOAc, 1:1). mp 88–89°C (Found: $(M)^+$ 341.1638. $C_{20}H_{23}NO_4$ requires 341.1627). ν_{max} (KBr)/cm^{-1} 1650, 1614, 1578, 1477, 1438, 1360, 1317, 1196, 1154, 1115, 1062, 1009, 825, 759. δ_H (CDCl$_3$) 2.35 (3H, s, ArCH$_3$), 3.02 (6H, s, N(CH$_3$)$_2$), 3.73 (6H, s, 2 OCH$_3$), 6.06 (1H, t, J 2.1, H4′), 6.16 (2H, d, J 2.1, H2′, H6′), 7.06 (1H, br s, HC=), 7.11–7.18 (2H, m, H3, H5), 7.51–7.58 (2H, m, H2, H6). δ_C (CDCl$_3$) 21.3, 42.5, 55.1, 93.5, 93.9, 126.7, 128.4, 128.5, 136.8, 140.2, 144.7, 160.8, 161.4, 188.7. *m/z* 341 (M$^+$, 49%), 324 (56), 294 (19), 281 (21), 222 (91), 194 (96), 171 (66), 162 (52), 119 (100), 91 (33).

*(Z)-2-(3,5-Dimethoxyphenoxy)-1-(4-fluorophenyl)-3-dimethylaminoprop-2-en-1-one **4h***

Following the procedure as for **4a**, with **8h** (0.25 g, 0.86 mmol) and DMFDMA (0.205 g, 1.72 mmol) afforded **4h** as a pale brown oil (0.278 g, 93%). R_f 0.32 (hexane/EtOAc, 1:1) (Found: $(M+H)^+$ (FAB, 3NBA) 346.1460. $C_{19}H_{21}NO_4F$ requires 346.1455). ν_{max} (film)/cm^{-1} 1652, 1599, 1474, 1429, 1320, 1230, 1204, 1153, 1124, 1055, 823, 766. δ_H (CDCl$_3$) 3.04 (6H, s, N(CH$_3$)$_2$), 3.72 (6H, s, OCH$_3$), 6.05 (1H, t, J 2.1, H4′), 6.11 (2H, d, J 2.1, H2′, H6′), 6.95–7.05 (2H, m, H3, H5), 7.14 (1H, br s, HC=), 7.64–7.72 (2H, m, H2, H6). δ_C (CDCl$_3$) 44.0, 55.3, 93.6, 94.0, 114.8, 126.5, 130.6, 135.6, 144.1, 160.8, 161.5, 163.9, 187.7. *m/z* 345 (M$^+$, 30%), 328 (28), 222 (93), 194 (100), 191 (47), 163 (34), 152 (42), 123 (84), 109 (14), 95 (21).

*(Z)-1-(4-Benzyloxyphenyl)-3-dimethylamino-2-(3-methoxyphenoxy)prop-2-en-1-one **4i***

Following the procedure as for **4a**, with **8i** (0.50 g, 1.44 mmol) and DMFDMA (0.34 g, 2.86 mmol) afforded **4i** as a pale yellow oil (0.47 g, 81%). R_f 0.21 (hexane/EtOAc, 1:1) (Found: C 74.2, H 6.4, N 3.3. $C_{25}H_{25}NO_4$ requires C 74.4, H 6.3, N 3.5%). ν_{max}

(film)/cm^{-1} 1651, 1601, 1489, 1319, 1231, 1172, 1148, 1116, 1040, 840, 766. δ_{H} (CDCl$_3$) 3.02 (6H, s, NMe$_2$), 3.74 (3H, s, OCH$_3$), 5.06 (2H, s, OCH$_2$PH), 6.46 (1H, ddd, *J* 8.1, 2.1, 0.6, H4′ or H6′), 6.50–6.57 (2H, m, H2, H6′ or H4′), 6.80–6.94 (2H, m, H3), 7.11 (1H, t, *J* 8.1, H5′), 7.13 (1H, br s, HC=), 7.30–7.44 (5H, m, ArH), 7.67–7.73 (2H, m, H2). δ_{C} (CDCl$_3$) 42.0, 55.2, 69.9, 101.3, 106.8, 107.3, 114.0, 126.7, 127.4, 128.0, 128.5, 129.9, 130.5, 132.2, 136.5, 143.7, 160.1, 160.5, 160.8, 188. *m/z* 403 (M$^+$, 18%), 386 (15), 280 (58), 263 (43), 239 (23), 211 (42), 172 (60), 164 (100), 121 (25), 91 (98).

General Procedure for the Preparation of 2-Benzoylbenzofurans ***2a–i****: 2-Benzoyl-6-methoxybenzofuran* ***2a***

Under a N$_2$ atmosphere at room temperature, a mixture of **4a** (0.20 g, 0.67 mmol) and ZnCl$_2$ (0.46 g, 3.38 mmol) in dry CH$_2$Cl$_2$ (80 mL) was stirred at room temperature for 72 h. The mixture was filtered, washed with H$_2$O (2 × 20 mL), dried (Na$_2$SO$_4$), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (25 g, hexane/EtOAc, 9:1) to give **2a** as a white solid (0.122 g, 72%). R_{f} 0.46 (hexane/EtOAc, 8:2). mp 104–105°C (lit.[16] 105°C). $\nu_{\max}$ (KBr)/cm^{-1} 1644, 1619, 1542, 1494, 1266, 1228, 1153, 1112, 1026, 976, 823, 722, 697. δ_{H} (CDCl$_3$) 3.85 (3H, s, OCH$_3$), 6.92 (1H, dd, *J* 8.4, 2.1, H5), 7.06 (1H, br d, *J* 2.1, H7), 7.42 (1H, d, *J* 0.9, H3), 7.45–7.54 (3H, m, H4, H3′, H5′), 7.54–7.62 (1H, m, H4′), 7.94–8.00 (2H, m, H2′, H6′). δ_{C} (CDCl$_3$) 55.7, 95.5, 114.5, 117.4, 120.3, 123.6, 128.4, 129.2, 132.6, 137.5, 151.7, 157.6, 161.2, 183.9. *m/z* 252 (M$^+$, 89%), 209 (100), 181 (22), 175 (60), 153 (26), 119 (41), 105 (28), 77 (16).

6-Methoxy-2-(3-methylbenzoyl)benzofuran ***2b***

Following the procedure as for **2a**, with **4b** (0.20 g, 0.64 mmol) and ZnCl$_2$ (0.43 g, 3.16 mmol) afforded **2b** as a white solid (0.121 g, 71%). R_{f} 0.51 (hexane/EtOAc, 8:2). mp 83–84°C (Found: (M + H)$^+$ (FAB, 3NBA) 267.1021. C$_{17}$H$_{15}$O$_3$ requires 267.1021). $\nu_{\max}$ (KBr)/cm^{-1} 1644, 1619, 1542, 1494, 1268, 1165, 1112, 1025, 980, 845, 751, 736. δ_{H} (CDCl$_3$) 2.45 (3H, s, ArCH$_3$), 3.89 (3H, s, OCH$_3$), 6.95 (1H, dd, *J* 8.7, 2.1, H5), 7.10 (1H, br d, *J* 2.1, H7), 7.37–7.43 (2H, m, H4′, H5′), 7.44 (1H, d, *J* 0.9, H3), 7.57 (1H, d, *J* 8.7, H4), 7.75–7.81 (2H, m, H2′, H6′). δ_{C} (CDCl$_3$) 21.3, 55.6, 95.5, 114.4, 117.3, 120.2, 123.6, 126.4, 128.2, 129.6, 133.3, 137.4, 138.3, 151.7, 157.5, 161.1, 184.1. *m/z* 266 (M$^+$, 68%), 251 (37), 223 (90), 195 (14), 175 (66), 152 (14), 119 (100), 91 (30).

6-Methoxy-2-(4-methylbenzoyl)benzofuran ***2c****[20]*

Following the procedure as for **2a**, with **4c** (0.20 g, 0.64 mmol) and ZnCl$_2$ (0.43 g, 3.16 mmol) afforded **2c** as a white solid (0.109 g, 64%). R_{f} 0.50 (hexane/EtOAc, 8:2). mp 135–136°C. $\nu_{\max}$ (film)/cm^{-1} 1647, 1615, 1542, 1491, 1268, 1233, 1173, 1152, 1131, 1110, 1029, 974, 807, 756. δ_{H} (CDCl$_3$) 2.46 (3H, s, ArCH$_3$), 3.89 (3H, s, OCH$_3$), 6.95 (1H, dd, *J* 8.7, 2.1, H5), 7.10 (1H, br d, *J* 2.1, H7), 7.28–7.35 (2H, m, H3′, H5′), 7.45 (1H, d, *J* 0.9, H3), 7.56 (1H, d, *J* 8.7, H4), 7.89–7.95 (2H, m, H2′, H6′). δ_{C} (CDCl$_3$) 21.7, 55.7, 95.6, 114.4, 116.9, 120.3, 123.5, 129.1, 129.4, 134.8, 143.4, 151.9, 157.5, 161.0, 183.6. *m/z* 266 (M$^+$, 85%), 251 (42), 223 (90), 195 (15), 175 (36), 119 (100), 91 (34).

2-(4-Fluorobenzoyl)-6-methoxybenzofuran ***2d****[20]*

Following the procedure as for **2a**, with **4d** (0.20 g, 0.635 mmol) and ZnCl$_2$ (0.43 g, 3.16 mmol) afforded **2d** as a white solid (0.13 g, 76%). R_{f} 0.52 (hexane/EtOAc, 8:2). mp 158–159°C. $\nu_{\max}$ (KBr)/cm^{-1} 1635, 1599, 1502, 1343, 1303, 1272, 1220, 1156, 1133, 1118, 1100, 1027, 880, 843, 820, 762. δ_{H} (CDCl$_3$) 3.90 (3H, s, OCH$_3$), 6.97 (1H, dd, *J* 8.7, 2.3, H5), 7.10 (1H, br d, *J* 2.3, H7), 7.17–7.25 (2H, m, H3′, H5′), 7.48 (1H, d, *J* 0.9, H3), 7.58 (1H, d, *J* 8.7, H4), 8.05–8.12 (2H, m, H2′, H6′). δ_{C} (CDCl$_3$) 55.7, 95.6, 114.6, 115.7, 117.0, 120.3, 123.6, 131.9, 133.6, 151.8, 157.6, 161.3, 165.5, 182.2. *m/z* 270 (M$^+$, 100%), 255 (22), 227 (94), 199 (30), 175 (59), 171 (32).

6-Methoxy-2-(3-methoxybenzoyl)benzofuran ***2e***

Following the procedure as for **2a**, with **4e** (0.20 g, 0.61 mmol) and ZnCl$_2$ (0.41 g, 3.01 mmol) afforded **2e** as a pale orange oil (0.095 g, 55%). R_{f} 0.31 (hexane/EtOAc, 8:2) (Found: (M)$^+$ (FAB, 3NBA) 282.0897. C$_{17}$H$_{14}$O$_4$ requires 282.0892). $\nu_{\max}$ (film)/cm^{-1} 1644, 1619, 1542, 1494, 1269, 1219, 1154, 1113, 986, 756. δ_{H} (CDCl$_3$) 3.88 (6H, s, OCH$_3$), 6.95 (1H, dd, *J* 8.9, 2.3, H5), 7.08 (1H, br d, *J* 1.8, H7), 7.15 (1H, ddd, *J* 8.1, 2.7, 0.9, H4′), 7.42 (1H, t, *J* 8.1, H5′), 7.46 (1H, d, *J* 0.9, H3), 7.50 (1H, dd, *J* 2.7, 1.8, H2′), 7.56 (1H, d, *J* 8.9, H4), 7.59 (1H, ddd, *J* 8.1, 1.8, 0.9, H6′). δ_{C} (CDCl$_3$) 55.4, 55.6, 95.5, 113.7, 114.4, 117.4, 118.8, 120.2, 121.7, 123.6, 129.4, 138.6, 151.6, 157.5, 159.5, 161.1, 183.5. *m/z* 282 (M$^+$, 100%), 267 (13), 251 (46), 239 (95), 223 (17), 175 (64), 135 (29), 119 (50), 107 (23).

2-(Benzoyl)-4,6-dimethoxybenzofuran ***2f***

Following the procedure as for **2a**, with **4f** (0.20 g, 0.612 mmol) and ZnCl$_2$ (0.42 g, 3.06 mmol) afforded **2f** as a pale green solid (0.135 g, 78%). R_{f} 0.36 (hexane/EtOAc, 8:2). mp 140–141°C (lit.[48] 140–141°C). $\nu_{\max}$ (film)/cm^{-1} 1639, 1618, 1539, 1504, 1281, 1220, 1155, 1132, 1039, 967, 821, 724. δ_{H} (CDCl$_3$) 3.88 (3H, s, OCH$_3$), 3.91 (3H, s, OCH$_3$), 6.33 (1H, d, *J* 1.8, H5), 6.70 (1H, br s, H7), 7.44–7.55 (3H, m, H3, H3′, H5′), 7.57–7.65 (1H, m, H4′), 7.94–8.00 (2H, m, H2′, H6′). δ_{C} (CDCl$_3$) 55.5, 55.7, 87.9, 95.1, 112.1, 115.5, 128.3, 129.1, 132.3, 137.6, 150.4, 155.2, 158.3, 162.7, 183.5. *m/z* 282 (M$^+$, 93%), 267 (20), 239 (70), 211 (33), 205 (38), 149 (36), 105 (100), 77 (18).

4,6-Dimethoxy-2-(4-methylbenzoyl)benzofuran ***2g***

Following the procedure as for **2a**, with **4g** (0.20 g, 0.587 mmol) and ZnCl$_2$ (0.40 g, 2.93 mmol) afforded **2g** as a pale green solid (0.113 g, 65%). R_{f} 0.39 (hexane/EtOAc, 8:2). mp 126–127°C (Found: (M + H)$^+$ (FAB, 3NBA) 297.1118. C$_{18}$H$_{17}$O$_4$ requires 297.1127). $\nu_{\max}$ (KBr)/cm^{-1} 1648, 1615, 1547, 1489, 1265, 1233, 1191, 1151, 1120, 1108, 1027, 977, 828, 806, 756. δ_{H} (CDCl$_3$) 2.46 (3H, s, ArCH$_3$), 3.88 (3H, s, OCH$_3$), 3.91 (3H, s, OCH$_3$), 6.33 (1H, d, *J* 1.8, H5), 6.71 (1H, dd, *J* 1.8, 0.9, H7), 7.28–7.34 (2H, m, H3′, H5′), 7.51 (1H, d, *J* 0.9, H3), 7.84–7.92 (2H, m, H2′, H6′). δ_{C} (CDCl$_3$) 21.5, 55.5, 55.7, 87.9, 95.1, 112.0, 115.0, 129.0, 129.2, 134.8, 143.1, 150.5, 155.1, 158.1, 162.5, 183.1. *m/z* 296 (M$^+$, 100%), 281 (26), 253 (97), 225 (24), 205 (18), 149 (20), 119 (76), 91 (21).

2-(4-Fluorobenzoyl)-4,6-dimethoxybenzofuran ***2h***

Following the procedure as for **2a**, with **4h** (0.20 g, 0.58 mmol) and ZnCl$_2$ (0.39 g, 2.9 mmol) afforded **2h** as a white solid (0.14 g, 78%). R_{f} 0.41 (hexane/EtOAc, 8:2). mp 129–130°C (Found: (M + H)$^+$ (FAB, 3NBA) 301.0879. C$_{17}$H$_{14}$FO$_4$ requires 301.0876). $\nu_{\max}$ (KBr)/cm^{-1} 1642, 1619, 1600, 1539, 1503, 1297, 1280, 1221, 1201, 1156, 1133, 762. δ_{H} (CDCl$_3$) 3.88 (3H, s, OCH$_3$), 3.91 (3H, s, OCH$_3$), 6.33 (1H, d, *J* 1.8, H5), 6.69 (1H, dd, *J* 1.8, 0.6, H7), 7.15–7.23 (2H, m, H3′), 7.52 (1H, d, *J* 0.6, H3), 8.00–8.07 (2H, m, H2′). δ_C ($CDCl_3$) 55.6, 55.8, 87.9, 95.3, 112.1, 115.3, 115.5, 131.7, 133.8, 150.3, 155.2, 158.3, 162.8, 165.3, 181.8. *m/z* 300 (M^+, 70%), 285 (17), 257 (47), 229 (17), 205 (19), 123 (100), 95 (14).

*2-(4-Benzyloxybenzoyl)-6-methoxybenzofuran **2i***

Following the procedure as for **2a**, with **4i** (0.20 g, 0.49 mmol) and $ZnCl_2$ (0.2 g, 1.47 mmol), and stirring the reaction mixture for 48 h, afforded **2i** as a white solid (0.12 g, 68%). R_f 0.49 (hexane/EtOAc, 7:3). mp 135–136°C (Found: C 76.9, H 5.0. $C_{23}H_{18}O_4$ requires C 77.1, H 5.1%). ν_{max} (film)/cm^{-1} 1633, 1602, 1543, 1494, 1455, 1384, 1302, 1256, 1235, 1154, 1113, 1024, 978, 760, 740. δ_H ($CDCl_3$) 3.89 (3H, s, OCH_3), 5.17 (2H, s, OCH_2PH), 6.96 (1H, dd, *J* 8.7, 2.1, H5), 7.05–7.10 (2H, m, H3′), 7.10 (1H, br s, H7), 7.35–7.48 (5H, m, ArH), 7.46 (1H, d, *J* 0.9, H3), 7.57 (1H, d, *J* 8.7, H4), 8.04–8.09 (2H, m, H2′). δ_C ($CDCl_3$) 55.7, 70.1, 95.6, 114.3, 114.6, 116.3, 120.3, 123.5, 127.5, 128.2, 128.7, 130.3, 131.7, 136.1, 152.1, 157.4, 160.9, 162.5, 182.4. *m/z* (EI) 358 (M^+, 30%), 267 (1), 253 (1), 238 (82), 211 (11), 196 (5), 91 (100).

*General Procedure for the Preparation of 2-Benzylbenzofurans **3a–i**. 2-Benzyl-6-methoxybenzofuran **3a***

Under a N_2 atmosphere, a mixture of **2a** (0.1 g, 0.4 mmol) in ethylene glycol (1 mL) and dry N_2H_4 (0.083 g, 2.59 mmol) was stirred at 150°C for 15 min. At room temperature, KOH (0.145 g, 2.59 mmol) was added and the mixture was heated to 150°C for 4 h. A 2% aqueous solution of HCl was added until neutral, and the mixture was washed with CH_2Cl_2 (2 × 20 mL) and dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane/EtOAc, 9:1) to give **3a** as a pale yellow oil (0.084 g, 89%). R_f 0.60 (hexane/EtOAc, 9:1) (Found: $(M+H)^+$ (FAB, 3NBA) 239.1069. $C_{16}H_{15}O_2$ requires 239.1072). ν_{max} (film)/cm^{-1} 1627, 1587, 1492, 1439, 1291, 1149, 1107, 1029, 961, 824, 705. δ_H ($CDCl_3$) 3.80 (3H, s, OCH_3), 4.06 (2H, br s, CH_2Ph), 6.28–6.31 (1H, m, H3), 6.80 (1H, dd, *J* 8.4, 2.4, H5), 6.95 (1H, br d, *J* 2.4, H7), 7.20–7.36 (6H, m, H4, ArH). δ_C ($CDCl_3$) 34.9, 55.7, 95.9, 103.0, 111.2, 120.4, 122.0, 126.7, 128.6, 128.8, 137.4, 155.9, 156.7, 157.3. *m/z* 238 (M^+, 100%), 195 (22), 165 (25), 161 (88), 105 (10).

*2-(3-Methylbenzyl)-6-methoxybenzofuran **3b***

Following the procedure as for **3a**, with **2b** (0.10 g, 0.38 mmol), N_2H_4 (0.079 g, 2.47 mmol), and KOH (0.138 g, 2.47 mmol) afforded **3b** as a colourless oil (0.085 g, 90%). R_f 0.61 (hexane/EtOAc, 9:1) (Found: $(M+H)^+$ (FAB, 3NBA) 253.1232. $C_{17}H_{17}O_2$ requires 253.1229). ν_{max} (film)/cm^{-1} 1625, 1588, 1491, 1438, 1289, 1149, 1106, 1028, 820. δ_H ($CDCl_3$) 2.33 (3H, s, $ArCH_3$), 3.81 (3H, s, OCH_3), 4.03 (2H, s, CH_2Ar), 6.29–6.31 (1H, m, H3), 6.81 (1H, dd, *J* 8.6, 2.4, H5), 6.96 (1H, br d, *J* 2.4, H7), 7.03–7.12 (3H, m, H2′, H4′, H6′), 7.17–7.24 (1H, m, H5′), 7.32 (1H, d, *J* 8.6, H4). δ_C ($CDCl_3$) 21.4, 34.9, 55.7, 95.9, 102.9, 111.2, 120.4, 122.0, 125.9, 127.4, 128.4, 129.6, 137.3, 138.2, 155.8, 156.9, 157.3. *m/z* 252 (M^+, 100%), 237 (36), 209 (18), 165 (27), 161 (94), 119 (11).

*2-(4-Methylbenzyl)-6-methoxybenzofuran **3c***

Following the procedure as for **3a**, with **2c** (0.10 g, 0.38 mmol), N_2H_4 (0.079 g, 2.47 mmol), and KOH (0.138 g, 2.47 mmol) afforded **3c** as a colourless oil (0.086 g, 91%). R_f 0.52 (hexane/EtOAc, 9:1) (Found: (M^+) 252.1125. $C_{17}H_{16}O_2$ requires 252.1150). ν_{max} (film)/cm^{-1} 1621, 1594, 1501, 1454, 1435, 1419, 1219, 1200, 1156, 1128, 1001, 814. δ_H ($CDCl_3$) 2.32 (3H, s, $ArCH_3$), 3.80 (3H, s, OCH_3), 4.02 (2H, s, CH_2Ar), 6.26–6.28 (1H, m, H3), 6.80 (1H, dd, *J* 8.7, 2.3, H5), 6.95 (1H, br d, *J* 2.3, H7), 7.08–7.20 (4H, m, ArH), 7.30 (1H, d, *J* 8.7, H4). δ_C ($CDCl_3$) 21.0, 34.5, 55.7, 95.9, 102.8, 111.2, 120.3, 122.1, 128.7, 129.2, 134.4, 136.2, 155.8, 157.0, 157.3. *m/z* 252 (M^+, 100%), 251 (55), 237 (43), 209 (18), 165 (28), 161 (60).

*2-(4-Fluorobenzyl)-6-methoxybenzofuran **3d***

Following the procedure as for **3a**, with **2d** (0.10 g, 0.37 mmol), N_2H_4 (0.077 g, 2.41 mmol), and KOH (0.135 g, 2.41 mmol) afforded **3d** as a colourless oil (0.082 g, 78%). R_f 0.63 (hexane/EtOAc, 9:1) (Found: $(M+H)^+$ (FAB, 3NBA) 257.0975. $C_{16}H_{14}O_2F$ requires 257.0978). ν_{max} (film)/cm^{-1} 1627, 1588, 1509, 1492, 1439, 1222, 1193, 1291, 1150, 1107, 1029, 960, 822. δ_H ($CDCl_3$) 3.80 (3H, s, OCH_3), 4.09 (2H, s, CH_2Ar), 6.43–6.45 (1H, m, H3), 6.82 (1H, dd, *J* 8.9, 2.3, H5), 7.02 (1H, br d, *J* 2.3, H7), 7.05–7.14 (2H, m, H3′, H5′), 7.31–7.40 (3H, m, H4, H2′, H6′). δ_C ($CDCl_3$) 34.2, 55.8, 96.3, 103.7, 112.2, 115.9, 121.4, 122.7, 131.4, 134.8, 156.7, 157.5, 158.5, 162.5. *m/z* 256 (M^+, 70%), 241 (9), 213 (21), 183 (20), 165 (48), 161 (100), 123 (14).

*2-(3-Methoxybenzyl)-6-methoxybenzofuran **3e***

Following the procedure as for **3a**, with **2e** (0.10 g, 0.355 mmol), N_2H_4 (0.074 g, 2.30 mmol), and KOH (0.123 g, 2.3 mmol) afforded **3e** as a colourless oil (0.086 g, 90%). R_f 0.45 (hexane/EtOAc, 9:1) (Found: $(M+H)^+$ (FAB, 3NBA) 269.1184. $C_{17}H_{17}O_3$ requires 269.1178). ν_{max} (film)/cm^{-1} 1625, 1587, 1491, 1438, 1289, 1261, 1149, 1107, 960, 822. δ_H ($CDCl_3$) 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.04 (2H, s, CH_2Ar), 6.30–6.33 (1H, m, H3), 6.77–6.81 (1H, m, H4′), 6.82 (1H, dd, *J* 8.7, 2.4, H5), 6.83–6.85 (1H, m, H2′), 6.88 (1H, br d, *J* 7.8, H6′), 6.96 (1H, br d, *J* 2.4, H7), 7.23 (1H, t, *J* 7.8, H5′), 7.32 (1H, d, *J* 8.7, H4). δ_C ($CDCl_3$) 34.9, 55.1, 55.7, 95.9, 103.1, 111.2, 112.0, 114.6, 120.4, 121.2, 122.0, 129.5, 139.0, 155.8, 156.5, 157.3, 159.7. *m/z* (EI) 268 (M^+, 67%), 253 (19), 237 (31), 225 (17), 165 (25), 161 (100), 118 (9).

*2-(Benzyl)-4,6-dimethoxybenzofuran **3f***

Following the procedure as for **3a**, with **2f** (0.10 g, 0.355 mmol), N_2H_4 (0.074 g, 2.3 mmol), and KOH (0.123 g, 2.3 mmol) afforded **3f** as a white solid (0.084 g, 88%). R_f 0.5 (hexane/EtOAc, 9:1). mp 73–74°C (Found: $(M+H)^+$ (FAB, 3NBA) 269.1168. $C_{17}H_{17}O_3$ requires 269.1178). ν_{max} (film)/cm^{-1} 1621, 1592, 1502, 1454, 1435, 1420, 1219, 1200, 1155, 1127, 1101, 816, 701. δ_H ($CDCl_3$) 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.05 (2H, s, CH_2Ar), 6.28 (1H, d, *J* 1.8, H5), 6.36–6.39 (1H, m, H3), 6.58–6.60 (1H, m, H7), 7.20–7.34 (5H, m, BnH). δ_C ($CDCl_3$) 34.9, 55.5, 55.7, 88.2, 93.9, 100.5, 112.3, 126.6, 128.5, 128.8, 137.5, 152.9, 155.1, 156.5, 158.4. *m/z* 268 (M^+, 100%), 253 (12), 191 (86), 165 (34), 105 (23).

*2-(4-Methylbenzyl)-4,6-dimethoxybenzofuran **3g***

Following the procedure as for **3a**, with **2g** (0.10 g, 0.34 mmol), N_2H_4 (0.071 g, 2.21 mmol), and KOH (0.124 g, 2.21 mmol) afforded **3g** as a white solid (0.085 g, 90%). R_f 0.65 (hexane/EtOAc, 9:1). mp 56–57°C (Found: $(M+H)^+$ (FAB, 3NBA) 283.1335. $C_{18}H_{19}O_3$ requires 283.1334). ν_{max} (KBr)/cm^{-1} 1624, 1588, 1491, 1439, 1290, 1189, 1153, 1105, 1025, 938,

816. δ_H ($CDCl_3$) 2.32 (3H, s, $ArCH_3$), 3.79 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.00 (2H, s, CH_2Ar), 6.27 (1H, d, *J* 2.0, H5), 6.35–6.36 (1H, m, H3), 6.58 (1H, dd, *J* 2.0, 0.9, H7), 7.07–7.19 (4H, m, ArH). δ_C ($CDCl_3$) 21.0, 34.4, 55.4, 55.7, 88.2, 93.9, 100.3, 112.3, 128.7, 129.2, 134.4, 136.1, 152.9, 155.4, 156.5, 158.3. *m/z* 282 (M^+, 100%), 267 (35), 191 (65), 179 (18), 119 (20).

*2-(4-Fluorobenzyl)-4,6-dimethoxybenzofuran **3h***

Following the procedure as for **3a**, with **2h** (0.10 g, 0.33 mmol), N_2H_4 (0.069 g, 2.15 mmol), and KOH (0.12 g, 2.66 mmol) afforded **3h** as a pale yellow oil (0.072 g, 75%). R_f 0.62 (hexane/EtOAc, 9:1) (Found: $(M+H)^+$ (FAB, 3NBA) 287.1086. $C_{17}H_{16}O_3F$ requires 287.1083). ν_{max} (film)/cm^{-1} 1620, 1503, 1455, 1419, 1219, 1200, 1155, 1127, 1101, 1043, 816. δ_H ($CDCl_3$) 3.79 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.00 (2H, s, CH_2Ar), 6.28 (1H, d, *J* 2.1, H5), 6.36 (1H, d, *J* 0.9, H3), 6.58 (1H, dd, *J* 2.1, 0.9, H7), 6.94–7.03 (2H, m, H3′, H5′), 7.18–7.28 (2H, m, H2′, H6′). δ_C ($CDCl_3$) 34.0, 55.5, 55.7, 88.2, 93.9, 100.5, 112.2, 115.2, 130.2, 133.2, 153.0, 154.8, 156.6, 158.5, 161.7. *m/z* 286 (M^+, 100%), 271 (14), 255 (13), 191 (94), 183 (34), 123 (27).

*2-(4-Benzyloxybenzyl)-6-methoxybenzofuran **3i***

A mixture of Zn–Hg (1.50 g, 5.64 mmol) and HCl (36%; 1 mL) was heated to 65°C, and **2i** (0.05 g, 0.14 mmol) in EtOH (1 mL) and HCl (36%; 2 mL) was added dropwise. The mixture was stirred for 8 h and washed with CH_2Cl_2 (5 × 10 mL). The organic layer was washed with a 5% aqueous solution of $NaHCO_3$ until neutral, dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (5 g, hexane/EtOAc, 9:1) to give **3i** as a colourless oil (0.039 g, 81%). R_f 0.64 (hexane/EtOAc, 8:2) (Found: (M^+) (FAB, 3NBA) 344.1407. $C_{23}H_{20}O_3$ requires 344.1412). ν_{max} (film)/cm^{-1} 1623, 1509, 1491, 1440, 1384, 1149, 1026. δ_H ($CDCl_3$) 3.82 (3H, s, OCH_3), 4.01 (2H, s, CH_2Ar), 5.05 (2H, s, OCH_2Ph), 6.28 (1H, br s, H3), 6.81 (1H, dd, *J* 8.7, 2.4, H5), 6.92–6.95 (2H, m, H3′), 6.96 (1H, br d, *J* 1.5, H7), 7.18–7.24 (2H, m, H2′), 7.32 (1H, d, *J* 8.7, H4), 7.32–7.45 (5H, m, BnH). δ_C ($CDCl_3$) 34.1, 55.7, 70.0, 95.9, 102.8, 111.2, 114.9, 120.4, 122.0, 127.5, 127.9, 128.6, 129.7, 129.8, 137.0, 155.8, 157.1, 157.2, 157.6. *m/z* 344 (M^+, 10%), 253 (25), 237 (8), 211 (100), 137 (4), 91 (82).

*2-(4-Hydroxybenzyl)-6-methoxybenzofuran **1***

Method A

Under an H_2 atmosphere (1.43 atm), a mixture of **3i** (0.06 g, 0.17 mmol) and Pd/C (5%) (0.004 g) in EtOAc (4 mL) was stirred at 20°C for 12 h. The mixture was filtered over Celite, the solvent removed under vacuum, and the residue purified by column chromatography over silica gel (10 g, hexane/EtOAc, 9:1) to give **1** as a pale yellow oil (0.034 g, 77%).

Method B

A mixture of Zn (3.0 g, 46.0 mmol), $HgCl_2$ (1.2 g, 4.4 mmol), and HCl (36%) (2 mL) was heated to 65°C for 20 min, and a suspension of **2i** (0.05 g, 0.14 mmol) in EtOH (2 mL) and HCl (36%; 2 mL) was added dropwise. The mixture was stirred at 65°C for 12 h, filtered, and an aqueous solution of $NaHCO_3$ was added until neutral. The mixture was washed with EtOAc (5 × 10 mL), the organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (10 g, hexane/EtOAc, 9:1) to give **1** as a pale yellow oil (0.024 g, 68%).

Method C

At 0°C and under a N_2 atmosphere, $BF_3{\cdot}OEt_2$ (0.224 g, 1.58 mmol) was added to a solution of triethylsilane (0.42 g, 3.62 mmol) in CH_2Cl_2 (10 mL). After stirring for 10 min, **2i** (0.05 g, 0.14 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred at 0°C for 1 h, then at room temperature for 3 h. The mixture was poured into a cold aqueous saturated solution of NaCl (20 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (10 g, hexane/EtOAc, 9:1) to give **1** as a pale yellow oil (0.014 g, 40%). R_f 0.27 (hexane/EtOAc, 8:2) (Found: (M^+) (FAB, 3NBA) 254.0948. $C_{16}H_{14}O_3$ requires 254.0943). ν_{max} (film)/cm^{-1} 3420, 2929, 1707, 1616, 1515, 1492, 1441, 1271, 1194, 1149, 1107, 1028, 822. δ_H ($CDCl_3$) 3.83 (3H, s, OCH_3), 4.00 (2H, br s, CH_2Ph), 6.26–6.28 (1H, m, H3), 6.77–6.81 (2H, m, H4′, H6′), 6.81 (1H, dd, *J* 8.4, 2.2, H5), 6.96 (1H, br d, *J* 2.2, H7), 7.12–7.18 (2H, m, H3′, H7′), 7.32 (1H, d, *J* 8.4, H4). δ_C ($CDCl_3$) 34.1, 55.7, 95.9, 102.8, 111.2, 115.4, 120.4, 122.0, 129.0, 130.0, 154.3, 155.8, 157.2, 157.3. *m/z* 254 (M^+, 4%), 210 (23), 181 (22), 167 (85), 165 (75), 161 (100), 149 (73), 118 (14), 105 (13), 77 (24).

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