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An efficient synthesis of benzofurans and their application in the preparation of natural products of the genus *Calea*

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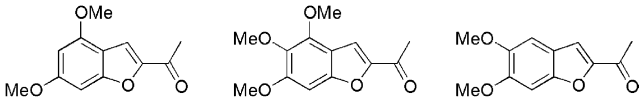
Dedicated to Professor Gustavo García de la Mora on his 60th birthday

Abstract—The intramolecular cyclization of the β-substituted olefins methyl 2-aryloxy-3-dimethylaminopropenoates **3a**–**3f** catalyzed by Lewis acids leads to a short and novel synthesis of benzofurans **2a**–**2f**. When the olefins 4-dimethylamino-3-aryloxy-3-buten-2-ones **4a**–**4f** were used, the cyclization process was faster and provided the corresponding substituted 2-acetylbenzofurans **1a**–**1f**. Among the latter, naturally occurring compounds calebertin (**1a**), caleprunin A (**1b**), and caleprunin B (**1c**) were prepared in good overall yields. These benzofurans were also obtained by direct treatment under MW irradiation of the precursors 1-aryloxypropan-2-ones **7a**–**7c** with DMFDMA, followed by addition of the catalyst, resulting in a route that was one step shorter.

1. Introduction

An intense effort has been made directed towards the synthesis of benzofurans,[1] due to their biological activity as potential pharmacological agents,[2] and to their occurrence in nature.[3] Among the reported synthetic strategies, those approaches designed for building the heterocyclic ring have been widely preferred, because of their simplicity when the starting materials are already carrying the functionalized benzene moiety. Thus, a great number of methods have been developed for the heterocyclic ring closure,[1,4] being particularly versatile those approaches leading to the C3–C3a bond formation as the key step.[5]

Natural 2-acetylbenzofurans calebertin (**1a**), caleprunin A (**1b**), and caleprunin B (**1c**) have been isolated from *Calea* species.[6] Caleprunin B (**1c**) had been previously isolated from *Eupatorium sternbergianum* and called eupatarone.[7] The syntheses of these compounds were carried out through an aldolic condensation of the corresponding *ortho*-formylphenoxyketone.[8] Partial synthesis of compound **1c** has also been reported by oxidation of natural 5,6-dimethoxy-2-isopropylbenzofuran.[9]



1a **1b** **1c**

Recently, we reported our preliminary results about a new straightforward synthesis of benzofurans **2**,[10] taking advantage of the high reactivity of captodative olefins in Friedel–Crafts reactions.[11] Thus, the intramolecular cyclization of the previously functionalized methyl 2-aryloxy-3-dimethylaminopropenoates (**3**) promoted by a Lewis acid ($ZnCl_2$) allowed for the preparation of benzofurans **2** in good yields (Scheme 1). Compounds **3** are acting as enaminones, which have proved to be privileged Michael acceptors for the addition of a large number of nucleophiles.[12]

With the aim of optimizing and extending our methodology, we hereby describe the development of some alternative conditions for the preparation of benzofurans **2**, and the study of preparation and intramolecular cyclization of 3-aryloxy-4-dimethylamino-3-buten-2-ones **4** as versatile and reactive precursors of compounds **1** (Scheme 1), including the total synthesis of natural products **1a**–**1c**.

Keywords: 2-Aryloxy-3-dimethylaminopropenoates; Natural 2-acetylbenzofurans; Cyclization; Lewis acid catalysis; Microwaves.
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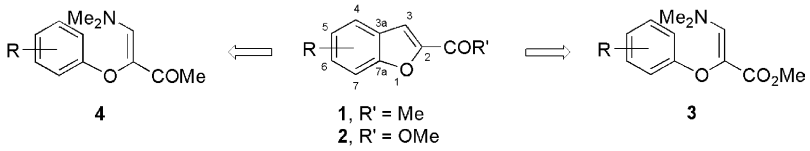
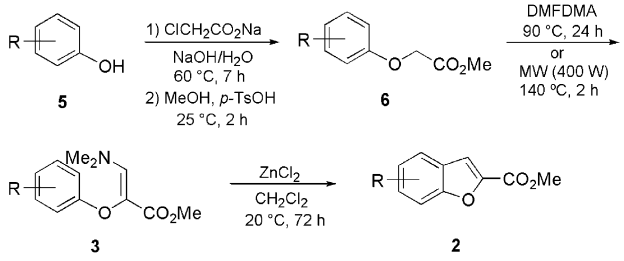


Scheme 1.

2. Results and discussion

Scheme 2 depicts the synthesis of benzofurans **2** starting from phenols **5**. Thus, phenols **5a–5i** were converted to methyl phenoxyacetates **6a–6i** in good yields (81–92%) by reacting with the sodium salt of chloroacetic acid or with chloroacetic acid in aqueous NaOH, and heating at 60 °C for 7 h, followed by esterification in the presence of dry methanol and 10 mol% of *p*-TsOH.[13]



Scheme 2.

Methyl 3-dimethylaminopropenoates **3a–3i** were readily obtained by treatment of methyl phenoxyacetates **6a–6i** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) at 90 °C for 24 h (Scheme 2; Table 1, entries 1–9).[14] The reaction times were reduced by increasing the temperature, but the yields were not significantly enhanced (Table 1, entries 10–12). This conversion could be also carried out by MW irradiation in comparable yields, but in shorter reaction times (Table 1, entries 13–15). Other advantage of the latter method was the fact that the crude mixtures were cleaner and then the purification process by column chromatography on silica gel was easier. In all cases, the propenoates **3** were only obtained as the *Z* stereoisomers, as shown by NOE experiments (irradiation of the signal assigned to protons of dimethylamino group produced an enhancement of the signals corresponding to the aromatic protons). This stereoisomeric preference is probably due to the higher stability gained by the efficient resonance effect of the β-amino unsaturated ester system when the bulky dimethylamino group is located *trans* to the methoxycarbonyl group.[15]

Cyclization of the corresponding 2-aryloxy-3-dimethylaminopropenoates **3a–3c** under thermal conditions (100 °C, 48 h) provided benzofurans **2a–2c** in fair yields (40–45%) (Table 2, entries 1–3). The yields were improved for the series **3a–3f** when a Lewis acid catalyst ($ZnCl_2$) was used (Table 2, entries 4–9). The reaction was regioselective, since we were unable to detect by NMR the isomers with the ring closure towards the *ortho* position of the substituent in the benzene ring. We also found that under microwave (MW) irradiation,[16] the cyclization of compounds **3b** and **3c** took place in modest yields (Table 2, entries 10 and 11). It is noteworthy that analogs **3g–3i**, whose aryl ring is substituted by methyl groups or corresponds to the β-naphthyl ring, were unable to be cyclized by any of the methods described in Table 2. This is probably due to the weak electron-releasing activation of the aryl ring by their substituents, during the intramolecular Friedel–Crafts process.

We investigated the preparation of benzofurans **2a–2c** by a one-step tandem reaction, starting from the phenoxyacetic methyl esters **6a–6c** with DMFDMA (2 mol equiv) in acetonitrile under thermal conditions, either with ($ZnCl_2$) or without catalyst. The desired benzofurans **2a–2c** were obtained in low yields (<25%) along with a higher proportion of their corresponding methyl propenoates **3a–3c** (<58%) (Eq. 1). Looking to improve the yields of

Table 1. Preparation of methyl 2-aryloxy-3-dimethylaminopropenoates **3a–3i**[a]

Entry	**6** (R)	Temperature (°C)	Time *t* (h)	**3**	Yield (%)[b]
1	**6a** (3-OMe)	90	24	**3a**	61
2	**6b** (3,4-$(OMe)_2$)	90	24	**3b**	68
3	**6c** (3,4-OCH_2O)	90	24	**3c**	60
4	**6d** (3-OMe, 4-OEt)	90	24	**3d**	74
5	**6e** (3-OMe, 4-OBn)	90	24	**3e**	63
6	**6f** (2,3,4-$(OMe)_3$)	90	24	**3f**	76
7	**6g** (3-Me)	90	24	**3g**	64
8	**6h** (2,5-$(Me)_2$)	90	24	**3h**	65
9	**6i** (3,4-C_4H_4)	90	24	**3i**	66
10	**6a** (3-OMe)	140	16	**3a**	56
11	**6b** (3,4-$(OMe)_2$)	140	16	**3b**	68
12	**6c** (3,4-OCH_2O)	140	16	**3c**	71
13	**6a** (3-OMe)	140[c]	2	**3a**	65
14	**6b** (3,4-$(OMe)_2$)	140[c]	2	**3b**	67
15	**6c** (3,4-OCH_2O)	140[c]	2	**3c**	70

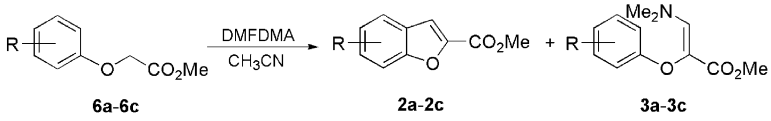
[a] Under N_2 atmosphere, with 3.0 mol equiv of DMFDMA.
[b] After column chromatography and recrystallization.
[c] Under MW irradiation (400 W).

Table 2. Preparation of benzofurans **2a–2h**

Entry	**3** (R)	Conditions	Solvent	Temperature (°C)	Time *t* (h)	**2**	Yield (%)[a]
1	**3a** (3-OMe)	Thermal	MeCN	100	48	**2a**	40
2	**3b** (3,4-$(OMe)_2$)	Thermal	MeCN	100	48	**2b**	42
3	**3c** (3,4-OCH_2O)	Thermal	MeCN	100	48	**2c**	45
4	**3a** (3-OMe)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2a**	62
5	**3b** (3,4-$(OMe)_2$)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2b**	68
6	**3c** (3,4-OCH_2O)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2c**	68
7	**3d** (3-OMe, 4-OEt)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2d**	65
8	**3e** (3-OMe, 4-OBn)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2e**	70
9	**3f** (2,3,4-$(OMe)_3$)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2f**	72
10	**3b** (3,4-$(OMe)_2$)	MW[c]	MeCN	100	5	**2b**	48
11	**3c** (3,4-OCH_2O)	MW[c]	MeCN	100	5	**2c**	51

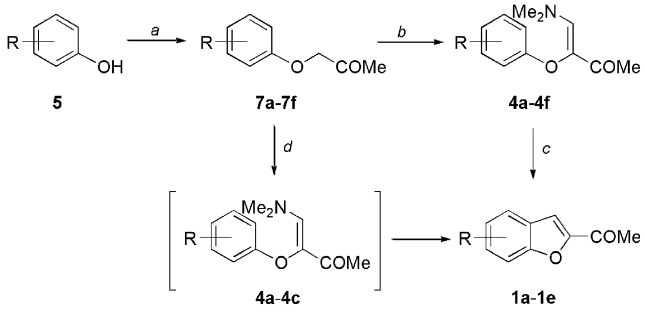
[a] After column chromatography and recrystallization.
[b] Three mole equivalents.
[c] Four hundred watts.

the desired benzofurans, the reactions were also carried out under MW irradiation, but the ratios of **2a–2c/3a–3c** were similar.



(1)

For the synthesis of 2-acetylbenzofurans **1**, it was necessary to prepare the corresponding 1-aryloxypropan-2-ones **7**, followed by the intramolecular cyclization of 3-aryloxy-4-dimethylamino-3-buten-2-ones **4** (Scheme 3). Compounds **7a–7f** were prepared in good yields (70–87%) by a base-promoting Williamson reaction between the substituted phenols, **5**, and chloroacetone (**8**) in refluxing acetone.[17] The series of compounds **4a–4f** was prepared in high yields (81–88%) by reacting the corresponding 1-aryloxypropan-2-ones **7a–7f** with 1.0 mol equiv of DMFDMA (Scheme 3). A larger amount of DMFDMA can lead to a mixture of the mono- and bis-dimethylaminomethylene derivatives. Of the complete series of compounds **4a–4f**, only derivatives **4a–4e** were able to undergo cyclization to obtain benzofurans **1a–1e** under Lewis acid catalysis efficiently (Table 3, entries 1–5). Although other catalysts such as $BF_3 \cdot OEt_2$ were used (Table 3, entries 6 and 7), $ZnCl_2$ was more efficient to promote such a process. Like compound **3h**, derivative **4f** (R = 2,5-$(Me)_2$) was not enough reactive to carry out the cyclization process.



Scheme 3. Reagents and conditions: (a) $ClCH_2COCH_3$ (**8**), K_2CO_3, acetone, reflux, 12 h; (b) DMFDMA (1.0 mol equiv), 80 °C, 6 h; (c) $ZnCl_2$, CH_2Cl_2, 20 °C, 48 h; (d) (i) DMFDMA (1.0 mol equiv), MW (200 W), 80 °C, 10 min; (ii) $ZnCl_2$, CH_3CN, MW (200 W), 80 °C, 30 min.

It is noteworthy that derivatives **4a–4e** cyclized to the corresponding benzofurans much faster (48 h) than the 3-dimethylaminopropenoates **3a–3e** (72 h) did under similar conditions (Table 2). This difference in reactivity is a consequence of the enone moiety of derivatives **4** being

Table 3. Preparation of 2-acetylbenzofurans **1a–1e**[a]

Entry	Precursor (R)	Conditions	Solvent	Temperature (°C)	Time *t* (h)	**1**	Yield (%)[b]
1	**4a** (3,5-$(OMe)_2$)	$ZnCl_2$	CH_2Cl_2	20	48	**1a**	60
2	**4b** (3,4,5-$(OMe)_3$)	$ZnCl_2$	CH_2Cl_2	20	48	**1b**	61
3	**4c** (3,4-$(OMe)_2$)	$ZnCl_2$	CH_2Cl_2	20	48	**1c**	62
4	**4d** (3,4-OCH_2O)	$ZnCl_2$	CH_2Cl_2	20	48	**1d**	61
5	**4e** (3-OMe)	$ZnCl_2$	CH_2Cl_2	20	48	**1e**	62
6	**4c** (3,4-$(OMe)_2$)	$BF_3 \cdot OEt_2$	CH_2Cl_2	20	24	**1c**	52
7	**4d** (3,4-OCH_2O)	$BF_3 \cdot OEt_2$	CH_2Cl_2	20	24	**1d**	55
8	**7a** (3,5-$(OMe)_2$)	DMFDMA	MeCN	90	48	**1a**	19
9	**7b** (3,4,5-$(OMe)_3$)	DMFDMA	MeCN	90	48	**1b**	18
10	**7c** (3,4-$(OMe)_2$)	DMFDMA	MeCN	90	48	**1c**	21
11	**7a** (3,5-$(OMe)_2$)	[c]	[c]	[c]	[c]	**1a**	35
12	**7b** (3,4,5-$(OMe)_3$)	[c]	[c]	[c]	[c]	**1b**	38
13	**7c** (3,4-$(OMe)_2$)	[c]	[c]	[c]	[c]	**1c**	42

[a] Under N_2 atmosphere, with 3.0 mol equiv of $ZnCl_2$ or $BF_3 \cdot OEt_2$ and 1.0 mol equiv of DMFDMA.
[b] After column chromatography and recrystallization.
[c] Under N_2 atmosphere: (a) MW irradiation (400 W), with DMFDMA at 100 °C for 10 min; (b) addition of $ZnCl_2$ in MeCN, and MW irradiation (400 W) at 100 °C for 30 min.

more activated than the methyl propenoate moiety in compounds **3** towards a nucleophilic conjugate addition.[18]

Therefore, natural benzofurans **1a–1c** were obtained in good overall yields starting from phenols **5a–5c** in a three-step synthesis: calebertin (**1a**) was obtained in 35%, caleprunin A (**1b**) in 37%, and caleprunin B (**1c**) in 48%. However, we investigated a shorter strategy by the tandem reaction of condensation–cyclization of 1-aryloxypropan-2-ones **7a–7c** with DMFDMA (Scheme 3). A first method consisted of heating this mixture in acetonitrile at 90 °C for 48 h. Although the desired products were obtained, the yields were low (Table 3, entries 8–10), and a large amount of the intermediates 3-dimethylaminopropan-2-ones **4a–4c** was found. These results prompted us to follow a one-pot two-step sequence in order to achieve the cyclization of the latter to obtain the benzofurans. Thus, the second method included, as the first step, the free-solvent MW irradiation (400 W) of the mixture of **7** and DMFDMA at 100 °C for 10 min, followed by the addition of $ZnCl_2$ in MeCN and irradiation at the same temperature for 30 min. The natural products **1a–1c** were readily isolated from the crude mixtures in better yields (Table 3, entries 11–13) than the first tandem method, but they were lower than the overall yields obtained by the two-step methodology.

3. Conclusions

We have described the full details of the new methodology for the preparation of the 2-carbomethoxybenzofurans **2a–2f** series via intramolecular cyclization of the methyl 2-aryloxy-3-dimethylaminopropenoates **3a–3f**, respectively. We are also reporting an alternative method for the tandem thermal condensation–cyclization process between phenoxyacetates **6** and DMFDMA, based on a solvent-free process under MW irradiation. As an extension of this synthetic route, a series of 2-acetylbenzofurans, **1a–1e**, was prepared through analogous reaction conditions from **4a–4e**, a cyclization process which was faster than that when obtaining benzofurans **2a–2f** from **3a–3f**. Among the compounds **1a–1e**, the naturally occurring benzofurans **1a–1c** were prepared in good overall yields, starting from 1-aryloxypropan-2-ones **7a–7c**. A shorter method for the preparation of these natural products consisted of a one-pot two-step reaction promoted by MW irradiation, which involved the in situ preparation of the precursors **4a–4c** and their cyclization in the presence of Lewis acid catalysts.

4. Experimental

4.1. General

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Varian Mercury-300 instrument, in $CDCl_3$ or acetone-d_6 as solvents and TMS as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained, in electron impact (EI) (70 eV) mode, on a Hewlett-Packard 5971A and on a Jeol JMS-AX 505 HA spectrometers, respectively. Microwave (MW) irradiation was performed on a SEV/MIC-1 (Puebla, Mexico) MW reactor.[19] Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ, USA), and Centro de Investigaciones Químicas, Universidad Autónoma de Hidalgo (Pachuca, Hgo., Mexico). Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} coated 0.25 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. Toluene was freshly distilled over sodium, and methylene chloride, ethyl acetate, acetonitrile, and DMSO over calcium hydride, prior to use. Acetone was distilled after refluxing over $KMnO_4$ for 4 h. K_2CO_3 was dried overnight at 200 °C before use. Triethylamine was distilled over sodium hydroxide. All other reagents were used without further purification. For the preparation and spectroscopic data of **2b**, **3b**, and **6b**, see Ref. 10.

4.2. Preparation of phenols 5d, 5e, and 5f

4.2.1. 4-Ethoxy-3-methoxyphenol (5d). (i) A mixture of 3.0 g (19.7 mmol) of vanillin and 4.08 g (29.5 mmol) of dry K_2CO_3 in 30 mL of dry acetone was stirred and heated to reflux for 30 min, and 2.35 g (21.6 mmol) of ethyl bromide were added dropwise. The mixture was refluxed for 8 h, then filtered, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (30 mL), successively washed with saturated solutions of $NaHCO_3$ and NaCl (3×5 mL), and dried (Na_2SO_4). The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel (80 g, hexane/EtOAc 95:5) to give 3.19 g (90%) of 4-ethoxy-3-methoxybenzaldehyde as a white solid: R_f 0.38 (hexane/EtOAc 8:2); mp 59–60 °C (hexane/EtOAc 9:1) [lit.[20] 58 °C]. (ii) To a solution of 3.0 g (16.6 mmol) of the latter in dry CH_2Cl_2 (40 mL) 4.09 g (16.6 mmol) of MCPBA was added, and the mixture was stirred at room temperature for 3 h. The mixture was filtered, the solution was washed with a saturated solution of $NaHCO_3$ until neutral, and the organic layer was dried (Na_2SO_4). The solvent was removed under vacuum, the residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 9:1) to give 2.34 g (72%) of 4-ethoxy-3-methoxyphenyl formate as a white solid: R_f 0.36 (hexane/EtOAc 8:2); mp 61–62 °C (hexane/EtOAc 9:1); IR (KBr) 1736, 1698, 1601, 1508, 1263, 1189, 1125, 1158, 1101, 1032, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, $J=7.1$ Hz, 3H, OCH_2CH_3), 3.81 (s, 3H, OMe), 4.04 (t, $J=7.1$ Hz, 2H, OCH_2CH_3), 6.60–6.66 (m, 2H, ArH), 6.78–6.84 (m, 1H, ArH), 8.25 (s, 1H, OCHO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.6 (OCH_2CH_3), 55.9 (OMe), 64.6 (OCH_2CH_3), 105.3 (C-2), 112.2 (C-6), 112.7 (C-5), 143.4 (C-4), 146.4 (C-1), 149.8 (C-3), 159.6 (OCHO). (iii) Under an N_2 atmosphere and at room temperature, 1.0 mL of a 5% aqueous solution of K_2CO_3 was slowly added to a solution of 1.0 g (5.1 mmol) of 4-ethoxy-3-methoxyphenyl formate in methanol (10 mL). The mixture was stirred at room temperature for 30 min and the solvent was removed under vacuum. The residue was saturated with 1.0 g of NaCl and extracted with EtOAc (3×5 mL). The organic extracts were washed with brine (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 (15 g, hexane/EtOAc 8:2) to give 0.754 g (88%) of **5d** as a yellow oil: R_f 0.40 (hexane/EtOAc 6:4); IR (film) 3424, 2978, 1605, 1512, 1457, 1288, 1218, 1160, 1127, 1033, 954 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J= 7.0 Hz, 3H, OCH_2CH_3), 3.68 (s, 3H, OMe), 3.98 (t, J= 7.1 Hz, 2H, OCH_2CH_3), 6.32 (dd, J=8.7, 2.7 Hz, 1H, H-6), 6.43 (d, J=2.7 Hz, 1H, H-2), 6.65 (br s, 1H, OH), 6.70 (d, J=8.7 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.7 (OCH_2CH_3), 55.4 (OMe), 65.4 (OCH_2CH_3), 100.6 (C-2), 105.0 (C-6), 114.7 (C-5), 141.5 (C-4), 150.0 (C-3), 150.6 (C-1). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.38.

4.2.2. 4-Benzyloxy-3-methoxyphenol (5e). Following the procedures as for **5d**: (i) With 3.0 g (19.7 mmol) of vanillin, 4.08 g (29.5 mmol) of dry K_2CO_3, and 2.72 g (21.6 mmol) of benzyl chloride, to yield 4.1 g (86%) of 4-benzyloxy-3-methoxybenzaldehyde as a white solid: R_f 0.34 (hexane/EtOAc 8:2); mp 74–75 °C (hexane/EtOAc 9:1); IR (KBr) 1682, 1588, 1508, 1460, 1267, 1133, 1023, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H, OMe), 5.23 (s, 2H, OCH_2), 6.98 (d, J=8.2 Hz, 1H, H-5), 7.28–7.46 (m, 7H, H-2, H-6, PhH), 9.82 (s, 1H, CHO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.9 (OMe), 70.7 (OCH_2), 109.3 (C-5), 112.3 (C-2), 126.4 (C-6), 127.1 (PhCH), 128.1 (PhCH), 128.6 (PhCH), 130.2 (C-1), 135.9 (PhC), 150.0 (C-3), 153.5 (C-4), 190.8 (CHO); MS (70 eV) m/z 242 (M^+, 9), 151 (1), 91 (100), 79 (6), 65 (19), 51 (8). (ii) With 3.0 g (12.4 mmol) of 4-benzyloxy-3-methoxybenzaldehyde and 3.06 g (12.4 mmol) of MCPBA to yield 1.92 g (60%) of 4-benzyloxy-3-methoxyphenyl formate as a white solid: R_f 0.40 (hexane/EtOAc 8:2); mp 69–71 °C (hexane/EtOAc 9:1); IR (KBr) 1736, 1604, 1508, 1452, 1218, 1192, 1159, 1128, 1104, 1028, 953 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OMe), 5.11 (s, 2H, OCH_2), 6.59 (dd, J=8.7, 2.4 Hz, 1H, H-6), 6.68 (d, J=2.4 Hz, 1H, H-2), 6.85 (d, J= 8.7 Hz, 1H, H-5), 7.24–7.44 (m, 5H, PhH), 8.25 (s, 1H, OCHO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.0 (OMe), 71.3 (OCH_2), 105.5 (C-2), 112.3 (C-6), 114.1 (C-5), 127.2 (PhCH), 127.8 (PhCH), 128.5 (PhCH), 136.7 (PhC), 143.8 (C-4), 146.2 (C-1), 150.2 (C-3), 159.6 (OCHO). (iii) With 1.0 g (3.9 mmol) of 4-benzyloxy-3-methoxyphenyl formate to yield 0.762 g (85%) of **5e** as a white solid: R_f 0.46 (hexane/EtOAc 6:4); mp 85–86 °C (hexane/EtOAc 7:3); IR (KBr) 3417, 3038–2978, 1606, 1510, 1456, 1288, 1210, 1160, 1225, 1024, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H, OMe), 5.04 (s, 2H, OCH_2), 5.46 (br s, 1H, OH), 6.24 (dd, J=8.7, 2.7 Hz, 1H, H-6), 6.43 (d, J=2.7 Hz, 1H, H-2), 6.70 (d, J=8.7 Hz, 1H, H-5), 7.20–7.42 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.7 (OMe), 72.3 (OCH_2), 100.8 (C-2), 106.0 (C-6), 116.2 (C-5), 127.5 (PhCH), 127.7 (PhCH), 128.4 (PhCH), 137.2 (PhC), 141.7 (C-4), 150.7 (C-3), 150.8 (C-1). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.85; H, 6.21.

4.2.3. 2,3,4-Trimethoxyphenol (5f).[21] Following the procedures as for **5d**: (ii) With 3.0 g (15.3 mmol) of 2,3,4-trimethoxybenzaldehyde and 3.77 g (15.3 mmol) of MCPBA to yield 2.33 g (72%) of 2,3,4-trimethoxyphenyl formate. (iii) With 2.33 g of the latter to yield 1.66 g (82%) of **5f** as a colorless oil: R_f 0.29 (hexane/EtOAc 8:2); IR (film) 3407, 2941, 1711, 1488, 1431, 1266, 1201, 1161, 1091, 1052, 903 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.10–6.30 (br s, 1H, OH), 6.52 (d, J=8.7 Hz, 1H, H-5), 6.60 (d, J=8.7 Hz, 1H, H-6); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.4 (OMe), 60.8 (OMe), 61.1 (OMe), 107.6 (C-5), 108.6 (C-6), 130.0 (C-3), 140.4 (C-2), 143.3 (C-1), 146.8 (C-4).

4.3. Preparation of the phenoxyacetic methyl esters 6a–6i (For spectral data, see Supplementary data)

4.3.1. Methyl 3-methoxyphenoxyacetate (6a).[22] (i) An aqueous solution (5 mL) of 1.1 g (27.5 mmol) of NaOH and 3.2 g (27.5 mmol) of sodium chloroacetate in water (5 mL) were successively added dropwise to 3.1 g (25.0 mmol) of 3-methoxyphenol (**5a**) at room temperature. The mixture was stirred at 60 °C for 7 h. A concentrated aqueous solution of HCl (36%) was added until pH 2, and the precipitate was filtered. The solid was recrystallized from hexane/EtOAc 1:4, giving 3.64 g (80%) of 3-methoxyphenoxyacetic acid as a white solid: R_f 0.51 (hexane/EtOAc 1:1); mp 117–119 °C [lit.[23] 116–118 °C]; IR (KBr) 3300–2350, 1744, 1599, 1495, 1431, 1246, 1208, 1161, 1047, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, OMe), 4.67 (s, 2H, CH_2O), 6.48–6.60 (m, 3H, ArH), 7.17–7.23 (m, 1H, ArH), 8.92 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.3 (MeO), 64.7 (CH_2O), 101.3 (ArH), 106.3 (ArH), 107.8 (ArH), 130.1 (ArH), 158.5 (Ar), 160.9 (Ar), 174.0 (CO_2H). (ii) A mixture of 1.0 g (5.5 mmol) of 3-methoxyphenoxyacetic acid and 0.095 g (0.55 mmol) of *p*-toluenesulfonic acid in dry methanol (5 mL) was stirred at room temperature for 2 h. The solvent was removed under vacuum. The residue was dissolved in EtOAc (5 mL) and washed with saturated solution of $NaHCO_3$ until neutral. 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 (15 g, hexane/EtOAc 9:1), to give 0.99 g (92%) of **6a** as a colorless oil: R_f 0.30 (hexane/EtOAc 8:2).

4.3.2. Methyl (benzo[1,3]dioxol-5-yloxy)acetate (6c). Following the procedures as for **6a**: (i) With an aqueous solution (20 mL) of 5.0 g (72.4 mmol) of NaOH, 4.1 g (43.4 mmol) of chloroacetic acid in 20 mL of H_2O, and 5.0 g (36.2 mmol) of benzo[1,3]dioxol-5-ol (**5c**), to give 6.6 g (80%) of (benzo[1,3]dioxol-5-yloxy)acetic acid as a pale brown solid: R_f 0.38 (hexane/EtOAc/AcOH 2:3:0.1); mp 104–105 °C (hexane/EtOAc 1:4); IR (KBr) 3230–2400, 1732, 1487, 1424, 1264, 1190, 1146, 1035, 922, 783 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 4.62 (s, 2H, CH_2O), 5.93 (s, 2H, OCH_2O), 6.10–6.30 (br, 1H, CO_2H), 6.38 (dd, J= 8.7, 3.0 Hz, 1H, H-6), 6.57 (d, J=3.0 Hz, 1H, H-4), 6.73 (d, J=8.7 Hz, 1H, H-7); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 65.6 (CH_2O), 98.1 (C-4), 101.5 (OCH_2O), 106.0 (C-6), 107.9 (C-7), 142.3 (C-7a), 148.5 (C-3a), 153.8 (C-5), 169.8 (CO_2H); MS (70 eV) m/z 196 (M^+, 100), 137 (99), 109 (11), 79 (14), 65 (6). (ii) With 5.0 (25.5 mmol) of (benzo[1,3]dioxol-5-yloxy)acetic acid and 0.44 g (2.55 mmol) of *p*-toluenesulfonic acid in dry methanol (25 mL), to give 4.72 g (88%) of **6c** as a white solid: R_f 0.42 (hexane/EtOAc 7:3); mp 152–154 °C (hexane/EtOAc 9:1). Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.79. Found: C, 57.03; H, 4.74.

4.3.3. Methyl 4-ethoxy-3-methoxyphenoxyacetate (6d). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 1.42 g (35.6 mmol) of NaOH, 2.02 g (21.4 mmol) of chloroacetic acid in 5 mL of H_2O, and 3.0 g (17.8 mmol) of 4-ethoxy-3-methoxyphenol (**5d**), to give 3.15 g (78%) of 4-ethoxy-3-methoxyphenoxyacetic acid as colorless crystals: R_f 0.32 (hexane/EtOAc/AcOH 2:3:0.1); mp 122–123 °C (hexane/EtOAc 1:4); IR (KBr) 3300–2300, 1738, 1709, 1597, 1513, 1472, 1434, 1267, 1223, 1195, 1086, 955 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 1.31 (t, $J=6.9$ Hz, 3H, OCH_2CH_3), 3.78 (s, 3H, OMe), 3.95 (q, $J=6.9$ Hz, 2H, OCH_2CH_3), 4.62 (s, 2H, CH_2O), 6.39 (dd, $J=9.0$, 3.0 Hz, 1H, H-6), 6.60 (d, $J=3.0$ Hz, 1H, H-2), 6.82 (d, $J=9.0$ Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 14.7 (OCH_2CH_3), 55.3 (OMe), 65.0 (OCH_2CH_3), 65.2 (OCH_2), 101.4 (C-2), 104.4 (C-6), 114.7 (C-5), 143.5 (C-4), 151.0 (C-3), 153.1 (C-1), 169.9 (CO_2H); MS (70 eV) *m/z* 226 (M^+, 100), 197 (58), 169 (11), 139 (89), 125 (33), 111 (40), 95 (11), 65 (9). (ii) With 3.0 (13.3 mmol) of 4-ethoxy-3-methoxyphenoxyacetic acid, and 0.23 g (1.33 mmol) of *p*-toluenesulfonic acid in dry methanol (15 mL), to give 2.87 g (90%) of **6d** as a white solid: R_f 0.72 (hexane/EtOAc 7:3); mp 53–54 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.90; H, 6.87.

4.3.4. Methyl 4-benzyloxy-3-methoxyphenoxyacetate (6e). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 1.04 g (26.05 mmol) of NaOH, 1.48 g (15.66 mmol) of chloroacetic acid in 5 mL of H_2O, and 3.0 g (13.0 mmol) of 4-benzyloxy-3-methoxyphenol (**5e**), to give 2.7 g (72%) of 4-benzyloxy-3-methoxyphenoxyacetic acid as a white solid: R_f 0.34 (hexane/EtOAc/AcOH 2:3:0.1); mp 114–115 °C (hexane/EtOAc 1:4); IR (KBr) 3600–2400, 1737, 1600, 1511, 1451, 1262, 1220, 1196, 1165, 1081, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OMe), 4.60 (s, 2H, OCH_2), 5.07 (s, 2H, OCH_2Ph), 6.27 (dd, $J=8.7$, 3.0 Hz, 1H, H-6), 6.61 (d, $J=3.0$ Hz, 1H, H-2), 6.77 (d, $J=8.7$ Hz, 1H, H-5), 7.20–7.44 (m, 5H, PhH), 10.29 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.9 (OMe), 65.2 (OCH_2), 71.7 (OCH_2Ph), 101.4 (C-2), 103.6 (C-6), 114.9 (C-5), 127.3 (PhH), 127.8 (PhH), 128.4 (PhH), 137.1 (Ph), 143.3 (C-4), 150.8 (C-3), 152.3 (C-1), 174.6 (CO_2H). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.38; H, 6.02. (ii) With 3.0 g (10.4 mmol) of 4-benzyloxy-3-methoxyphenoxyacetic acid and 0.18 g (1.04 mmol) of *p*-toluenesulfonic acid in dry methanol (15 mL), to give 2.86 g (91%) of **6e** as a white solid: R_f 0.72 (hexane/EtOAc 6:4); mp 72–73 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.53; H, 6.00. Found: C, 67.39; H, 5.95.

4.3.5. Methyl 2,3,4-trimethoxyphenoxyacetate (6f). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 0.78 g (19.5 mmol) of NaOH, 2.27 g (19.5 mmol) of sodium chloroacetate in 5 mL of H_2O, and 3.0 g (16.3 mmol) of 2,3,4-trimethoxyphenol (**5f**), to give 3.16 g (80%) of 2,3,4-trimethoxyphenoxyacetic acid as a white solid: R_f 0.46 (hexane/EtOAc 2:8); mp 90–91 °C (hexane/EtOAc 1:4); IR (KBr) 3650–2300, 1738, 1491, 1430, 1268, 1244, 1201, 1117, 1094, 1014 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.76 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.65 (s, 2H, OCH_2), 4.95–5.40 (br, 1H, CO_2H), 6.61–6.70 (m, 2H, H-5, H-6); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 55.8 (OMe), 60.4 (OMe), 60.6 (OMe), 66.1 (OCH_2), 106.9 (ArCH), 109.0 (ArCH), 143.7 (ArC), 144.1 (ArC), 146.4 (ArC), 148.9 (ArC), 169.9 (CO_2H). (ii) With 2.0 g (8.26 mmol) of 2,3,4-trimethoxyphenoxyacetic acid and 0.144 g (0.83 mmol) of *p*-toluenesulfonic acid in dry methanol (10 mL), to give 1.84 g (87%) of **6f** as a colorless oil: R_f 0.23 (hexane/EtOAc 7:3). Anal. Calcd for $C_{12}H_{16}O_5$: C, 56.24; H, 6.29. Found: C, 56.04; H, 6.92.

4.3.6. Methyl 3-methylphenoxyacetate (6g). Following the procedures as for **6a**: (i) With an aqueous solution (10 mL) of 3.7 g (92.5 mmol) of NaOH, 4.8 g (50.8 mmol) of chloroacetic acid in 10 mL of H_2O, and 5.0 g (46.3 mmol) of 3-methylphenol (**5g**), to give 6.5 g (85%) of 3-methylphenoxyacetic acid as white needles: R_f 0.57 (hexane/EtOAc/AcOH 1:1:0.2); mp 104–105 °C (hexane/EtOAc 1:4) [lit.[24] 102 °C]; IR (KBr) 3175–2350, 1733, 1709, 1609, 1584, 1485, 1459, 1422, 1290, 1275, 1254, 1161, 1098, 1088, 920, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, Me), 4.67 (s, 2H, OCH_2), 6.70 (dd, $J=8.2$, 2.3 Hz, 1H, H-6), 6.75 (br s, 1H, H-2), 6.83 (br d, $J=7.7$ Hz, 1H, H-4), 7.18 (dd, $J=8.2$, 7.7 Hz, 1H, H-5), 9.43 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.4 (Me), 64.6 (OCH_2), 111.2 (C-6), 115.4 (C-2), 122.8 (C-4), 129.3 (C-5), 139.8 (C-3), 157.3 (C-1), 175.1 (CO_2H); MS (70 eV) *m/z* 166 (M^+, 100), 121 (96), 108 (19), 91 (90), 77 (15), 65 (17). Anal. Calcd for $C_9H_{10}O_3$: C, 65.06; H, 6.06. Found: C, 65.08; H, 6.08. (ii) With 1.0 g (6.02 mmol) of 3-methylphenoxyacetic acid and 0.11 g (0.64 mmol) of *p*-toluenesulfonic acid in dry methanol (4.7 mL), to give 0.97 g (90%) of **6g** as a colorless oil: R_f 0.50 (hexane/EtOAc 8:2). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.35; H, 6.83.

4.3.7. Methyl 2,5-dimethylphenoxyacetate (6h). Following the procedures as for **6a**: (i) With an aqueous solution (10 mL) of 3.3 g (81.0 mmol) of NaOH, 4.25 g (49.1 mmol) of chloroacetic acid in 10 mL of H_2O, and 5.0 g (40.0 mmol) of 2,5-dimethylphenol (**5h**), to give 6.0 g (82%) of 2,5-dimethylphenoxyacetic acid as white needles: R_f 0.43 (hexane/EtOAc/AcOH 2:3:0.1); mp 138–139 °C (hexane/EtOAc 1:4) [lit.[25] 113–114 °C]; IR (KBr) 3024–2363, 1722, 1615, 1583, 1509, 1429, 1292, 1273, 1242, 1158, 1136, 1078, 938, 812 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.18 (s, 3H, Me), 2.25 (s, 3H, Me), 4.69 (s, 2H, OCH_2), 6.29 (br s, 1H, CO_2H), 6.64–6.72 (m, 2H, H-4, H-6), 7.00 (d, $J=8.1$ Hz, 1H, H-3); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 15.3 (Me-2), 20.6 (Me-5), 64.7 (OCH_2), 112.2 (C-6), 121.6 (C-4), 123.5 (C-2), 130.6 (C-3), 136.5 (C-5), 156.3 (C-1), 169.9 (CO_2H); MS (70 eV) *m/z* 180 (M^+, 100), 162 (5), 136 (23), 135 (22), 122 (15), 121 (94), 106 (21), 105 (22), 91 (54), 77 (35), 65 (6). (ii) With 5.0 g (27.8 mmol) of 2,5-dimethylphenoxyacetic acid and 0.48 g (2.78 mmol) of *p*-toluenesulfonic acid in dry methanol (25 mL), to give 4.6 g (85%) of **6h** as a colorless oil: R_f 0.60 (hexane/EtOAc 7:3). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.89; H, 7.39.

4.3.8. Methyl (naphthalen-2-yloxy)acetate (6i). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 1.66 g (41.5 mmol) of NaOH, 2.36 g (25.0 mmol)

of chloroacetic acid in 5 mL of H_2O, and 3.0 g (20.8 mmol) of 2-naphthol (**5i**), to give 3.78 g (90%) of (naphthalen-2-yloxy)acetic acid as a white solid: R_f 0.32 (hexane/EtOAc/AcOH 2:3:0.1); mp 154–155 °C (hexane/EtOAc 1:4) [lit.[26] 154 °C]. (ii) With 5.0 g (24.7 mmol) (naphthalen-2-yloxy)-acetic acid and 0.427 g (2.47 mmol) of *p*-toluenesulfonic acid in dry methanol (25 mL), to give 4.92 g (92%) of **6i** as a white solid: R_f 0.50 (hexane/EtOAc 7:3); mp 76–77 °C (hexane/EtOAc 8:2) [lit.[27] 75–77 °C].

4.4. General procedure for the preparation of methyl 2-aryloxy-3-dimethylaminopropenoates 3a–3i (Table 4).

Method A. A mixture of 1.0 mol equiv of the methyl phenoxyacetates **6a–6i** and 3.0 mol equiv of *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) was heated to 90 °C for 24 h. The crude mixture was evaporated under vacuum until dried and purified by column chromatography over silica gel (20 g/g sample, hexane/EtOAc 8:2) to give the corresponding compounds **3a–3i**.

Method B. The same procedure as method A for substrates **6a–6c**, and heating the reaction mixture to 140 °C for 2 h under MW irradiation (400 W) to give products **3a–3c** (Table 4).

4.4.1. Methyl (*Z*)-3-dimethylamino-2-(3-methoxyphenoxy)propenoate (3a). Using method A with 0.5 g (2.55 mmol) of **6a** and 0.91 g (7.65 mmol) of DMFDMA, to give 0.39 g (61%) of **3a** as a colorless oil: R_f 0.37 (hexane/EtOAc 6:4). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.26; H, 6.68; N, 5.43.

4.4.2. Methyl (*Z*)-2-(benzo[1,3]dioxol-5-yloxy)-3-dimethylaminopropenoate (3c). Using method A with 0.5 g (2.38 mmol) of **6c** and 0.85 g (7.14 mmol) of DMFDMA, to give 0.38 g (60%) of **3c** as a white solid: R_f 0.72 (hexane/EtOAc 6:4); mp 99–100 °C (hexane/EtOAc 1:1). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.73; H, 5.62; N, 5.48.

4.4.3. Methyl (*Z*)-3-dimethylamino-2-(4-ethoxy-3-methoxyphenoxy)propenoate (3d). Using method A with 0.5 g (2.08 mmol) of **6d** and 0.742 g (6.24 mmol) of DMFDMA, to give 0.45 g (74%) of **3d** as a white solid: R_f 0.30 (hexane/EtOAc 6:4); mp 80–82 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.22; H, 6.88; N, 4.60.

4.4.4. Methyl (*Z*)-2-(4-benzyloxy-3-methoxyphenoxy)-3-dimethylaminopropenoate (3e). Using method A with 0.5 g (1.65 mmol) of **6e** and 0.59 g (4.97 mmol) of DMFDMA, to give 0.37 g (63%) of **3e** as a white solid: R_f 0.25 (hexane/EtOAc 6:4); mp 73–74 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.12; H, 6.39; N, 3.82.

4.4.5. Methyl (*Z*)-3-dimethylamino-2-(2,3,4-trimethoxyphenoxy)propenoate (3f). Using method A with 0.5 g (1.95 mmol) of **6f** and 0.697 g (5.86 mmol) of DMFDMA, to give 0.46 g (76%) of **3f** as a white solid: R_f 0.20 (hexane/EtOAc 6:4); mp 72–73 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.64; H, 6.69; N, 4.39.

4.4.6. Methyl (*Z*)-3-dimethylamino-2-(3-methylphenoxy)propenoate (3g). Using method A with 0.5 g (2.78 mmol) of **6g** and 0.99 g (8.3 mmol) of DMFDMA, to give 0.41 g (64%) of **3g** as a white solid: R_f 0.44 (hexane/EtOAc 7:3); mp 42–43 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.51; H, 7.07; N, 5.78.

4.4.7. Methyl (*Z*)-3-dimethylamino-2-(2,5-dimethylphenoxy)propenoate (3h). Using method A with 0.5 g (2.58 mmol) of **6h** and 0.92 g (7.73 mmol) of DMFDMA, to give 0.42 g (65%) of **3h** as a white solid: R_f 0.38 (hexane/EtOAc 7:3); mp 93–94 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.53; H, 7.76; N, 5.49.

4.4.8. Methyl (*Z*)-3-dimethylamino-2-(naphthalen-2-yloxy)propenoate (3i). Using method A with 0.5 g (2.31 mmol) of **6i** and 0.825 g (6.93 mmol) of DMFDMA, to give 0.41 g (66%) of **3i** as a white solid: R_f 0.32 (hexane/EtOAc 7:3); mp 120–121 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.64; H, 6.12; N, 5.35.

4.5. General procedures for the preparation of methyl benzofuran-2-carboxylates 2a–2f

See Table 5.

Method A. Under an N_2 atmosphere at room temperature, a mixture of 1.0 mol equiv of the corresponding 3-dimethylaminopropenoate **3a–3f**, 3.0 mol equiv of $ZnCl_2$ in dry CH_2Cl_2 (50 mL) was stirred at the same temperature for 72 h. The mixture was filtered, washed with H_2O (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 (10 g, hexane/EtOAc 95:5) to give the corresponding benzofurans **2a–2f**.

Method B. A mixture of 1.0 mol equiv of the methyl phenoxyacetate **6a–6c** and 3.0 mol equiv of DMFDMA in dry acetonitrile (10 mL) was heated to 100 °C for 48 h. The solvent was evaporated under vacuum, and the residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **2a–2c**.

Method C. A mixture of 1.0 mol equiv of the methyl phenoxyacetate **6a–6c** and 2.0 mol equiv of DMFDMA in dry acetonitrile (20 mL) was heated to 140 °C for 16 h. Then, 1.0 mol equiv of $ZnCl_2$ was added and the mixture was heated to 140 °C for 20 h. The mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **2a–2c**.

Method D. A mixture of 1.0 mol equiv of the methyl phenoxyacetate **6a–6c**, 2.0 mol equiv of DMFDMA, and 2.0 mol equiv of $ZnCl_2$ in dry acetonitrile (20 mL) was

Table 4. Spectral data of compounds **3a–3i** and **4a–4f**[a]

Compound	IR (cm^{-1})	GC–MS *m/z*	^1H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
3a	1759, 1598, 1491, 1439, 1294, 1197, 1153, 1087, 917, 839, 764		2.91 (s, 6H, NMe), 3.60 (s, 3H, CO_2Me), 3.74 (s, 3H, OMe), 6.46–6.54 (m, 3H, ArH), 7.10–7.16 (m, 1H, ArH), 7.11 (s, 1H, H-3)	42.0 (NMe), 51.0 (CO_2CH_3), 55.1 (MeO), 101.1 (C-2′), 106.7 (C-6′), 107.0 (C-4′), 114.6 (C-2), 129.8 (C-5′), 139.6 (C-3), 160.5 (C-1′ or C-3′), 160.7 (C-3′ or C-1′), 166.2 (CO_2CH_3)
3c	1695, 1634, 1482, 1436, 1300, 1219, 1173, 1125, 1086, 1036	265 (M^+), 234, 206 (100), 188, 178, 149, 116, 107, 84, 65	2.93 (s, 6H, NMe), 3.60 (s, 3H, CO_2Me), 5.86 (s, 2H, OCH_2O), 6.34 (dd, J=8.7, 2.4 Hz, 1H, H-6′), 6.50 (d, J=2.4 Hz, 1H, H-4′), 6.64 (d, J=8.7 Hz, 1H, H-7′), 7.08 (s, 1H, H-3)	42.0 (NMe), 51.0 (CO_2CH_3), 97.5 (C-4′), 101.1 (OCH_2O), 106.1 (C-6′), 107.9 (C-7′), 115.2 (C-2), 139.6 (C-3), 141.9 (C-7a′), 148.1 (C-3a′), 154.6 (C-5′), 166.3 (CO_2CH_3)
3d	1695, 1633, 1506, 1440, 1358, 1299, 1220, 1190, 1154, 1120, 1087, 1034	295 (M^+), 236 (100), 208, 190, 179, 153, 139, 116, 88, 84, 57, 42	1.34 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.90 (s, 6H, NMe), 3.57 (s, 3H, CO_2Me), 3.77 (s, 3H, OMe), 3.95 (q, J=7.0 Hz, 2H, OCH_2CH_3), 6.33 (dd, J=8.9, 2.9 Hz, 1H, H-6′), 6.53 (d, J=2.9 Hz, 1H, H-2′), 6.70 (d, J=8.9 Hz, 1H, H-5′), 7.08 (s, 1H, H-3)	14.7 (OCH_2CH_3), 42.0 (NMe), 50.9 (CO_2CH_3), 55.6 (OMe), 64.7 (OCH_2CH_3), 100.1 (C-2′), 104.4 (C-6′), 113.6 (C-5′), 114.9 (C-2), 139.5 (C-3), 142.7 (C-4′), 150.1 (C-3′), 153.6 (C-1′), 166.3 (CO_2Me)
3e	1695, 1634, 1505, 1445, 1358, 1299, 1218, 1189, 1119, 1086, 1025	357 (M^+), 298, 266, 238, 210, 153, 116, 91 (100), 65	2.93 (s, 6H, NMe), 3.61 (s, 3H, CO_2Me), 3.83 (s, 3H, OMe), 5.04 (s, 2H, OCH_2Ph), 6.35 (dd, J=8.8, 2.7 Hz, 1H, H-6′), 6.59 (d, J=2.7 Hz, 1H, H-2′), 6.76 (d, J=8.8 Hz, 1H, H-5′), 7.11 (s, 1H, H-3), 7.23–7.44 (m, 5H, PhH)	42.0 (NMe), 51.0 (CO_2CH_3), 55.7 (OMe), 71.7 (OCH_2Ph), 100.3 (C-2′), 104.5 (C-6′), 114.9 (C-2), 115.1 (C-5′), 127.2 (PhCH), 127.6 (PhCH), 128.3 (PhCH), 137.4 (PhC), 139.6 (C-3), 142.7 (C-4′), 150.6 (C-3′), 154.2 (C-1′), 166.2 (CO_2Me)
3f	1696, 1638, 1483, 1432, 1359, 1299, 1245, 1220, 1093, 1054	311 (M^+), 252 (100), 224, 195, 166, 137, 116, 84, 56, 42	2.95 (s, 6H, NMe), 3.59 (s, 3H, CO_2Me), 3.77 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.95 (OMe), 6.46–6.55 (m, 2H, H-5′, H-6′), 7.13 (s, 1H, H-3)	42.0 (NMe), 51.0 (CO_2CH_3), 56.1 (OMe), 61.1 (OMe), 61.2 (OMe), 106.2 (ArCH), 107.7 (ArCH), 114.9 (C-2), 139.7 (C-3), 142.8 (ArC), 143.2 (ArC), 147.0 (ArC), 147.8 (ArC), 166.2 (CO_2Me)
3g	1697, 1634, 1486, 1434, 1358, 1299, 1253, 1218, 1146, 1116, 1087, 775	235 (M^+), 204, 176 (100), 158, 148, 119, 116, 84, 77, 65	2.30 (s, 3H, Me), 2.95 (s, 6H, NMe), 3.62 (s, 3H, CO_2Me), 6.70–6.80 (m, 3H, ArH), 7.10–7.18 (m, 1H, H-5′), 7.14 (s, 1H, H-3)	21.5 (Me), 42.0 (NMe), 51.2 (CO_2CH_3), 111.7 (C-6′), 114.9 (C-2), 115.5 (C-2′), 122.3 (C-4′), 129.2 (C-5′), 139.5 (C-3′), 139.6 (C-3), 159.2 (C-1′), 166.1 (CO_2Me)
3h	1698, 1637, 1506, 1434, 1359, 1299, 1253, 1218, 1123, 1085	249 (M^+, 100), 218, 190, 174, 162, 144, 129, 114, 98, 84, 70	2.26 (br s, 6H, Me), 2.95 (s, 6H, NMe), 3.61 (s, 3H, CO_2Me), 6.59 (d, J=1.5 Hz, 1H, H-6′), 6.67 (dd, J=7.8, 1.5 Hz, 1H, H-4′), 7.01 (d, J=7.8 Hz, 1H, H-3′), 7.16 (s, 1H, H-3)	15.8 (Me-2), 21.3 (Me-5), 42.0 (NMe), 51.1 (CO_2CH_3), 113.1 (C-6′), 115.1 (C-2), 121.7 (C-4′), 122.8 (C-2′), 130.5 (C-3′), 136.5 (C-5′), 139.5 (C-3), 157.2 (C-1′), 166.7 (CO_2Me)
3i	1696, 1631, 1511, 1435, 1356, 1299, 1215, 1118, 1085, 848, 746	271 (M^+), 240, 212 (100), 194, 184, 155, 141, 127, 115, 84, 56, 42	2.96 (s, 6H, NMe), 3.63 (s, 3H, CO_2Me), 7.22 (d, J=2.4 Hz, 1H, H-1′), 7.24 (s, 1H, H-3), 7.26 (dd, J=8.7, 2.4 Hz, 1H, H-3′), 7.29–7.36 (m, 1H, H-6′), 7.38–7.45 (m, 1H, H-7′), 7.70 (d, J=8.1 Hz, 1H, H-8′), 7.74–7.80 (m, 2H, H-4′, H-5′)	42.1 (NMe), 51.2 (CO_2CH_3), 108.8 (C-1′), 114.8 (C-2), 117.7 (C-3′), 123.7 (C-6′), 126.3 (C-8′), 126.8 (C-5′), 127.6 (C-7′), 129.4 (C-4a′), 129.6 (C-4′), 134.4 (C-8a′), 139.8 (C-3), 157.2 (C-2′), 166.6 (CO_2Me)
4a	1667, 1595, 1470, 1350, 1309, 1203, 1138, 1062, 951		1.92 (br s, 3H, COMe), 2.91 (br s, 6H, NMe_2), 3.67 (br s, 6H, 2OMe), 6.05 (br s, 3H, H-2′, H-4′, H-6′), 7.20 (br s, 1H, H-4)	24.6 ($COCH_3$), 42.7 (NMe), 55.1 (2MeO), 93.5 (C-2′, C-4′, C-6′), 125.5 (C-3), 138.5 (C-4), 161.0 (C-1′), 161.5 (C-3′, C-5′), 194.1 ($COCH_3$)
4b	1666, 1592, 1501, 1463, 1422, 1311, 1222, 1126, 1008, 955		1.95 (br s, 3H, COMe), 2.95 (s, 6H, NMe_2), 3.71 (s, 3H, OMe), 3.75 (s, 6H, 2OMe), 6.11 (s, 2H, H-2′, H-6′), 7.23 (br s, 1H, H-4)	24.7 ($COCH_3$), 42.3 (NMe), 55.9 (2MeO), 60.7 (MeO), 91.8 (C-2′, C-6′), 125.5 (C-3), 132.3 (C-4′), 138.7 (C-4), 153.8 (C-3′, C-5′), 155.5 (C-1′), 194.5 ($COCH_3$)
4c	1666, 1588, 1507, 1436, 1308, 1226, 1191, 1153, 1122, 1025, 949		1.96 (br s, 3H, COMe), 2.95 (s, 6H, NMe_2), 3.78 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.33–6.40 (m, 1H, H-6′), 6.52 (d, J=3.0 Hz, 1H, H-2′), 6.72 (d, J=8.7 Hz, 1H, H-5′), 7.23 (br s, 1H, H-4)	24.7 ($COCH_3$), 42.0 (NMe), 55.8 (MeO), 56.2 (MeO), 99.8 (C-2′), 104.5 (C-6′), 111.8 (C-5′), 125.9 (C-3), 138.6 (C-4), 143.7 (C-4′), 149.9 (C-3′), 153.4 (C-1′), 192.6 ($COCH_3$)
4d	1667, 1588, 1481, 1307, 1173, 1125, 1035		1.96 (br s, 3H, COMe), 2.96 (s, 6H, NMe_2), 5.89 (s, 2H, OCH_2O), 6.32 (dd, J=8.1, 2.4 Hz, 1H, H-6′), 6.49 (d, J=2.4 Hz, 1H, H-4′), 6.66 (d, J=8.1 Hz, 1H, H-7′), 7.22 (br s, 1H, H-4)	24.7 ($COCH_3$), 42.0 (NMe), 97.5 (C-4′), 101.2 (OCH_2O), 106.0 (C-6′), 108.1 (C-7′), 126.1 (C-3), 138.5 (C-4), 142.0 (C-7a′), 148.4 (C-3a′), 153.4 (C-5′), 194.2 ($COCH_3$)
4e	1666, 1603, 1589, 1577, 1488, 1434, 1352, 1310, 1140, 1119, 1042, 963		1.84 (br s, 3H, COMe), 2.83 (s, 6H, NMe_2), 3.62 (s, 3H, OMe), 6.32–6.47 (m, 3H, H-2′, H-4′, H-6′), 6.97–7.08 (m, 1H, H-5′), 7.14 (br s, 1H, H-4)	24.3 ($COCH_3$), 41.9 (NMe), 54.8 (MeO), 100.7 (C-2′), 106.5 (C-4′ or C-6′), 106.7 (C-6′ or C-4′), 125.2 (C-3), 129.8 (C-5′), 138.1 (C-4), 159.9 (C-1′ or C-3′), 160.6 (C-3′ or C-1′), 193.8 ($COCH_3$)
4f	1666, 1589, 1505, 1434, 1353, 1313, 1253, 1123, 959		1.93 (br s, 3H, COMe), 2.24 (s, 3H, Me-5′), 2.25 (s, 3H, Me-2′), 2.96 (s, 6H, NMe_2), 6.58 (br s, 1H, H-6′), 6.67 (br d, J=7.5 Hz, 1H, H-4′), 7.02 (d, J=7.5 Hz, 1H, H-3′), 7.30 (br s, 1H, H-4)	15.8 (CH_3-2′), 21.2 (CH_3-5′), 24.5 ($COCH_3$), 42.0 (NMe), 112.8 (C-6′), 121.8 (C-2′), 122.5 (C-4′), 125.5 (C-3), 130.7 (C-3′), 136.9 (C-5′), 138.4 (C-4), 156.7 (C-1′), 194.8 ($COCH_3$)

[a] For spectral data of **3b**, see Ref. 10.

Table 5. Spectral data of compounds **1a**–**1e** and **2a**–**2f**[a]

Compound	IR (cm^{-1})	GC–MS *m/z*	^1H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
1a	1672, 1618, 1547, 1501, 1461, 1272, 1217, 1148, 1114	220 (M^+, 100), 205, 177, 149, 135, 119	2.53 (s, 3H, COMe), 3.85 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.30 (d, *J*=2.1 Hz, 1H, H-5), 6.63 (dd, *J*=2.1, 0.9 Hz, 1H, H-7), 7.52 (d, *J*=0.9 Hz, 1H, H-3)	26.0 ($COCH_3$), 55.6 (OMe), 55.8 (OMe), 87.8 (C-7), 95.1 (C-5), 112.0 (C-3a), 112.2 (C-3), 150.9 (C-2), 155.1 (C-4), 158.0 (C-7a), 162.5 (C-6), 187.2 ($COCH_3$)
1b	1675, 1618, 1547, 1486, 1468, 1425, 1299, 1265, 1216, 1196, 1137, 1110	250 (M^+, 100), 235, 207, 177, 151, 135	2.53 (s, 3H, COMe), 3.83 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.11 (s, 3H, OMe), 6.77 (d, *J*=0.9 Hz, 1H, H-7), 7.56 (d, *J*=0.9 Hz, 1H, H-3)	26.1 ($COCH_3$), 56.3 (OMe), 60.7 (OMe), 61.4 (OMe), 90.1 (C-7), 112.3 (C-3), 113.2 (C-3a), 137.4 (C-5), 147.1 (C-4 or C-6), 151.4 (C-2), 153.1 (C-7a), 155.9 (C-6 or C-4), 187.5 ($COCH_3$)
1c	1670, 1620, 1547, 1490, 1466, 1295, 1218, 1134, 1005	220 (M^+, 100), 205, 177, 149, 135, 121	2.55 (s, 3H, COMe), 3.92 (s, 3H, OMe), 3.94 (s, 3H, OMe), 7.04 (s, 1H, H-4), 7.05 (br d, *J*=0.9 Hz, 1H, H-7), 7.42 (d, *J*=0.9 Hz, 1H, H-3)	26.2 ($COCH_3$), 56.3 (2OMe), 95.0 (C-7), 102.6 (C-4), 113.9 (C-3), 119.0 (C-3a), 147.7 (C-5), 151.4 (C-6), 151.6 (C-2), 152.3 (C-7a), 187.7 ($COCH_3$)
1d	1667, 1558, 1458, 1318, 1297, 1242, 1185, 1146, 1035, 939	204 (M^+, 100), 189, 161, 133, 75	2.53 (s, 3H, COMe), 6.03 (s, 2H, OCH_2O), 6.98 (s, 1H, H-4), 7.00 (br s, 1H, H-7), 7.38 (d, *J*=0.9 Hz, 1H, H-3)	26.1 ($COCH_3$), 93.8 (C-7), 100.2 (OCH_2O), 101.9 (C-4), 114.1 (C-3), 120.5 (C-3a), 145.8 (C-5), 149.8 (C-6), 152.0 (C-2), 152.7 (C-7a), 187.5 ($COCH_3$)
1e	1740, 1677, 1620, 1551, 1494, 1461, 1304, 1265, 1222, 1153, 1112, 1023	190 (M^+), 175 (100), 147, 119, 77	2.56 (s, 3H, COMe), 3.86 (s, 3H, OMe), 6.93 (dd, *J*=8.8, 2.1 Hz, 1H, H-5), 7.03 (br d, *J*=2.1 Hz, 1H, H-7), 7.44 (d, *J*=0.9 Hz, 1H, H-3), 7.55 (d, *J*=8.8 Hz, 1H, H-4)	26.2 ($COCH_3$), 55.7 (OMe), 95.5 (C-7), 113.8 (C-3), 114.4 (C-5), 120.3 (C-3a), 123.6 (C-4), 152.2 (C-2), 157.2 (C-7a), 161.1 (C-6), 187.5 ($COCH_3$)
2a	1726, 1620, 1593, 1567, 1494, 1440, 1315, 1269, 1225, 1178, 1154, 1112, 1025, 840, 763		3.85 (s, 3H, CO_2Me), 3.94 (s, 3H, OMe), 6.92 (dd, *J*=8.7, 2.1 Hz, 1H, H-5), 7.04 (br d, *J*=2.1 Hz, 1H, H-7), 7.45 (d, *J*=0.9 Hz, 1H, H-3), 7.52 (d, *J*=8.7 Hz, 1H, H-4)	52.2 (CO_2CH_3), 55.7 (MeO), 95.6 (C-7), 114.0 (C-5), 114.3 (C-3), 120.1 (C-3a), 123.0 (C-4), 145.5 (C-2), 157.0 (C-6), 160.0 (C-7a), 160.5 (CO_2CH_3)
2c	1730, 1563, 1489, 1462, 1302, 1244, 1181, 1108, 1038, 940, 855	220 (M^+), 189, 177, 162, 133 (100), 103, 75, 74	3.93 (s, 3H, CO_2Me), 6.02 (s, 2H, OCH_2O), 6.96 (s, 1H, H-4), 7.01 (br s, 1H, H-7), 7.40 (d, *J*=0.9 Hz, 1H, H-3)	52.2 (CO_2CH_3), 93.8 (C-7), 100.0 (OCH_2O), 101.8 (C-4), 114.6 (C-3), 120.3 (C-3a), 145.0 (C-5), 145.6 (C-6), 149.2 (C-2), 151.7 (C-7a), 159.7 (CO_2CH_3)
2d	1724, 1619, 1555, 1486, 1445, 1296, 1205, 1141, 1013, 924, 864	250 (M^+), 222, 207 (100), 193, 179, 161, 135, 119, 92, 77, 63	1.48 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 3.91 (s, 3H, CO_2Me), 3.93 (s, 3H, OMe), 4.10 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 7.02 (s, 1H, H-4), 7.05 (s, 1H, H-7), 7.41 (s, 1H, H-3)	14.7 (OCH_2CH_3), 52.1 (CO_2CH_3), 56.2 (OMe), 64.8 (OCH_2CH_3), 95.2 (C-7), 104.0 (C-4), 114.4 (C-3), 118.8 (C-3a), 144.4 (C-5), 146.8 (C-2), 151.3 (C-7a), 151.4 (C-6), 159.9 (CO_2CH_3)
2e	1722, 1620, 1559, 1488, 1445, 1295, 1197, 1137, 1005, 742	312 (M^+), 281, 221, 193, 178, 161, 137, 119, 105, 91 (100), 65	3.930 (s, 3H, OMe), 3.932 (s, 3H, OMe), 5.16 (s, 2H, OCH_2Ph), 7.06 (s, 1H, H-4), 7.07 (br s, 1H, H-7), 7.27–7.47 (m, 6H, H-3, ArH)	52.1 (CO_2CH_3), 56.2 (OMe), 71.5 (OCH_2Ph), 95.3 (C-7), 105.6 (C-4), 114.5 (C-3), 118.8 (C-3a), 127.3 (PhCH), 127.9 (PhCH), 128.6 (PhCH), 136.7 (PhC), 144.4 (ArC), 146.5 (ArC), 151.5 (ArC), 151.7 (ArC), 159.9 (CO_2CH_3)
2f	1728, 1571, 1487, 1460, 1426, 1356, 1316, 1254, 1225, 1196, 1134, 1046	266 (M^+), 251 (100), 235, 193, 167, 137, 121	3.88 (s, 3H, OMe-5), 3.91 (s, 3H, OMe-6), 3.93 (s, 3H, CO_2Me), 4.21 (s, 3H, OMe-7), 6.76 (s, 1H, H-4), 7.42 (s, 1H, H-3)	52.2 (CO_2CH_3), 56.3 (OMe-5), 61.0 (OMe-7), 61.6 (OMe-6), 97.0 (C-4), 114.4 (C-3), 123.0 (C-3a), 139.2 (C-7), 141.4 (C-6), 142.9 (C-7a), 145.6 (C-2), 151.6 (C-5), 159.7 (CO_2CH_3)

[a] For spectral data of **2b**, see Ref. 10.

heated to 100 °C under MW irradiation (400 W) for 5 h. The mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **2a**–**2c**.

4.5.1. Methyl 6-methoxybenzofuran-2-carboxylate (2a). Using the general procedures: method A: with 0.05 g (0.199 mmol) of **3a**, and 0.081 g (0.59 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.025 g (62%) of **2a**; method B: with 0.05 g (0.25 mmol) of **6a** and 0.089 g (0.75 mmol) of DMFDMA, to yield 0.01 g (20%) of **2a**; method C: with 0.05 g (0.25 mmol) of **6a**, 0.059 g (0.50 mmol) of DMFDMA, and 0.035 g (0.25 mmol) of $ZnCl_2$, to yield 0.011 g (22%) of **2a**; method D: with 0.05 g (0.25 mmol) of **6a**, 0.059 g (0.50 mmol) of DMFDMA, and 0.069 g (0.50 mmol) of $ZnCl_2$, to yield 0.0095 g (19%) of **2a** as a white solid: R_f 0.63 (hexane/EtOAc 7:3); mp 93–95 °C (hexane/EtOAc 9:1) [lit.[28] 92–95 °C].

4.5.2. Methyl 1,3,5-trioxa-*s*-indacene-2-carboxylate (2c). Using the general procedures: method A: with 0.05 g (0.188 mmol) of **3c**, and 0.077 g (0.565 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.028 g (68%) of **2c**; method B: with 0.05 g (0.23 mmol) of **6c** and 0.085 g (0.714 mmol) of DMFDMA, to yield 0.013 g (25%) of **2c**; method C: with 0.05 g (0.23 mmol) of **6c**, 0.055 g (0.46 mmol) of DMFDMA, and 0.032 g (0.23 mmol) of $ZnCl_2$, to yield 0.01 g (20%) of **2c**; method D: with 0.05 g (0.23 mmol) of **6c**, 0.055 g (0.46 mmol) of DMFDMA, and 0.064 g (0.46 mmol) of $ZnCl_2$, to yield 0.01 g (20%) of **2c** as a white solid: R_f 0.44 (hexane/EtOAc 7:3); mp 181–182 °C (hexane/EtOAc 9:1). Anal. Calcd for $C_{11}H_8O_5$: C, 60.01; H, 3.66. Found: C, 60.21; H, 3.90.

4.5.3. Methyl 5-ethoxy-6-methoxybenzofuran-2-carboxylate (2d). Using the general procedure of method A with 0.05 g (0.169 mmol) of **3d**, and 0.069 g (0.508 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.028 g (65%) of **2d** as a white solid: R_f 0.43 (hexane/EtOAc 7:3); mp 159–160 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.37; H, 5.88.

4.5.4. Methyl 5-benzyloxy-6-methoxybenzofuran-2-carboxylate (2e). Using the general procedure of method A with 0.05 g (0.14 mmol) of **3e**, and 0.057 g (0.42 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.035 g (70%) of **2e** as a white solid: R_f 0.48 (hexane/EtOAc 7:3); mp 102–104 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.10; H, 5.30.

4.5.5. Methyl 5,6,7-trimethoxybenzofuran-2-carboxylate (2f). Using the general procedure of method A with 0.05 g (0.16 mmol) of **3f**, and 0.066 g (0.48 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.03 g (72%) of **2f** as a white solid: R_f 0.42 (hexane/EtOAc 7:3); mp 66–67 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.83; H, 5.54.

4.6. General procedure for the preparation of the 1-aryloxypropan-2-ones 7a–7f (For spectral data, see Supplementary data)

Under an N_2 atmosphere, a mixture of phenol **5** and anhydrous K_2CO_3 (1.5 mol equiv) in dry acetone (30 mL) was heated to 60 °C for 1 h. α-Chloroacetone (**8**) (1.1 mol equiv) was added dropwise, and the mixture was heated to 60 °C for 12 h. The mixture was filtered and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g sample, hexane/EtOAc 9:1), to give the corresponding products **7a**–**7f**.

4.6.1. 1-(3,5-Dimethoxyphenoxy)propan-2-one (7a). Using the general procedure with 3.0 g (19.5 mmol) of **5j**, 4.04 g (29.2 mmol) of K_2CO_3, and 1.98 g (21.4 mmol) of (**8**) to give 2.94 g (72%) of **7a** as a colorless oil: R_f 0.31 (hexane/EtOAc 6:4). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.02; H, 6.90.

4.6.2. 1-(3,4,5-Trimethoxyphenoxy)propan-2-one (7b). Using the general procedure with 3.0 g (16.3 mmol) of **5k**, 3.37 g (24.4 mmol) of K_2CO_3, and 1.66 g (17.9 mmol) of **8** to give 2.74 g (70%) of **7b** as a white solid: R_f 0.24 (hexane/EtOAc 6:4); mp 26–27 °C (hexane/EtOAc 7:3) [lit.[17] 26.8 °C].

4.6.3. 1-(3,4-Dimethoxyphenoxy)propan-2-one (7c). Using the general procedure with 3.0 g (19.5 mmol) of **5b**, 4.04 g (29.2 mmol) of K_2CO_3, and 1.98 g (21.4 mmol) of **8** to give 3.48 g (85%) of **7c** as a white solid: R_f 0.35 (hexane/EtOAc 6:4); mp 45–46 °C (hexane/EtOAc 7:3) [lit.[17] 45 °C].

4.6.4. 1-(Benzo[1,3]dioxol-5-yloxy)propan-2-one (7d). Using the general procedure with 3.0 g (21.7 mmol) of **5c**, 4.5 g (32.6 mmol) of K_2CO_3, and 2.21 g (23.9 mmol) of **8** to give 3.67 g (87%) of **7d** as a colorless oil: R_f 0.28 (hexane/EtOAc 8:2). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.66; H, 5.27.

4.6.5. 1-(3-Methoxyphenoxy)propan-2-one (7e).[29] Using the general procedure with 3.0 g (24.2 mmol) of **5a**, 5.01 g (36.3 mmol) of K_2CO_3, and 2.46 g (26.6 mmol) of **8** to give 3.57 g (82%) of **7e** as a colorless oil: R_f 0.33 (hexane/EtOAc 8:2).

4.6.6. 1-(2,5-Dimethylphenoxy)propan-2-one (7f).[30] Using the general procedure with 3.0 g (24.6 mmol) of **5h**, 5.09 g (36.9 mmol) of K_2CO_3, and 2.5 g (27.1 mmol) of **8** to give 3.75 g (86%) of **7f** as a colorless oil: R_f 0.55 (hexane/EtOAc 8:2).

4.7. General procedure for the preparation of the (*Z*)-3-aryloxy-4-dimethylamino-3-buten-2-ones 4a–4f

Under an N_2 atmosphere, a mixture of one of the 1-aryloxypropan-2-ones, **7a**–**7f**, and of DMFDMA (1.0 mol equiv) was heated to 80 °C for 6 h. The mixture was evaporated under vacuum and the residue was purified by column chromatography over silica gel (20 g/g sample, hexane/EtOAc 1:1), to give the corresponding products **4a**–**4f** (Table 4).

4.7.1. (*Z*)-4-Dimethylamino-3-(3,5-dimethoxyphenoxy)-3-buten-2-one (4a). Using the general procedure with 1.0 g (4.76 mmol) of **7a** and 0.57 g (4.76 mmol) of DMFDMA, to give 1.04 g (82%) of **4a** as a yellow solid: R_f 0.21 (hexane/EtOAc 6:4); mp 102–103 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.50; H, 7.05; N, 5.40.

4.7.2. (*Z*)-4-Dimethylamino-3-(3,4,5-trimethoxyphenoxy)-3-buten-2-one (4b). Using the general procedure with 0.5 g (2.08 mmol) of **7b** and 0.25 g (2.08 mmol) of DMFDMA, to give 0.53 g (86%) of **4b** as an orange solid: R_f 0.20 (hexane/EtOAc 6:4); mp 107–108 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.15; H, 6.97; N, 4.68.

4.7.3. (*Z*)-3-(3,4-Dimethoxyphenoxy)-4-dimethylamino-3-buten-2-one (4c). Using the general procedure with 0.5 g (2.38 mmol) of **7c** and 0.28 g (2.38 mmol) of DMFDMA, to give 0.53 g (85%) of **4c** as an orange solid: R_f 0.22 (hexane/EtOAc 6:4); mp 94–95 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.26; H, 7.35; N, 5.26.

4.7.4. (*Z*)-3-(Benzo[1,3]dioxol-5-yloxy)-4-dimethylamino-3-buten-2-one (4d). Using the general procedure with 1.0 g (5.15 mmol) of **7d** and 0.61 g (5.15 mmol) of DMFDMA, to give 1.05 g (81%) of **4d** as a yellow solid: R_f 0.23 (hexane/EtOAc 4:6); mp 166–167 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.58; H, 5.93; N, 5.69.

4.7.5. (*Z*)-4-Dimethylamino-3-(3-methoxyphenoxy)-3-buten-2-one (4e). Using the general procedure with 0.5 g (2.78 mmol) of **7e** and 0.33 g (2.78 mmol) of DMFDMA, to give 0.57 g (88%) of **4e** as a reddish solid: R_f 0.25 (hexane/EtOAc 6:4); mp 77–78 °C (hexane/EtOAc 3:7). Anal. Calcd

for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.50; H, 7.17; N, 6.00.

4.7.6. (*Z*)-4-Dimethylamino-3-(2,5-dimethylphenoxy)-3-buten-2-one (4f). Using the general procedure with 1.0 g (5.62 mmol) of **7f** and 0.67 g (5.62 mmol) of DMFDMA, to give 1.1 g (84%) of **4f** as an orange solid: R_f 0.36 (hexane/EtOAc 6:4); mp 148–149 °C (hexane/EtOAc 3:7). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.28; H, 7.97; N, 6.12.

4.8. General procedures for the preparation of 2-acetylbenzofurans 1a–1e (Table 5)

Method A. Under an N_2 atmosphere at room temperature, a mixture of 1.0 mol equiv of the corresponding 3-dimethylaminopropan-2-one **4a**–**4e**, 3.0 mol equiv of $ZnCl_2$ in dry CH_2Cl_2 (50 mL) was stirred at the same temperature for 48 h. The mixture was filtered, washed with H_2O (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 (10 g, hexane/EtOAc 95:5) to give the corresponding benzofurans **1a**–**1e**.

Method B. A mixture of 1.0 mol equiv of the 1-aryloxypropan-2-ones **7a**–**7c** and 1.0 mol equiv of DMFDMA was heated to 100 °C under MW irradiation (400 W) for 10 min; then 3.0 mol equiv of $ZnCl_2$ in dry acetonitrile (20 mL) were added and the mixture was heated 100 °C under MW irradiation (400 W) for 30 min. The mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **1a**–**1c**.

4.8.1. Calebertine (2-acetyl-4,6-dimethoxybenzofuran) (1a). Using method A with 0.05 g (0.189 mmol) of **4a**, and 0.077 g (0.567 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.025 g (60%) of **1a**; method B: with 0.1 g (0.476 mmol) of **7a**, 0.057 g (0.476 mmol) of DMFDMA, and 0.196 g (1.43 mmol) of $ZnCl_2$, to give 0.037 g (35%) of **1a** as a white solid: R_f 0.32 (hexane/EtOAc 7:3); mp 111–112 °C (hexane/EtOAc 8:2) [lit.[8a] 112–113 °C].

4.8.2. Caleprunine A (2-acetyl-4,5,6-trimethoxybenzofuran) (1b).[8a] Using method A with 0.05 g (0.17 mmol) of **4b**, and 0.069 g (0.508 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.026 g (61%) of **1b**; method B: with 0.1 g (0.417 mmol) of **7b**, 0.05 g (0.417 mmol) of DMFDMA, and 0.17 g (1.25 mmol) of $ZnCl_2$, to give 0.04 g (38%) of **1b** as a yellow oil: R_f 0.30 (hexane/EtOAc 7:3).

4.8.3. Caleprunine B (2-acetyl-5,6-dimethoxybenzofuran) (1c). Using method A with 0.05 g (0.189 mmol) of **4c**, and 0.077 g (0.567 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.026 g (62%) of **1c**; method B: with 0.1 g (0.476 mmol) of **7c**, 0.057 g (0.476 mmol) of DMFDMA, and 0.196 g (1.43 mmol) of $ZnCl_2$, to give 0.044 g (42%) of **1a** as a white solid: R_f 0.36 (hexane/EtOAc 7:3); mp 115–116 °C (hexane/EtOAc 8:2) [lit.[6] 115–117 °C].

4.8.4. 6-Acetyl-1,3,5-trioxa-*s*-indacene (1d). Using the general procedure for the preparation of **2a**–**2e** (method A) with 0.05 g (0.20 mmol) of **4d**, and 0.082 g (0.60 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.025 g (61%) of **1d** as a white solid: R_f 0.37 (hexane/EtOAc 7:3); mp 132–133 °C (hexane/EtOAc 8:2) [lit.[31] 156–157.5 °C]. Anal. Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.95; H, 4.07.

4.8.5. 2-Acetyl-6-methoxybenzofuran (1e). Using the general procedure for the preparation of **2a**–**2e** (method A) with 0.05 g (0.21 mmol) of **4e**, and 0.087 g (0.64 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.025 g (62%) of **1e** as a white solid: R_f 0.42 (hexane/EtOAc 7:3); mp 97–98 °C (hexane/EtOAc 8:2) [lit.[32] 98–99 °C].

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.015

Spectral data (IR, GC–MS, ^{1}H NMR, and ^{13}C NMR) of compounds **6a**–**6h** and **7a**–**7f**.

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