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A mild approach to diarylfuranones via functionalized 2-arylfurans

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ABSTRACT

5,5- and 3,5-Diarylfuranones have been obtained in a three-step one-pot manner. The procedure starts from photooxygenation of easily accessible arylfurans followed by in situ base treatment and finally by triflic anhydride mediated acylation of activated aromatic substrates. The regioselectivity of the acylation reaction depends on the reaction conditions and/or activation of both acid and aromatic reagents. The 5,5-diarylfuranone products have the same carbon skeleton as some rearranged tetrahydrofuran lignans.

1. Introduction

Furans are a class of heterocycles widely distributed in a large number of natural compounds, in aromatic forms, reduced forms as tetrahydrofurans, and oxidized forms as furanones.[1] This heterocycle has a prominent role in synthetic chemistry due to its ability to undergo a wide range of reactions, amongst these, oxidation to versatile 1,4-enedione or to the widely diffuse furanone ring.[2] Polysubstituted furans are important building blocks for the synthesis of natural and non-natural products.[2] In a previous study we reported a strategy allowing the preparation of some furans as precursors of lignan-like compounds.[3] Lignans are widespread plant secondary metabolites displaying a large series of bioactivities.[4] Their isolation from natural sources is a laborious expensive process and the yields are generally low. Hence, several routes to natural and synthetic derivatives have been proposed over the years. We obtained 4-aroyl-3-carbomethoxy-2-phenylfurans, having a β-β′-linked C6C3–C3C6 backbone typical of lignans, starting from a unique easily accessible furoic acid precursor via trifluoromethanesulfonic anhydride (Tf_2O)-mediated acylation.[3] Tf_2O is of high current interest in Friedel–Crafts (FC) acylation of carboxylic acids[5] and other substrates.[6] It can be used directly without the use of a catalyst and it reacts in short times and within a large range of temperatures.[3,5] Our method was based on tunable Tf_2O-mediated FC acylation under controlled conditions (low temperature, neat, high equivalents) otherwise leading to 3-aroyl-regioisomers.[3] In our effort to search for new synthetic methods for lignan-like compounds,[3,7] and stimulated by the potentiality of the Tf_2O-mediated acylation, we decided to explore further applications of the above methodology using 4-oxo-2-alkenoic acids prepared from 2-aryl-3,4-dicarbomethoxyfurans.

2. Results and discussion

It is reported that 4-oxoalkenoic acids can be obtained from furans via oxidation with sodium chlorite in an acidic aqueous solution followed by treatment with pyridine.[8] We have prepared these acids via dye-sensitized photooxygenation followed by in situ addition of diethylamine. The dye-sensitized photooxygenation is one of the most used and environmentally friendly furan oxidation procedures, often representing the key step in the synthesis of interesting natural compounds.[9–11] The methylene blue (MB)-sensitized photooxygenation of furans **1a**–**c**, synthesized according to a reported procedure,[12] was carried out at −20 °C. Endoperoxides **2** were obtained quantitatively and exhibited a sufficient thermal stability due to the presence of two electron-withdrawing groups.[9] The in situ treatment with diethylamine at rt gave monoacids **3** almost quantitatively (Scheme 1).

Acids **3** were the only products even using other bases as triethylamine and 1,4-diazabicyclo[2.2.2]octane. The base treatment of α- or α,α′-unsubstituted furan endoperoxides generally produces a conversion to γ-hydroxybutenolides.[9,10,13] In our cases it is probable that the once formed lactone rapidly converts to the

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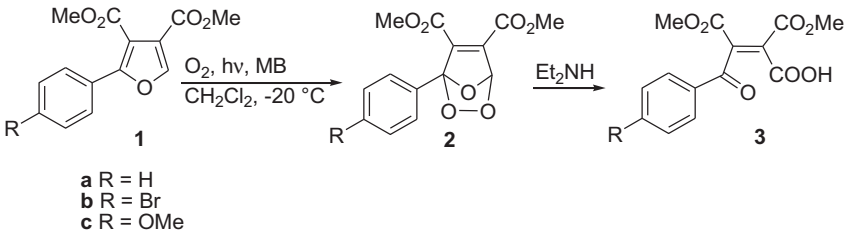


Scheme 1. Singlet oxygenation of furans **1** and base-assisted transformation of endoperoxides **2**.

corresponding acid open form **3** because of the particular substitution and high conjugation. On the other hand, the base-mediated conversion of butenolides into open structures is known.[8]

Initially, investigation of the Tf_2O-mediated acylation was proven starting from pure acid **3a** and using anisole (**4a**) as the aryl reagent. The reaction was carried out at low temperature using 2.5 equiv of Tf_2O and neat anisole as solvent. Unexpectedly the reaction led to a mixture of cyclic acylated products, e.g., 5,5-diarylfuranone **5a** and 3,5-diarylfuranones **6a** and **6′a** (Scheme 2). When the reaction was performed in dichloromethane as solvent using an excess of anisole (5 equiv) and 2.5 equiv of Tf_2O, the result did not change while it appeared to slightly increase the amounts of 3,5-diarylfuranones **6a** and **6′a** (Scheme 2). Further experiments changing the stoichiometry or using a highly polar solvent were unsuccessful. The use of equimolecular amounts of **3a** and **4a** in the presence of 1.5 equiv of Tf_2O in dichloromethane gave poor yield (27%). A lower yield (42%) was also obtained using acetonitrile as solvent while nitromethane gave a very complex reaction mixture.

diaylfuranone **6a** is promoted by the presence of the aroyl group that directs the aryl addition also to the 3-position by means of conjugation and/or steric effects.[16] Interestingly, 5,5-diarylfuranone **5a** had a structure similar to some rare natural lignans, for example, sacidumlignan D (Fig. 1), that is, a peculiar rearranged α,α-diaryltetrahydrofuran lignan.[17]

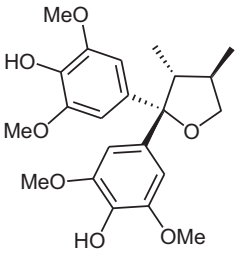
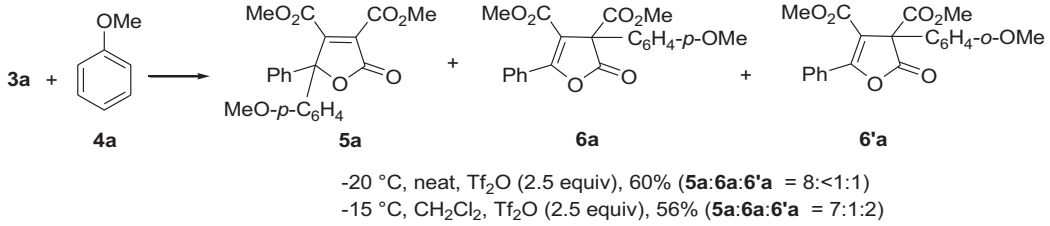


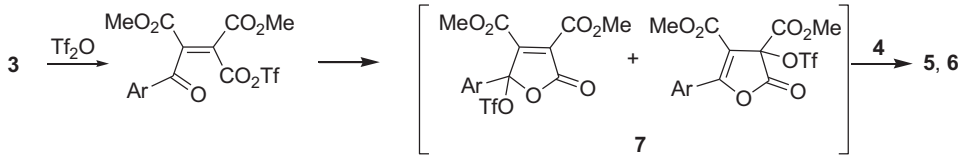
Fig. 1. Sacidumlignan D, a lignan with a rare structure.



Scheme 2. Tf_2O-assisted Friedel–Crafts acylation of anisole (**4a**) with acid **3a**.

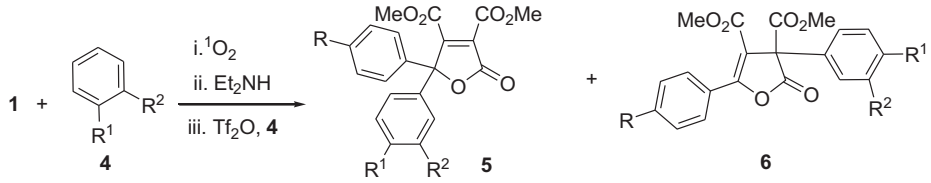
Cyclic products by FC acylation indicated an intramolecular addition of the carbonyl to the activated carboxylic function and the possible formation of pseudo anhydrides **7** (or a carbocation). These intermediates should undergo FC reaction to result in the cyclic arylated **5** and **6** (Scheme 3). The formation of pseudo anhydrides **7** is supported by ^1H NMR spectra acquired immediately after the addition of Tf_2O. A shift at higher field of *ortho* aryl protons was observed indicating the possible presence of the pseudo anhydrides. Few examples of obtaining furanones in FC reactions are reported in the literature such as the FC acylation of phthalic acids[14] or alkylated acrylic acids,[15] both leading to 5-arylfuranones. It is probable that the formation of 3,5-

These considerations induced us to verify the scope of the reaction. Preliminary experiments showed that starting from crude **3a** very similar results were obtained with regards to the final yields and the molar ratio of furanones **5a**, **6a**, and **6′a** for both optimized acylation approaches (with and without dichloromethane). Hence, we decided to apply the one-pot reaction to furans **1b**,**c** using both conditions (Table 1). Moreover, to extend the scope in the preparation of lignan-like compounds, starting from furans **1a** and **1c** the acylation was performed using other aromatic substrates, with lignan-typical aryl substitution, such as 1,2-dimethoxybenzene (**4b**, R^1=R^2=OMe), 3-benzodioxole (**4c**, R^1, R^2=−OCH_2O−) and phenol (**4d**, R^1=OH, R^2=H). Since triflic acid is generated the acylation was



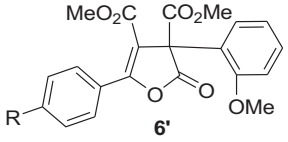
Scheme 3. Proposed conversion of acid **3** to furanones **5** and **6**.

Table 1
One-pot preparation of furanones **5** and **6**



1	R	4	R^1	R^2	5/6	FC-acylation condition			Yield[a] (%)	5/6 Ratio[b]
						Entry	Solvent	T (°C)/time (h)		
a	H	**a**	OMe	H	**a**	1	Neat	−20 to rt/20	52 (70)	88:12[c] (82:18)
						2	CH_2Cl_2	−15/2.5	48 (73)	83:17[c] (57:43)
b	Br	**a**	OMe	H	**b**	3	Neat	−20 to rt/20	53 (72)	77:23[c] (72:28)
						4	CH_2Cl_2	−10/2.5	35 (55)	45:55[c] (34:66)
c	OMe	**a**	OMe	H	**c**	5	Neat	−20/21	72 (97)	60:40 (42:58)
						6	CH_2Cl_2	−20/21	40 (61)	20:80 (25:75)
a	H	**b**	OMe	OMe	**d**	7	Neat	−10 to 10/8	39 (61)	61:39 (55:45)
a	H	**c**	−OCH_2O−		**e**	8	CH_2Cl_2	−15 to rt/20	34 (55)	55:45 (54:46)
a	H	**d**	OH	H	**f**	9	CH_2Cl_2	−20 to rt/2.5	39 (60)	46:54 (45:55)
c	OMe	**b**	OMe	OMe	**g**	10	Neat	−20 to rt/18	89	23:77
						11	CH_2Cl_2	−10/2	50 (76)	18:82 (29:71)
c	OMe	**c**	−OCH_2O−		**h**	12	CH_2Cl_2	−10/20	98	6:94

[a] Isolated yield from column chromatography. In parenthesis yield for the reaction performed in the presence of 2,6-lutidine (2.5 equiv).
[b] Ratio for the reaction performed in the presence of 2,6-lutidine (2.5 equiv).
[c] These reactions gave a mixture of **6** and **6′** isomers in ratio: entry 1 (1:11), entry 2 (7:10), entry 3 (10:13), and entry 4 (20:35). Similar isomeric ratios were obtained for the reactions performed in the presence of 2,6-lutidine (2.5 equiv).



also performed in the presence of a non-nucleophilic base, such as 2,6-lutidine. As shown in Table 1, higher yields were obtained while the product ratio was little, if at all, altered.

In all cases diarylfuranones **5** and **6** were formed. Starting from furans **1a** and **1b** with anisole (**4a**) *o*-isomers **6′** were also found. The molecular structures were elucidated by ^1H and ^{13}C NMR spectroscopy, 2D NMR experiments, and MS data. As shown in Table 1, the nature of the aryl substituent on acids **3** has no effect on the furanone formation while the use of the solvents generally decreases the yield. Low temperatures and the absence of a solvent favor 5,5-diarylfuranones **5** (compare entries 1 and 2, 3 and 4, 5 and 6). In some cases, the use of the solvent was effective in reversing the regioselectivity of the acylation in favor of 3,5-diaryl isomers **6** (compare entries 5 and 6). This also occurs independently from the reaction conditions in the presence of the highly activated acid **3c** and aromatic compound **4b** (compare entries 10 and 11).

3. Conclusion

In summary, we have prepared various novel 5,5- and 3,5-diarylfuranones **5** and **6** in a three-step one-pot manner starting from furans **1** under mild conditions. The key step is a Tf_2O-mediated acylation and the addition of a non-nucleophilic base increases the yields. Arylfuranones have been rarely obtained by FC acylation, especially 3-arylfuranones.[14–16] The furanone structural motif is widespread in bioactive natural products, also lignans,[18] as well as in synthetic products, also diarylderivatives,[19] with a wide range of activities such as antibiotic, antifungal, and anticancer agents.[1] Noteworthy, 5,5-diarylfuranones **5** combine the presence of a furanone moiety with a carbon skeleton of some recently isolated rare lignans.[17]

4. Experimental section

4.1. General information

NMR spectra were recorded on 500 MHz spectrometer; ^1H NMR recorded at 500 MHz and ^{13}C NMR recorded at 126 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent signal ($CDCl_3$: δ_H 7.26, δ_C 77.0). All reactions involving air or moisture sensitive reagents were carried out under a dry argon or nitrogen atmosphere using commercially dry solvents (Sigma–Aldrich 99.7%) stored over molecular sieves. When necessary, compounds were dried by azeotropic removal of water with toluene under reduced pressure. Analytical thin layer chromatography (TLC) was performed on aluminum plates precoated with Merck Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130 °C. Column chromatography was performed on Merck Kieselgel 60 (63–200 mesh).

Dimethyl 2-phenylfuran-3,4-dicarboxylate (**1a**, 70%), dimethyl 2-(4-bromophenyl)furan-3,4-dicarboxylate (**1b**, 34%), and dimethyl 2-(4-methoxyphenyl)furan-3,4-dicarboxylate (**1c**, 60%) were prepared according to a literature procedure.[11]

4.2. Preparation of diarylfuranones 5 and 6

*4.2.1. General procedure for synthesis of acids (**3**).* A solution of dry 2-aryl-3,4-dicarboxymethyl furan **1** (**1a**, 130 mg, 0.5 mmol) in dry CH_2Cl_2 (27.8 mL, 0.018 M) was irradiated at −20 °C in the presence of methylene blue (MB, 1 mg, 3×10^{-3} mmol) while dry oxygen was bubbled through the solution. The progress of the reaction was checked by periodically monitoring (^1H NMR) until the disappearance of **1** (typically 2–3 h) and the intermediate endoperoxide

2 was identified by its ^{1}H NMR spectroscopic data. Then, irradiation was stopped, diethylamine (62 μL, 0.6 mmol, 1.2 equiv) was added, and the mixture was kept at rt for 30 min. The solvent was evaporated and the crude acrylic acid **3** was dried in the presence of anhydrous P_2O_5 for 5 h in order to remove diethylamine.

*4.2.2. General procedure for Tf_2O-mediated Friedel–Crafts acylation of acids (**3**).* Crude reagent **3** (**3a**, 144 mg, 0.493 mmol) was dissolved in aromatic compound **4** (35 equiv, neat conditions) or in dry solvent (CH_2Cl_2, 2 mL) and then anisole (268 μL, 5 equiv) was added. The mixture was cooled to −20 °C and Tf_2O (207 μL, 1.23 mmol, 2.5 equiv) was added dropwise at this temperature. The resulting mixture was stirred under N_2 atmosphere at the temperature and for the time reported in Table 1. In the acylation with phenol (entry 9), Tf_2O (207 μL, 1.23 mmol, 2.5 equiv) was added dropwise in the acrylic acid **3a** (96.0 mg, 0.325 mmol) solution (dry CH_2Cl_2, 2 mL) cooled at −20 °C. The mixture was stirred for 30 min, then phenol was added and the resulting mixture warmed to rt for 2.5 h. On completion of the reaction (controlled by TLC), each mixture was washed with saturated aq $NaHCO_3$ solution and extracted twice with ethyl ether. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue that was chromatographed on silica gel with a gradient of petrol ether and ethyl acetate. Mixture of *p*- and *o*-isomers **6** and **6′** was subsequently separated by HPLC using RP-18 column and H_2O/MeOH/MeCN as eluent.

*4.2.3. General procedure for Tf_2O-mediated Friedel–Crafts acylation of acids (**3**) using 2,6-lutidine.* Crude reagent **3** (**3a**, 144 mg, 0.493 mmol) was dissolved in anisole (1.87 mL, 35 equiv, neat conditions) or in dry solvent (CH_2Cl_2, 2 mL) and then anisole (268 μL, 5 equiv) was added. The mixture was cooled to −20 °C and Tf_2O (207 μL, 1.23 mmol, 2.5 equiv) added dropwise at this temperature. Then 2,6-lutidine (143 μL, 2.5 equiv) was added at the same temperature. The resulting mixture was stirred under N_2 atmosphere at the temperature and for the time reported in Table 1.

*4.2.4. Dimethyl 1-phenyl-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5,6-dicarboxylate (**2a**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.3 Hz, 2H), 7.59–7.56 (m, 2H), 7.48–7.44 (m, 1H), 6.81 (s, 1H), 3.72 (s, 3H), 3.68 (s, 3H).

*4.2.5. Dimethyl 1-(4-bromophenyl)-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5,6-dicarboxylate (**2b**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J*=8.6 Hz, 2H), 7.47 (d, *J*=8.6 Hz, 2H), 6.81 (s, 1H), 3.88 (s, 3H), 3.74 (s, 3H).

*4.2.6. Dimethyl 1-(4-methoxyphenyl)-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5,6-dicarboxylate (**2c**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J*=9.1 Hz, 2H), 6.97 (d, *J*=9.1 Hz, 2H), 6.78 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H).

*4.2.7. (Z)-3-Benzoyl-4-methoxy-2-(methoxycarbonyl)-4-oxobut-2-enoic acid (**3a**).* Amorphous powder. IR (CH_2Cl_2) ν 3595–3478 (br), 2950, 1742, 1720, 1675, 1605, 1513, 1436, 1172, 1030, 850 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J*=7.6 Hz, 2H), 7.50 (t, *J*=7.6 Hz, 1H), 7.40 (t, *J*=7.6 Hz, 2H), 3.86 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 166.9, 165.6, 163.9, 145.0, 136.6, 134.5, 132.9, 128.6, 128.4, 52.8, 52.4; HRMS (ESI) (*m*/*z*): found 293.0664 $[M+H]^+$; calcd for $C_{14}H_{12}O_7$ 293.0661.

*4.2.8. (Z)-3-(4-Bromobenzoyl)-4-methoxy-2-(methoxycarbonyl)-4-oxobut-2-enoic acid (**3b**).* Amorphous powder. IR (CH_2Cl_2) ν 3590–3480 (br), 2960, 1742, 1718, 1680, 1601, 1512, 1430, 1170, 1040, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.5 Hz, 2H), 7.56 (d, *J*=8.5 Hz, 2H), 3.87 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 166.8, 165.5, 163.6, 145.2, 135.4, 131.9, 131.7, 130.3, 128.0, 53.0, 52.4; HRMS (ESI) (*m*/*z*): found 371.9770 $[M+H]^+$; calcd for $C_{14}H_{11}^{79}BrO_7$ 370.9766.

*4.2.9. (Z)-4-Methoxy-3-(4-methoxybenzoyl)-2-(methoxycarbonyl)-4-oxobut-2-enoic acid (**3c**).* Amorphous powder. IR (CH_2Cl_2) ν 3590–3480 (br), 2957, 1740, 1738, 1685, 1600, 1513, 1436, 1172, 1030, 842 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J*=8.8 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.0, 166.7, 166.3, 164.2, 163.3, 140.0, 131.5, 130.9, 130.0, 113.6, 55.4, 52.7, 52.5; HRMS (ESI) (*m*/*z*): found 323.0772 $[M+H]^+$; calcd for $C_{15}H_{14}O_8$ 323.0767.

*4.2.10. Dimethyl 2-(4-methoxyphenyl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**5a**, Table 1, entry 1).* Yellow oil (88 mg, 46%). R_f (25% EtOAc/hexane): 0.27. IR (CH_2Cl_2) ν 2960, 1760, 1738, 1602, 1441, 1170, 1036, 980, 890 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 7.23 (d, *J*=8.8 Hz, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 3.92 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 161.5, 161.0, 160.5, 160.3, 136.8, 129.3, 128.6, 128.5, 128.2, 127.7, 126.7, 113.9, 91.9, 55.3, 53.2, 53.1; HRMS (ESI) (*m*/*z*): found 383.1136 $[M+H]^+$; calcd for $C_{21}H_{18}O_7$ 383.1131.

*4.2.11. Dimethyl 3-(4-methoxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**6a**, Table 1, entry 2).* Yellow oil (5 mg, 3%). R_f (25% EtOAc/hexane): 0.38, separated from **6′a** by RP-HPLC H_2O/MeOH/MeCN (3:3:4 v/v/v). IR (CH_2Cl_2) ν 2980, 1812, 1755, 1717, 1607, 1510, 1460, 1170, 1032, 970, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J*=7.8 Hz, 2H), 7.53–7.41 (m, 5H), 6.92 (d, *J*=8.8 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 166.8, 162.6, 161.7, 160.0, 132.1, 129.6, 128.9, 128.8, 128.5, 128.2, 114.1, 114.0, 63.8, 55.1, 54.0, 52.0; HRMS (ESI) (*m*/*z*): found 383.1136 $[M+H]^+$; calcd for $C_{21}H_{18}O_7$ 383.1131.

*4.2.12. Dimethyl 3-(2-methoxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**6′a**, Table 1, entry 1).* Yellow oil (6 mg, 6%). R_f (25% EtOAc/hexane): 0.38, separated from **6a** by RP-HPLC H_2O/MeOH/MeCN (3:3:4 v/v/v). IR (CH_2Cl_2) ν 2982, 1815, 1752, 1711, 1600, 1515, 1465, 1174, 1030, 974, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J*=7.1 Hz, 2H), 7.57–7.43 (m, 5H), 7.33 (t, *J*=8.8 Hz, 1H), 7.03 (t, *J*=7.7 Hz, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 166.5, 162.5, 160.9, 156.5, 131.5, 131.4, 130.1, 129.8, 129.4, 128.1, 127.5, 123.6, 120.9, 111.9, 63.1, 55.8, 53.8, 51.4; HRMS (ESI) (*m*/*z*): found 383.1133 $[M+H]^+$; calcd for $C_{21}H_{18}O_7$ 383.1131.

*4.2.13. Dimethyl 2-(4-bromophenyl)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**5b**, Table 1, entry 3).* Yellow oil (43 mg, 41%). R_f (25% EtOAc/hexane): 0.28. IR (CH_2Cl_2) ν 3090, 2930, 1750, 1740, 1658, 1608, 1513, 1436, 1343, 1220, 927, 834 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J*=8.7 Hz, 2H), 7.21 (d, *J*=8.8 Hz, 2H), 7.19 (d, *J*=8.8 Hz, 2H), 6.88 (d, *J*=8.7 Hz, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 161.3, 160.5, 160.3, 160.1, 136.0, 131.7, 129.4, 129.2, 128.1, 127.1, 123.8, 114.0, 91.3, 55.3, 53.3, 53.2; HRMS (ESI) (*m*/*z*): found 461.0240 $[M+H]^+$; calcd for $C_{21}H_{17}^{79}BrO_7$ 461.0236.

*4.2.14. Dimethyl 5-(4-bromophenyl)-3-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**6b**, Table 1, entry 4).* Yellow oil (6.7 mg, 7%). R_f (25% EtOAc/hexane): 0.45, separated from **6′b** by RP-HPLC H_2O/MeOH/MeCN (2:5:3 v/v/v). IR (CH_2Cl_2) ν 2928, 1816, 1608, 1590, 1512, 1172, 1149 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.5 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.21 (d, *J*=8.9 Hz, 2H), 6.85 (d, *J*=8.9 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 166.3, 162.4, 159.7, 156.4, 131.4, 130.9, 129.9, 126.2, 123.4, 120.9, 114.2, 111.9, 63.4, 55.8, 53.8, 51.5; HRMS

(ESI) (*m*/*z*): found 461.0239 $[M+H]^+$; calcd for $C_{21}H_{17}^{79}BrO_7$ 461.0236.

*4.2.15. Dimethyl 5-(4-bromophenyl)-3-(2-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**6′b**, Table 1, entry 4).* Yellow oil (11.4 mg, 12%). R_f (25% EtOAc/hexane): 0.45, separated from **6b** by RP-HPLC H_2O/MeOH/MeCN (2:5:3 v/v/v). IR (CH_2Cl_2) ν 2930, 1800, 1602, 1592, 1512, 1172, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.8 Hz, 2H), 7.61 (d, *J*=8.8 Hz, 2H), 7.48 (dd, *J*=7.9, 1.5 Hz, 1H), 7.33 (td, *J*=8.0, 1.5 Hz, 1H), 7.04 (t, *J*=7.8 Hz, 1H), 6.90 (d, *J*=7.7 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 166.3, 162.4, 159.7, 156.4, 131.6, 131.4, 130.9, 129.9, 129.3, 126.2, 123.4, 120.9, 114.2, 111.9, 63.2, 55.8, 53.8, 51.5; HRMS (ESI) (*m*/*z*): found 461.0238 $[M+H]^+$; calcd for $C_{21}H_{17}^{79}Br\,O_7$ 461.0236.

*4.2.16. Dimethyl 2,2-bis(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**5c**, Table 1, entry 5).* Yellow oil (45 mg, 43%). R_f (40% EtOAc/hexane): 0.32. IR (CH_2Cl_2) ν 2930, 1780, 1741, 1608, 1461, 1180, 1033, 978, 895 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J*=9.0 Hz, 4H), 6.88 (d, *J*=8.9 Hz, 4H), 3.92 (s, 3H), 3.82 (s, 6H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 161.6, 161.3, 160.5, 160.2, 129.2, 128.6, 126.3, 113.8, 91.8, 55.3, 53.2, 53.1; HRMS (ESI) (*m*/*z*): found 413.1242 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

*4.2.17. Dimethyl 3,5-bis(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**6c**, Table 1, entry 6).* Yellow oil (15 mg, 32%). R_f (40% EtOAc/hexane): 0.40. IR (CH_2Cl_2) ν 2956, 1813, 1758, 1720, 1606, 1512, 1461, 1172, 1028, 971, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J*=9.0 Hz, 2H), 7.46 (d, *J*=9.1 Hz, 2H), 6.99 (d, *J*=9.0 Hz, 2H), 6.94 (d, *J*=9.1 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 167.1, 162.9, 162.6, 161.8, 159.8, 131.8, 131.4, 129.4, 125.5, 118.8, 113.9, 113.6, 63.7, 55.5, 55.3, 53.6, 51.9; HRMS (ESI) (*m*/*z*): found 413.1240 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

*4.2.18. Dimethyl 2-(3,4-dimethoxyphenyl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**5d**, Table 1, entry 7).* Yellow oil (20 mg, 24%). R_f (30% EtOAc/hexane): 0.19. IR (CH_2Cl_2) ν 2950, 1797, 1748, 1720, 1605, 1507, 1465, 1175, 1018, 968, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.34 (m, 3H), 7.32 (dd, *J*=8.0, 1.5 Hz, 2H), 6.90 (dd, *J*=8.4, 2.2 Hz, 1H), 6.83 (d, *J*=9.0 Hz, 1H), 6.81 (d, *J*=2.0 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 161.6, 161.4, 160.4, 149.9, 148.9, 136.8, 129.4, 128.8, 128.5, 127.7, 126.3, 120.7, 111.1, 110.7, 91.9, 56.0, 55.9, 53.3, 53.2; HRMS (ESI) (*m*/*z*): found 413.1239 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

*4.2.19. Dimethyl 3-(3,4-dimethoxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**6d**, Table 1, entry 7).* Yellow oil (13 mg, 15%). R_f (30% EtOAc/hexane): 0.25. IR (CH_2Cl_2) ν 2980, 1811, 1756, 1718, 1608, 1505, 1465, 1178, 1032, 971, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J*=7.4 Hz, 2H), 7.58–7.53 (m, 1H), 7.50 (t, *J*=7.5 Hz, 2H), 7.22 (d, *J*=2.2 Hz, 1H), 6.95 (dd, *J*=8.5, 2.2 Hz, 1H), 6.84 (d, *J*=8.5 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 166.8, 162.7, 161.7, 149.6, 148.9, 132.1, 129.6, 128.2, 126.7, 125.5, 125.3, 120.1, 112.1, 110.8, 63.8, 56.0, 55.9, 53.7, 52.1; HRMS (ESI) (*m*/*z*): found 413.1240 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

*4.2.20. Dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**5e**, Table 1, entry 8).* Yellow oil (16 mg, 19%). R_f (27% EtOAc/hexane): 0.43. IR (CH_2Cl_2) ν 3008, 2958, 1795, 1758, 1718, 1604, 1508, 1491, 1182, 1157, 1008, 978, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (m, 3H), 7.33 (d, *J*=6.9 Hz, 2H), 6.80 (dd, *J*=9.0, 1.4 Hz, 1H), 6.79 (d, *J*=1.5 Hz, 1H), 6.74 (d, *J*=8.5 Hz, 1H), 5.99 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 161.4, 161.0, 160.4, 147.9, 136.6, 130.3, 129.4, 128.6, 128.5, 127.6, 127.5, 122.0, 108.5, 108.0, 101.6, 91.7, 53.3, 53.2; HRMS (ESI) (*m*/*z*): found 397.0929 $[M+H]^+$; calcd for $C_{21}H_{16}O_8$ 397.0923.

*4.2.21. Dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**6e**, Table 1, entry 8).* Yellow oil (12 mg, 15%). R_f (27% EtOAc/hexane): 0.52. IR (CH_2Cl_2) ν 3010, 2956, 1815, 1748, 1720, 1605, 1515, 1485, 1176, 1156, 1008, 974, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J*=7.4 Hz, 2H), 7.55 (br d, *J*=7.3 Hz, 1H), 7.50 (t, *J*=7.5 Hz, 2H), 7.13 (br s, 1H), 6.92 (dd, *J*=8.2, 1.8 Hz, 1H), 6.79 (d, *J*=8.3 Hz, 1H), 5.98 (s, 2H), 3.83 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 166.6, 162.5, 161.8, 148.2, 147.9, 132.1, 129.6, 128.2, 126.8, 126.6, 121.5, 115.5, 109.3, 108.0, 101.4, 64.0, 53.7, 52.1; HRMS (ESI) (*m*/*z*): found 397.0936 $[M+H]^+$; calcd for $C_{21}H_{16}O_8$ 397.0939.

*4.2.22. Dimethyl 2-(4-hydroxyphenyl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**5f**, Table 1, entry 9).* Yellow oil (21.5 mg, 18%). R_f (35% EtOAc/hexane): 0.24. IR (CH_2Cl_2) ν 3009, 2958, 1780, 1758, 1715, 1600, 1510, 1491, 1180, 1010, 981, 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.34 (m, 3H), 7.32 (dd, *J*=8.1, 1.5 Hz, 2H), 7.16 (d, *J*=8.8 Hz, 2H), 6.80 (d, *J*=8.7 Hz, 2H), 3.92 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 161.5, 161.3, 160.5, 156.9, 136.6, 129.5, 129.4, 128.5, 128.4, 127.7, 126.5, 115.4, 92.1, 53.3, 53.2; HRMS (ESI) (*m*/*z*): found 369.0973 $[M+H]^+$; calcd for $C_{20}H_{16}O_7$ 369.0969.

*4.2.23. Dimethyl 3-(4-hydroxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**6f**, Table 1, entry 9).* Yellow oil (25.5 mg, 21%). R_f (35% EtOAc/hexane): IR (CH_2Cl_2) ν 3001, 2956, 1810, 1762, 1720, 1601, 1490, 1158, 1008, 980, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J*=7.5 Hz, 2H), 7.54 (br t, *J*=7.3 Hz, 1H), 7.50 (br t, *J*=7.8 Hz, 2H), 7.40 (d, *J*=8.7 Hz, 2H), 6.84 (d, *J*=8.7 Hz, 2H), 3.83 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 166.9, 162.7, 161.8, 156.2, 132.1, 129.6, 128.2, 126.6, 125.3, 115.5, 110.7, 63.7, 53.8, 52.1; HRMS (ESI) (*m*/*z*): found 369.0975 $[M+H]^+$; calcd for $C_{20}H_{16}O_7$ 369.0969.

*4.2.24. Dimethyl 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**5g**, Table 1, entry 10).* Yellow oil (17 mg, 18%). R_f (30% EtOAc/hexane): 0.20. IR (CH_2Cl_2) ν 3009, 2928, 1780, 1741, 1605, 1514, 1464, 1180, 1027, 995, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J*=9.0 Hz, 2H), 6.92–6.81 (m, 5H), 3.92 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 161.7, 160.3, 149.8, 148.7, 134.0, 131.8, 129.3, 125.9, 124.0, 120.5, 113.8, 113.7, 110.9, 110.5, 91.5, 55.9, 55.8, 55.3, 53.3, 53.2; HRMS (ESI) (*m*/*z*): found 443.1349 $[M+H]^+$; calcd for $C_{23}H_{22}O_9$ 443.1342.

*4.2.25. Dimethyl 3-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**6g**, Table 1, entry 10).* Yellow oil (68 mg, 54%). R_f (30% EtOAc/hexane): 0.30. IR (CH_2Cl_2) ν 3010, 2933, 1810, 1740, 1600, 1518, 1466, 1037, 844 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J*=8.9 Hz, 2H), 7.21 (d, *J*=2.1 Hz, 1H), 6.99 (d, *J*=9.0 Hz, 2H), 6.95 (dd, *J*=8.5, 2.2 Hz, 1H), 6.83 (d, *J*=8.5 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 167.0, 163.0, 162.7, 161.7, 149.6, 148.8, 131.7, 125.8, 120.2, 118.8, 113.7, 113.6, 112.2, 110.6, 63.5, 56.0, 55.8, 55.4, 53.6, 51.9; HRMS (ESI) (*m*/*z*): found 443.1352 $[M+H]^+$; calcd for $C_{23}H_{22}O_9$ 443.1342.

*4.2.26. Dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**5h**, Table 1, entry 12).* Yellow oil (3 mg, 6%). R_f (40% EtOAc/hexane): IR (CH_2Cl_2) ν 3010, 2956, 1780, 1759, 1718, 1601, 1510, 1481, 1185, 1160, 982, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J*=6.9 Hz) and 7.00–7.84 (m) (together 7H), 6.00 (s, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 161.0, 160.8, 160.0,

147.9, 146.5, 136.6, 130.3, 129.4, 128.6, 127.6, 124.5, 121.0, 108.5, 108.0, 101.6, 90.7, 55.0, 53.3, 53.2; HRMS (ESI) (*m*/*z*): found 427.1041 $[M+H]^+$; calcd for $C_{22}H_{18}O_9$ 427.1029.

*4.2.27. Dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-5-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**6h**, Table 1, entry 12).* Yellow oil (64 mg, 92%). R_f (40% EtOAc/hexane): 0.49. IR (CH_2Cl_2) ν 3011, 2956, 1813, 1759, 1721, 1605, 1506, 1491, 1180, 1157, 1010, 980, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J=9.0 Hz, 2H), 7.12 (d, J=1.9 Hz, 1H), 6.98 (d, J=9.0 Hz, 2H), 6.91 (dd, J=8.2, 1.9 Hz, 1H), 6.78 (d, J=8.3 Hz, 1H), 5.97 (s, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 166.8, 162.8, 162.7, 161.8, 148.1, 147.8, 131.8, 131.4, 127.1, 121.5, 118.8, 113.8, 109.3, 108.8, 101.4, 63.9, 55.4, 53.6, 51.9; HRMS (ESI) (*m*/*z*): found 427.1032 $[M+H]^+$; calcd for $C_{22}H_{18}O_9$ 427.1029.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.03.101.

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