Synthesis of 1,3-Dihydro-3-oxo-2-benzofuran-1-carboxylates *via* Intramolecular Cyclization of 2-[2-(Dimethoxymethyl)phenyl]-2-hydroxyalkanoates Followed by Oxidation

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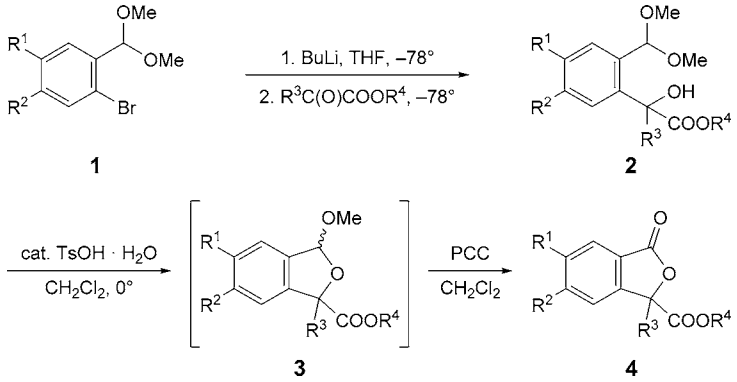
A novel and efficient method for the preparation of 1,3-dihydro-3-oxo-2-benzofuran-1-carboxylates **4** under mild conditions has been developed. Thus, the reaction of [2-(dimethoxymethyl)phenyl]lithiums, generated easily from 1-bromo-2-(dimethoxymethyl)benzenes **1**, with α-keto esters gives the corresponding 2-[2-(dimethoxymethyl)phenyl]-2-hydroxyalkanoates **2**. The TsOH-catalyzed cyclization of these hydroxy acetals is followed by the oxidation of the resulting cyclic acetals **3** with PCC to give the desired products in satisfactory yields. The reaction of [2-(dimethoxymethyl)-4,5-dimethoxyphenyl]-lithium with $(MeOC{=}O)_2$, followed by treatment with $NaBH_4$ or organolithiums, affords 2-[2-(dimethoxymethyl)-4,5-dimethoxyphenyl]-2-hydroxyalkanoates **6**, which can similarly be transformed into the corresponding 1,3-dihydro-3-oxo-2-benzofuran-1-carboxylates **7** in reasonable yields.

Introduction. – The 1,3-dihydro-3-oxo-2-benzofuran-1-carboxylic acid structure has been recently reported to be found in some biologically active compounds [1]. This type of heterocycles has been prepared by the method based on base-mediated alkoxycarbonylation of 2-benzofuran-1(3*H*)-ones followed by alkylation [2] so far, though recently novel methods involving a Rh^{III}-catalyzed direct functionalization of *ortho* C–H bonds of benzoic acid derivatives [3] or an N-heterocyclic carbene-catalyzed oxidation/oxa-*Michael* addition of 2-alkenylbenzaldehydes [4] have been reported. On the other hand, we have recently developed new approaches to benzene-fused heterocycles, such as *N*-substituted 3-alkoxybenzo[*c*]thiophen-1(3*H*)-imines [5], 3-(ω-hydroxyalkoxy)-2-benzofuran-1(3*H*)-ones [6], and 3-alkoxy-1*H*-isoindoles [7], through the employment of reactions of [2-(dialkoxymethyl)phenyl]lithium compounds with the respective electrophiles. We therefore decided to investigate the possibility of utilizing these Li compounds for the preparation of 1,3-dihydro-3-oxo-2-benzofuran-1-carboxylates, and envisaged that the reaction of these Li compounds with α-keto esters would furnish 2-[2-(dialkoxymethyl)phenyl]-2-hydroxyalkanoates **2**, of which treatment with an acid followed by oxidation would provide 1,3-dihydro-3-oxo-2-benzofuran-1-carboxylates **4**. In this article, we describe the results of our study, which provide a facile general method for the preparation of this type of 2-benzofuran-1(3*H*)-ones (phthalides).

Results and Discussion. – The synthesis of **4** from 1-bromo-2-(dimethoxymethyl)-benzenes **1** was conducted according to the process depicted in *Scheme 1*. We first

Scheme 1



examined the reaction of [2-(dimethoxymethyl)phenyl]lithiums, readily generated *in situ* from the Br/Li exchange between **1** and BuLi, with α-keto esters in THF at $-78°$. The reaction proved to proceed relatively cleanly to give, after usual aqueous work-up and the subsequent purification by column chromatography (silica gel), the corresponding hydroxy esters **2** in fair to good yields as compiled in *Table 1*.

The hydroxy esters **2**, thus obtained, underwent ring closure cleanly and smoothly by treatment with a catalytic amount of $TsOH \cdot H_2O$ in CH_2Cl_2 at 0° to afford 1,3-dihydro-3-methoxy-2-benzofuran-1-carboxylates **3** as mixtures of diastereoisomers, contaminated by their hemiacetal forms in some cases judging from ^{1}H-NMR spectroscopy. We were pleased to find that the desired oxidation of unpurified **3** had taken place with excess pyridinium chlorochromate (PCC) in CH_2Cl_2, and that the corresponding products **4** were produced in generally good yields as shown in *Table 1* as well. Similar oxidation of 1-methoxy-1*H*-2-benzopyrans to the corresponding 1*H*-2-benzopyran-1-ones with PCC has been reported previously [8]. Although most of

Table 1. *Preparation of 1,3-Dihydro-3-oxoisobenzofuran-1-carboxylates* **4**

Entry	**1**	R^3	R^4	**2**	Yield [%][a])	Temp.	Time	**4**	Yield [%][a])[b])
1	**1a** ($R^1 = R^2 = H$)	Me	Me	**2a**	80	r.t.	5 d	**4a**	88[c])
2	**1a**	Ph	Me	**2b**	77	r.t.	5 d	**4b**	68[c])
3	**1b** (R^1 = Cl, $R^2 = H$)	Me	Me	**2c**	71	reflux	6 d	**4c**	50[c])
4	**1c** (R^1 = MeO, $R^2 = H$)	Ph	Me	**2d**	83	r.t.	3 d	**4d**	59[d])
5	**1d** ($R^1 = R^2$ = MeO)	Me	Me	**2e**	72	r.t.	2 h	**4e**	86[d])
6	**1d**	Me	Et	**2f**	68	r.t.	2 h	**4f**	86[d])
7	**1d**	Ph	Et	**2g**	68	r.t.	2 h	**4g**	84[d])
8	**1d**	4-Cl–C_6H_4	Me	**2h**	65	r.t.	2 h	**4h**	84[d])
9	**1e** (R^1–R^2 = OCH_2O)	Me	Me	**2i**	68	r.t.	5 h	**4i**	68[d])
10	**1e**	Ph	Me	**2j**	70	r.t.	5 h	**4j**	78[d])

[a]) Yields of isolated products. [b]) Yields based on **2**. [c]) Three equiv. of PCC were used. [d]) Two equiv. of PCC were used.

compounds **3** can be oxidized at room temperature, **3c** required reflux temperature, and the yield of the corresponding product **4c** was only moderate (*Entry 3*). Presumably, an electron-withdrawing Cl substituent decreases the reactivity to the oxidation. *Table 1* also indicates that the O-bearing substituent(s) (especially the 6-MeO group; *Entries 5–8*) on the benzene ring of the dihydroisobenzofuran structure accelerate the oxidation.

With a new reliable method for the preparation of 1,3-dihydro-3-oxo-2-benzofuran-1-carboxylates in hand, we turned our attention to the development of the procedure, which enables to introduce various substituents at the 1-position of the 1,3-dihydroisobenzofuranone ring. As outlined in *Scheme 2*, 1-bromo-2-(dimethoxymethyl)-4,5-dimethoxybenzene (**1d**) was treated with BuLi as described above, and the resulting Li compound was allowed to react with $(MeOC{=}O)_2$. After aqueous work-up, followed by purification by column chromatography (silica gel), methyl [2-(dimethoxymethyl)-4,5-dimethoxyphenyl](oxo)acetate (**5**) was obtained in satisfactory yield. Treatment of **5** with $NaBH_4$ or organolithiums, such as BuLi, thien-2-yllithium, and (2-chloropyridin-3-yl)lithium, resulted in smooth conversion to [2-(dimethoxymethyl)-4,5-dimethoxyphenyl](hydroxy)alkanoates **6** in fair yields. Transformation of **6** into the corresponding 1,3-dihydro-3-oxo-2-benzofuran-1-carboxylates **7** could be achieved by following the same reaction conditions as described for the transformation of **2e–2h** into **4e–4h** in reasonable overall yields from **6** as shown in *Table 2*.

Scheme 2

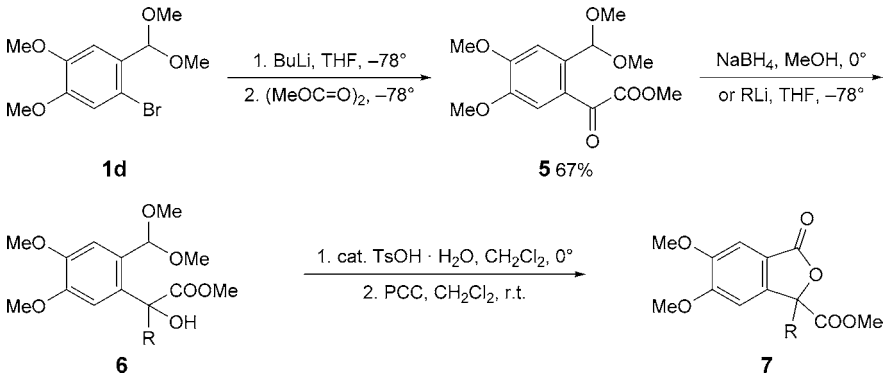


Table 2. *Preparation of 1,3-Dihydro-3-oxoisobenzofuran-1-carboxylates* **7**

Entry	**6**	R	Yield [%][a])	**7**	Yield [%][a])
1	**6a**	H	73	**7a**	45
2	**6b**	Bu	57	**7b**	56
3	**6c**	thiophen-2-yl	66	**7c**	79
4	**6d**	2-chloropyridin-3-yl	72	**7d**	78

[a]) Yields of isolated products.

In conclusion, we have demonstrated that 2-[2-(dimethoxymethyl)phenyl]-2-hydroxyalkanoates, easily accessible *via* the reactions of 1-bromo-2-(dimethoxymethyl)benzenes with α-keto esters or $(MeOC{=}O)_2$, undergo cyclization by treatment with a catalytic amount of TsOH under mild conditions to give the corresponding cyclic acetals, oxidation of which with PCC provides 1,3-dihydro-3-oxoisobenzofuran-1-carboxylates. The present sequences, which allow novel and convenient synthetic approaches to this type of heterocycles from readily available starting materials without using any precious reagents, are also operationally simple making them of considerably synthetic utility.

The authors would like to thank Mrs. *Miyuki Tanmatsu* of our university for assistance in obtaining MS and elemental analyses data.

Experimental Part

General. All org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. Thin layer chromatography (TLC): *Merck* silica gel *60 PF_{254}* (SiO_2). Column chromatography (CC): *Wako Gel C-200E* (SiO_2). IR Spectra: *PerkinElmer Spectrum65* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *JEOL ECP500* FT NMR spectrometer (500 and 125 MHz, resp.); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-DART-MS (pos.) and HR-ESI-MS (pos.): *Thermo Scientific Exactive* spectrometer; in m/z. Elemental analyses: *Elementar Vario EL II* instrument; in %.

1-Bromo-2-(dimethoxymethyl)benzene (**1a**) [9], 1-bromo-4-chloro-2-(dimethoxymethyl)benzene (**1b**) [10], 1-bromo-2-(dimethoxymethyl)-4-methoxybenzene (**1c**) [11], 1-bromo-2-(dimethoxymethyl)-4,5-dimethoxybenzene (**1d**) [10], and 5-bromo-6-(dimethoxymethyl)-1,3-benzodioxole (**1e**) [10] were prepared according to appropriate reported procedures. Methyl (4-chlorophenyl)(oxo)acetate [12] was prepared by the reaction of 4-Cl–C_6H_4–MgBr with $(MeOC{=}O)_2$ under the conditions reported in [13]. BuLi was supplied by *Asia Lithium Corporation*. All other chemicals used in this study were commercially available.

Methyl 2-[2-(Dimethoxymethyl)phenyl]-2-hydroxypropanoate (**2a**). *Representative Procedure.* To a stirred soln. of 1-bromo-2-(dimethoxymethyl)benzene (**1a**; 0.46 g, 2.0 mmol) in THF (6 ml) at $-78°$ was added dropwise BuLi (1.6M in hexane, 2.0 mmol). After 15 min, MeC(O)COOMe (0.20 g, 2.0 mmol) was added dropwise, and stirring was continued for 5 min at the same temp. before addition of a sat. aq. NH_4Cl soln. (20 ml). The mixture was warmed to r.t. and extracted with AcOEt (3×15 ml). The combined extracts were washed with brine (15 ml), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by CC (SiO_2; AcOEt/hexane 1:6) to give **2a** (0.28 g, 56%). Colorless solid. M.p. 43–44° (hexane/CH_2Cl_2). IR (KBr): 3466, 1738. ^1H-NMR: 1.86 (*s*, 3 H); 3.27 (*s*, 3 H); 3.37 (*s*, 3 H); 3.71 (*s*, 3 H); 4.48 (*s*, 1 H); 5.76 (*s*, 1 H); 7.34–7.38 (*m*, 2 H); 7.48–7.52 (*m*, 1 H); 7.66–7.70 (*m*, 1 H). Anal. calc. for $C_{13}H_{18}O_5$ (254.28): C 61.41, H 7.14; found: C 61.48, H 6.97.

Methyl [2-(Dimethoxymethyl)phenyl](hydroxy)phenylacetate (**2b**). Colorless oil. R_f (AcOEt/hexane 1:6) 0.31. IR (neat): 3480, 1733, 1600. ^1H-NMR: 3.09 (*s*, 3 H); 3.30 (*s*, 3 H); 3.84 (*s*, 3 H); 4.73 (*s*, 1 H); 5.50 (*s*, 1 H); 6.92 (*d*, $J = 7.6$, 1 H); 7.23 (*t*, $J = 7.6$, 1 H); 7.34–7.39 (*m*, 4 H); 7.51 (*dd*, $J = 7.6, 1.5$, 2 H); 7.71 (*dd*, $J = 7.6, 1.5$, 1 H). Anal. calc. for $C_{18}H_{20}O_5$ (316.35): C 68.34, H 6.37; found: C 68.18, H 6.50.

Methyl 2-[4-Chloro-2-(dimethoxymethyl)phenyl]-2-hydroxypropanoate (**2c**). Pale-yellow oil. R_f (AcOEt/hexane 1:3) 0.32. IR (neat): 3462, 1739. ^1H-NMR: 1.84 (*s*, 3 H); 3.24 (*s*, 3 H); 3.39 (*s*, 3 H); 3.71 (*s*, 3 H); 4.31 (*s*, 1 H); 5.78 (*s*, 1 H); 7.32 (*dd*, $J = 8.4, 2.3$, 1 H); 7.42 (*d*, $J = 8.4$, 1 H); 7.69 (*d*, $J = 2.3$, 1 H). Anal. calc. for $C_{13}H_{17}ClO_5$ (288.72): C 54.08, H 5.94; found: C 54.06, H 6.08.

Methyl [2-(Dimethoxymethyl)-4-methoxyphenyl](hydroxy)phenylacetate (**2d**). Pale-yellow oil. R_f (AcOEt/hexane 1:3) 0.30. IR (neat): 3474, 1733. ^1H-NMR: 2.98 (*s*, 3 H); 3.30 (*s*, 3 H); 3.81 (*s*, 3 H); 3.83 (*s*, 3 H); 4.58 (*s*, 1 H); 5.48 (*s*, 1 H); 6.73 (*dd*, $J = 8.4, 3.1$, 1 H); 6.83 (*d*, $J = 8.4$, 1 H); 7.26 (*d*, $J = 3.1$, 1 H); 7.33–7.38 (*m*, 3 H); 7.51 (*dd*, $J = 8.4, 1.6$, 2 H). Anal. calc. for $C_{19}H_{22}O_6$ (346.38): C 65.88, H 6.40; found: C 65.82, H 6.57.

Methyl 2-[2-(Dimethoxymethyl)-4,5-dimethoxyphenyl]-2-hydroxypropanoate (**2e**). Yellow oil. R_f (AcOEt/hexane 1:1) 0.29. IR (neat): 3491, 1738, 1610. ^{1}H-NMR: 1.85 (*s*, 3 H); 3.29 (*s*, 3 H); 3.36 (*s*, 3 H); 3.72 (*s*, 3 H); 3.91 (*s*, 6 H); 4.36 (*s*, 1 H); 5.72 (*s*, 1 H); 7.00 (*s*, 1 H); 7.22 (*s*, 1 H). Anal. calc. for $C_{15}H_{22}O_7$ (314.33): C 57.32, H 7.05; found: C 57.26, H 7.18.

Ethyl 2-[2-(Dimethoxymethyl)-4,5-dimethoxyphenyl]-2-hydroxypropanoate (**2f**). Yellow oil. R_f (AcOEt/hexane 2:3) 0.27. IR (neat): 3483, 1732, 1610. ^{1}H-NMR: 1.23 (*t*, *J* = 7.6, 3 H); 1.84 (*s*, 3 H); 3.28 (*s*, 3 H); 3.36 (*s*, 3 H); 3.91 (*s*, 6 H); 4.10–4.30 (*m*, 2 H); 4.43 (*s*, 1 H); 5.78 (*s*, 1 H); 6.98 (*s*, 1 H); 7.23 (*s*, 1 H). Anal. calc. for $C_{16}H_{24}O_7$ (328.36): C 58.53, H 7.37; found: C 58.29, H 7.08.

Ethyl [2-(Dimethoxymethyl)-4,5-dimethoxyphenyl](hydroxy)phenylacetate (**2g**). Colorless oil. R_f (AcOEt/hexane 1:2) 0.29. IR (neat): 3480, 1730, 1609. ^{1}H-NMR: 1.29 (*t*, *J* = 7.6, 3 H); 3.05 (*s*, 3 H); 3.30 (*s*, 3 H); 3.69 (*s*, 3 H); 3.91 (*s*, 3 H); 4.28–4.35 (*m*, 2 H); 4.64 (*s*, 1 H); 5.42 (*s*, 1 H); 6.53 (*s*, 1 H); 7.22 (*s*, 1 H); 7.32–7.38 (*m*, 3 H); 7.54 (*d*, *J* = 6.9, 2 H). Anal. calc. for $C_{21}H_{26}O_7$ (390.43): C 64.60, H 6.71; found: C 64.53, H 6.76.

Methyl (4-Chlorophenyl)[2-(dimethoxymethyl)-4,5-dimethoxyphenyl]hydroxyacetate (**2h**). Colorless oil. R_f (AcOEt/hexane 1:2) 0.29. IR (neat): 3474, 1733, 1608. ^{1}H-NMR: 3.13 (*s*, 3 H); 3.30 (*s*, 3 H); 3.69 (*s*, 3 H); 3.85 (*s*, 3 H); 3.91 (*s*, 3 H); 4.73 (*s*, 1 H); 5.41 (*s*, 1 H); 6.44 (*s*, 1 H); 7.22 (*s*, 1 H); 7.35 (*d*, *J* = 8.4, 2 H); 7.49 (*d*, *J* = 8.4, 2 H). Anal. calc. for $C_{20}H_{23}ClO_7$ (410.85): C 58.47, H 5.64; found: C 58.21, H 5.71.

Methyl 2-[6-(Dimethoxymethyl)-1,3-benzodioxol-5-yl]-2-hydroxypropanoate (**2i**). Pale-yellow oil. R_f (AcOEt/hexane 1:2) 0.28. IR (neat): 3474, 1738, 1622. ^{1}H-NMR: 1.81 (*s*, 3 H); 3.26 (*s*, 3 H); 3.34 (*s*, 3 H); 3.72 (*s*, 3 H); 4.28 (*s*, 1 H); 5.70 (*s*, 1 H); 5.98 (*s*, 1 H); 5.99 (*s*, 1 H); 6.99 (*s*, 1 H); 7.19 (*s*, 1 H). Anal. calc. for $C_{14}H_{18}O_7$ (298.29): C 56.37, H 6.08; found: C 56.09, H 6.36.

Methyl [6-(Dimethoxymethyl)-1,3-benzodioxol-5-yl](hydroxy)phenylacetate (**2j**). Colorless solid. M.p. 109–110° (hexane/CH_2Cl_2). IR (neat): 3468, 1734, 1624. ^{1}H-NMR: 3.08 (*s*, 3 H); 3.29 (*s*, 3 H); 3.84 (*s*, 3 H); 4.58 (*s*, 1 H); 5.45 (*s*, 1 H); 5.95 (*s*, 2 H); 6.41 (*s*, 1 H); 7.20 (*s*, 1 H); 7.34–7.39 (*m*, 3 H); 7.52 (*dd*, *J* = 8.4, 1.6, 2 H). Anal. calc. for $C_{19}H_{20}O_7$ (360.36): C 63.33, H 5.59; found: C 63.10, H 5.67.

1,3-Dihydro-3-oxo-2-benzofuran-1-carboxylates **4**. *General Procedure.* To a stirred soln. of **2** (1.0 mmol) in CH_2Cl_2 (3 ml) at 0° was added TsOH · H_2O (9.6 mg, 0.050 mmol). Stirring was continued for 10 min, then, the mixture was diluted with CH_2Cl_2 (20 ml) and a sat. aq. $NaHCO_3$ soln. (20 ml) was added. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (2 × 5 ml). The combined org. layers were washed with brine (15 ml), dried (Na_2SO_4), and concentrated by evaporation. A mixture of the residual crude product **3** and excess PCC (see *Table 1*) in CH_2Cl_2 (10 ml) containing *Celite*® (1.9 g) was stirred at the temp. indicated in *Table 1*. The progress of the reaction was monitored by TLC (SiO_2; AcOEt/hexane 1:7). After consumption of the starting material, the mixture was filtered under reduced pressure. The filtrate was concentrated by evaporation and the residue was purified by CC (SiO_2; AcOEt/hexane 1:5) to afford the desired product.

Methyl 1,3-Dihydro-1-methyl-3-oxo-2-benzofuran-1-carboxylate (**4a**). Colorless solid. M.p. 56–57° (hexane/CH_2Cl_2; [14]: 57–58°). The ^{1}H-NMR data of this product were identical to those reported in [2].

Methyl 1,3-Dihydro-3-oxo-1-phenyl-2-benzofuran-1-carboxylate (**4b**). Colorless solid. M.p. 94–96° (hexane/CH_2Cl_2; [15]: 96°). IR (KBr): 1779, 1743. ^{1}H-NMR: 3.82 (*s*, 3 H); 7.37–7.40 (*m*, 3 H); 7.49–7.53 (*m*, 2 H); 7.63 (*t*, *J* = 7.6, 1 H); 7.77 (*t*, *J* = 7.6, 1 H); 7.90 (*d*, *J* = 7.6, 1 H); 7.94 (*d*, *J* = 7.6, 1 H). ^{13}C-NMR: 53.60; 88.03; 124.74; 125.36; 125.88; 126.04; 128.85; 129.45; 130.34; 134.52; 136.13; 147.12; 168.63; 168.70.

Methyl 5-Chloro-1,3-dihydro-1-methyl-3-oxo-2-benzofuran-1-carboxylate (**4c**). Colorless solid. M.p. 104–105° (hexane/CH_2Cl_2). IR (KBr): 1781, 1746. ^{1}H-NMR: 1.91 (*s*, 3 H); 3.76 (*s*, 3 H); 7.57 (*d*, *J* = 8.4, 1 H); 7.68 (*dd*, *J* = 8.4, 1.5, 1 H); 7.87 (*d*, *J* = 1.5, 1 H). ^{13}C-NMR: 23.63; 53.50; 84.75; 123.49; 125.77; 126.84; 134.90; 136.59; 147.14; 167.61; 169.28. HR-DART-MS: 241.0260 ($[M+H]^+$, $C_{11}H_{10}ClO_4^+$; calc. 241.0262). Anal. calc. for $C_{11}H_9ClO_4$ (240.64): C 54.90, H 3.77; found: C 54.84, H 3.84.

Methyl 1,3-Dihydro-5-methoxy-3-oxo-1-phenyl-2-benzofuran-1-carboxylate (**4d**). White solid. M.p. 88–90° (hexane/CH_2Cl_2). IR (neat): 1778, 1742, 1621. ^{1}H-NMR: 3.81 (*s*, 3 H); 3.89 (*s*, 3 H); 7.30 (*dd*, *J* = 8.4, 2.3, 1 H); 7.34 (*d*, *J* = 2.3, 1 H); 7.37–7.39 (*m*, 3 H); 7.48–7.50 (*m*, 2 H); 7.75 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR: 53.50; 55.89; 87.87; 107.63; 123.28; 125.59; 126.13; 126.99; 128.80; 129.34; 136.35; 139.35; 161.57; 168.65; 168.90. HR-ESI-MS: 299.0914 ($[M+H]^+$, $C_{17}H_{15}O_5^+$; calc. 299.0914). Anal. calc. for $C_{17}H_{14}O_5$ (298.29): C 68.45, H 4.73; found: C 68.38, H 4.74.

Methyl 1,3-Dihydro-5,6-dimethoxy-1-methyl-3-oxo-2-benzofuran-1-carboxylate (**4e**). Colorless solid. M.p. 132–133° (hexane/CH_2Cl_2). IR (KBr): 1768, 1752 (sh.), 1601. ^{1}H-NMR: 1.89 (*s*, 3 H); 3.76 (*s*, 3 H); 3.95 (*s*, 3 H); 4.00 (*s*, 3 H); 6.99 (*s*, 1 H); 7.28 (*s*, 1 H). ^{13}C-NMR: 23.78; 53.26; 56.36; 56.54; 84.12; 103.30; 106.06; 116.93; 143.56; 151.19; 155.11; 169.35; 170.22. HR-ESI-MS: 267.0862 ($[M+H]^+$, $C_{13}H_{15}O_6^+$; calc. 267.0863). Anal. calc. for $C_{13}H_{14}O_6$ (266.25): C 58.64, H 5.30; found: C 58.34, H 5.18.

Ethyl 1,3-Dihydro-5,6-dimethoxy-1-methyl-3-oxo-2-benzofuran-1-carboxylate (**4f**). Colorless solid. M.p. 132–133° (hexane/CH_2Cl_2). IR (KBr): 1769, 1740, 1601. ^{1}H-NMR: 1.25 (*t*, *J* = 7.6, 3 H); 1.88 (*s*, 3 H); 3.95 (*s*, 3 H); 4.00 (*s*, 3 H); 4.12–4.20 (*m*, 1 H); 4.22–4.28 (*m*, 1 H); 6.99 (*s*, 1 H); 7.28 (*s*, 1 H). ^{13}C-NMR: 13.94; 23.79; 56.34; 56.51; 62.46; 84.14; 103.31; 106.04; 116.97; 143.68; 151.12; 155.03; 169.43; 169.64. HR-ESI-MS: 281.1023 ($[M+H]^+$, $C_{14}H_{17}O_6^+$; calc. 281.1020). Anal. calc. for $C_{14}H_{16}O_6$ (280.28): C 60.00, H 5.75; found: C 59.90, H 5.73.

Ethyl 1,3-Dihydro-5,6-dimethoxy-3-oxo-1-phenyl-2-benzofuran-1-carboxylate (**4g**). White solid. M.p. 117–119° (hexane/CH_2Cl_2). IR (neat): 1769, 1736, 1601. ^{1}H-NMR: 1.29 (*t*, *J* = 7.6, 3 H); 3.96 (*s*, 3 H); 4.00 (*s*, 3 H); 4.22–4.28 (*m*, 1 H); 4.31–4.37 (*m*, 1 H); 7.22 (*s*, 1 H); 7.31 (*s*, 1 H); 7.38–7.39 (*m*, 3 H); 7.44–7.46 (*m*, 2 H). ^{13}C-NMR: 14.00; 56.38; 56.58; 62.79; 87.49; 105.86; 105.88; 117.65; 126.24; 128.82; 129.37; 136.59; 141.66; 151.38; 154.66; 168.53; 168.98. HR-ESI-MS: 343.1167 ($[M+H]^+$, $C_{19}H_{19}O_6^+$; calc. 343.1176). Anal. calc. for $C_{19}H_{18}O_6$ (342.35): C 66.66, H 5.30; found: C 66.56, H 5.18.

Methyl 1-(4-Chlorophenyl)-1,3-dihydro-5,6-dimethoxy-3-oxo-2-benzofuran-1-carboxylate (**4h**). Colorless amorphous powder. R_f (AcOEt/hexane 1:2) 0.33. IR (neat): 1772, 1741, 1600. ^{1}H-NMR: 3.91 (*s*, 3 H); 3.96 (*s*, 3 H); 4.01 (*s*, 3 H); 7.17 (*s*, 1 H); 7.30 (*s*, 1 H); 7.36 (*d*, *J* = 9.2, 2 H); 7.42 (*d*, *J* = 9.2, 2 H). ^{13}C-NMR: 53.63; 56.42; 56.65; 86.74; 105.54; 106.00; 117.40; 127.68; 129.06; 135.00; 135.57; 141.29; 151.58; 155.15; 168.66; 168.90. HR-ESI-MS: 363.0624 ($[M+H]^+$, $C_{18}H_{16}ClO_6^+$; calc. 363.0630). Anal. calc. for $C_{18}H_{15}ClO_6$ (362.76): C 59.60, H 4.17; found: C 59.38, H 4.19.

Methyl 5,7-Dihydro-5-methyl-7-oxofuro[3,4-f][1,3]benzodioxole-5-carboxylate (**4i**). Colorless solid. M.p. 113–114° (hexane/CH_2Cl_2). IR (KBr): 1771, 1745 (sh.), 1611. ^{1}H-NMR: 1.85 (*s*, 3 H); 3.76 (*s*, 3 H); 6.13 (*s*, 1 H); 6.14 (*s*, 1 H); 6.96 (*s*, 1 H); 7.18 (*s*, 1 H). ^{13}C-NMR: 23.77; 53.29; 84.04; 102.06; 102.89; 104.34; 118.87; 145.65; 150.02; 153.94; 168.55; 169.60. HR-ESI-MS: 251.0546 ($[M+H]^+$, $C_{12}H_{11}O_6^+$; calc. 251.0550). Anal. calc. for $C_{12}H_{10}O_6$ (250.21): C 57.60, H 4.03; found: C 57.33, H 4.17.

Methyl 5,7-Dihydro-7-oxo-5-phenylfuro[3,4-f][1,3]benzodioxole-5-carboxylate (**4j**). Colorless solid. M.p. 162–163° (hexane/CH_2Cl_2). IR (KBr): 1772, 1740, 1610. ^{1}H-NMR: 3.82 (*s*, 3 H); 6.15 (*s*, 2 H); 7.19 (*s*, 1 H); 7.21 (*s*, 1 H); 7.38–7.39 (*m*, 3 H); 7.46–7.48 (*m*, 2 H). ^{13}C-NMR: 53.54; 87.29; 102.97; 104.17; 104.55; 119.30; 125.97; 128.87; 129.43; 136.26; 143.78; 150.18; 153.88; 168.11; 168.72. HR-ESI-MS: 313.0706 ($[M+H]^+$, $C_{17}H_{13}O_6^+$; calc. 313.0707). Anal. calc. for $C_{17}H_{12}O_6$ (312.28): C 65.39, H 3.87; found: C 65.15, H 3.85.

Methyl [2-(Dimethoxymethyl)-4,5-dimethoxyphenyl](oxo)acetate (**5**) was prepared by the reaction of [2-(dimethoxymethyl)-4,5-dimethoxyphenyl]lithium with $(MeOC{=}O)_2$ as described for the preparation of **2a**. Pale-yellow solid. M.p. 91–92° (hexane/CH_2Cl_2). IR (KBr): 1756, 1734, 1699, 1601. ^{1}H-NMR: 3.27 (*s*, 6 H); 3.91 (*s*, 3 H); 3.93 (*s*, 3 H); 3.96 (*s*, 3 H); 5.68 (*s*, 1 H); 7.08 (*s*, 1 H); 7.10 (*s*, 1 H). Anal. calc. for $C_{14}H_{18}O_7$ (298.29): C 56.37, H 6.08; found: C 56.30, H 6.12.

Methyl [2-(Dimethoxymethyl)-4,5-dimethoxyphenyl](hydroxy)acetate (**6a**). To a stirred soln. of **5** (0.20 g, 0.67 mmol) in MeOH (4 ml) at 0° was added $NaBH_4$ (25 mg, 0.67 mmol). After 5 min, the resulting mixture was worked up and the crude mixture was purified as described for the preparation of **2a** to give **6a** (0.17 g, 86%). Colorless oil. R_f (AcOEt/hexane 1:2) 0.43. IR (neat): 3475, 1744, 1609. ^{1}H-NMR: 3.30 (*s*, 3 H), 3.37 (*s*, 3 H); 3.63 (*d*, *J* = 4.6, 1 H); 3.76 (*s*, 3 H); 3.88 (*s*, 3 H); 3.91 (*s*, 3 H); 5.52 (*d*, *J* = 4.6, 1 H); 5.62 (*s*, 1 H); 6.84 (*s*, 1 H); 7.13 (*s*, 1 H). Anal. calc. for $C_{14}H_{20}O_7$ (300.31): C 55.99, H 6.71; found: C 55.75, H 6.72.

Methyl 2-[2-(Dimethoxymethyl)-4,5-dimethoxyphenyl]-2-hydroxyhexanoate (**6b**). To a stirred soln. of **5** (0.20 g, 0.67 mmol) in THF (3 ml) was added BuLi (1.6M in hexane, 0.67 mmol) dropwise. After 5 min, the resulting mixture was worked up, and the crude mixture was purified as described for the preparation of **2a** to give **6b** (0.14 g, 57%). Pale-yellow oil. R_f (AcOEt/hexane 1:1) 0.36. IR (neat): 3494, 1735, 1608. ^{1}H-NMR: 0.93 (*t*, *J* = 6.9, 3 H); 1.21–1.29 (*m*, 1 H); 1.35–1.47 (*m*, 3 H); 2.05–2.22 (*m*, 2 H); 3.26 (*s*, 3 H); 3.39 (*s*, 3 H); 3.72 (*s*, 3 H); 3.90 (*s*, 6 H); 4.42 (*s*, 1 H); 5.85 (*s*, 1 H); 6.99 (*s*, 1 H); 7.24 (*s*, 1 H). Anal. calc. for $C_{18}H_{28}O_7$ (356.42): C 60.66, H 7.92; found: C 60.64, H 8.07.

Methyl [2-(Dimethoxymethyl)-4,5-dimethoxyphenyl](hydroxy)(thiophen-2-yl)acetate (**6c**). Compound **6c** was prepared by treating **5** with thien-2-yllithium as described for the preparation of **6b**. Pale-yellow oil. R_f (AcOEt/hexane 1:2) 0.21. IR (neat): 3463, 1739, 1608. ^{1}H-NMR: 3.32 (*s*, 3 H); 3.32 (*s*, 3 H); 3.64 (*s*, 3 H); 3.85 (*s*, 3 H); 3.90 (*s*, 3 H); 4.88 (*s*, 1 H); 5.63 (*s*, 1 H); 6.52 (*s*, 1 H); 7.05 (*dd*, J = 4.6, 3.8, 1 H); 7.12 (*dd*, J = 3.8, 1.5, 1 H); 7.26 (*s*, 1 H); 7.37 (*dd*, J = 4.6, 1.5, 1 H). Anal. calc. for $C_{18}H_{22}O_7S$ (382.43): C 56.53, H 5.80; found: C 56.30, H 5.96.

Methyl (2-Chloropyridin-3-yl)[2-(dimethoxymethyl)-4,5-dimethoxyphenyl]hydroxyacetate (**6d**). Compound **6d** was prepared by treating **5** with (2-chloropyridin-3-yl)lithium, generated by the reported method [16]. Yellow oil. R_f (AcOEt/hexane 4:3) 0.32. IR (neat): 3469, 1743, 1608. ^{1}H-NMR: 3.20 (*s*, 3 H); 3.28 (*s*, 3 H); 3.78 (*s*, 3 H); 3.91 (*s*, 3 H); 3.95 (*s*, 3 H); 5.00 (*s*, 1 H); 5.64 (*s*, 1 H); 6.68 (*s*, 1 H); 7.17 (*dd*, J = 7.6, 4.6, 1 H); 7.34 (*s*, 1 H); 7.42 (*dd*, J = 7.6, 1.5, 1 H); 8.37 (*dd*, J = 4.6, 1.5, 1 H). Anal. calc. for $C_{19}H_{22}ClNO_7$ (411.84): C 55.41, H 5.38, N 3.40; found: C 55.38, H 5.60, N 3.18.

Compounds **7a**–**7d** were prepared as described for the preparation of **4e**–**4h** (see the *General Procedure* for **4** described above and *Table 1*).

Methyl 1,3-Dihydro-5,6-dimethoxy-3-oxo-2-benzofuran-1-carboxylate (**7a**). Pale-yellow solid. M.p. 124–126° (hexane/CH_2Cl_2). IR (KBr): 1770, 1740 (sh.), 1602. ^{1}H-NMR: 3.83 (*s*, 3 H); 3.95 (*s*, 3 H); 4.00 (*s*, 3 H); 5.80 (*s*, 1 H); 7.07 (*s*, 1 H); 7.30 (*s*, 1 H). ^{13}C-NMR: 53.14; 56.37; 56.56; 77.26; 103.95; 106.17; 116.91; 138.45; 151.37; 166.20; 167.70; 159.68. HR-ESI-MS (ESI): 253.0712 ($[M+H]^+$, $C_{12}H_{13}O_6^+$; calc. 253.0707). Anal. calc. for $C_{12}H_{12}O_6$ (252.22): C 57.14, H 4.80; found: C 56.91, H 4.93.

Methyl 1-Butyl-1,3-dihydro-5,6-dimethoxy-3-oxo-2-benzofuran-1-carboxylate (**7b**). Colorless solid. M.p. 118–119° (hexane/Et_2O). IR (KBr): 1769, 1741, 1602. ^{1}H-NMR: 0.87 (*t*, J = 7.6, 3 H); 1.22–1.35 (*m*, 4 H); 1.96–2.02 (*m*, 1 H); 2.38–2.44 (*m*, 1 H); 3.77 (*s*, 3 H); 3.95 (*s*, 3 H); 4.00 (*s*, 3 H); 7.00 (*s*, 1 H); 7.28 (*s*, 1 H). ^{13}C-NMR: 13.75; 22.37; 25.39; 37.01; 53.13; 56.33; 56.55; 87.08; 103.55; 106.95; 117.29; 142.45; 151.14; 155.08; 169.55; 170.11. HR-ESI-MS: 309.1334 ($[M+H]^+$, $C_{16}H_{21}O_6^+$; calc. 309.1333). Anal. calc. for $C_{16}H_{20}O_6$ (308.33): C 62.33, H 6.54; found: C 62.30, H 6.34.

Methyl 1,3-Dihydro-5,6-dimethoxy-3-oxo-1-(thiophen-2-yl)-2-benzofuran-1-carboxylate (**7c**). Pale-yellow oil. R_f (AcOEt/hexane 1:2) 0.21. IR (neat): 1771, 1743, 1601. ^{1}H-NMR: 3.85 (*s*, 3 H); 3.96 (*s*, 3 H); 4.01 (*s*, 3 H); 7.01 (*t*, J = 4.6, 1 H); 7.22 (br. *s*, 2 H); 7.29 (*s*, 1 H); 7.36 (*d*, J = 4.6, 1 H). ^{13}C-NMR: 53.75; 56.42; 56.65; 84.54; 105.34; 105.86; 117.05; 127.00; 127.19; 127.22; 138.99; 141.82; 151.63; 155.09; 168.41; 168.56. HR-ESI-MS: 335.0584 ($[M+H]^+$, $C_{16}H_{15}O_6S^+$; calc. 335.0584). Anal. calc. for $C_{16}H_{14}O_6S$ (334.34): C 57.48, H 4.22; found: C 57.18, H 4.26.

Methyl 1-(2-Chloropyridin-3-yl)-1,3-dihydro-5,6-dimethoxy-3-oxo-2-benzofuran-1-carboxylate (**7d**). Colorless solid. M.p. 86–87° (hexane/CH_2Cl_2). IR (KBr): 1774, 1741, 1600. ^{1}H-NMR: 3.85 (*s*, 3 H); 3.99 (*s*, 3 H); 4.00 (*s*, 3 H); 7.10 (*s*, 1 H); 7.23 (*dd*, J = 7.6, 4.6, 1 H); 7.36 (*s*, 1 H); 7.49 (*dd*, J = 7.6, 1.5, 1 H); 8.45 (*dd*, J = 4.6, 1.5, 1 H). ^{13}C-NMR: 53.92; 56.48; 56.74; 86.06; 105.13; 106.61; 118.32; 122.29; 131.80; 137.33; 139.24; 150.17; 151.38; 151.98; 155.21; 168.46; 168.53. HR-ESI-MS: 364.0582 ($[M+H]^+$, $C_{17}H_{15}ClNO_6^+$; calc. 364.0582). Anal. calc. for $C_{17}H_{14}ClNO_6$ (363.75): C 56.13, H 3.88, N 3.85; found: C 55.88, H 3.80, N 3.61.

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