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PAPER

Regiodivergent synthesis of trisubstituted furans through Tf_2O-catalyzed Friedel–Crafts acylation: a tool for access to tetrahydrofuran lignan analogues†

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3- or 4-Aroylfurans have been prepared selectively and in high yields from a common precursor by simple tuning of reaction conditions in Friedel–Crafts acylation promoted by triflic anhydride. The formation of products can be explained on the basis of the ring-chain tautomerism occurring in compounds equipped with two neighbouring carboxylic functions. Since 4-aroylfuran derivatives show a typical lignan backbone, suitable hydrogenation conditions were found out to gain tetrahydrofuran lignans.

Introduction

Furans are an intriguing class of heterocycles frequently occurring both in pharmaceuticals and in natural compounds endowed with significant biological activity.[1–4] Besides, the versatility of polysubstituted furans makes them very useful intermediates in organic synthesis.[5–7] Establishment of new synthetic methods for their preparation and elaboration would provide a significant tool with important implications in pharmacological applications.[8–10]

In this paper we report a simple and rapid way of accessing either 3- or 4-aroylfurans starting from a polysubstituted furan equipped with an acid carboxylic function at C-4 position.

The strategy is based on the Friedel–Crafts (FC) acylation reaction and the use of trifluoromethylsulfonic anhydride (Tf_2O)[11] as promoter. Currently, there is a great interest towards FC acylation with the aim to minimize some drawbacks of the classical procedure such as the use of acid chlorides and, generally, high amounts of the metallic oxophilic promoters that cause strongly acidic conditions.[12] New methods involve carboxylic acids as acylating agents in the presence of Lewis acid or Brønsted acid-catalysts,[13] or using anhydrides as activating agents in combination with a catalyst such as *p*-trifluoromethylbenzoic anhydride and $SiCl_4$–$AgClO_4$,[14] trifluoroacetic anhydride and H_3PO_4[15] or $AlPW_{12}O_{40}$.[16] A recent methodology applied to acetic and benzoic acids employs trifluoromethylsulfonic anhydride without the use of a catalyst and works in short times and within a large range of temperatures.[11] We therefore decided to apply this Tf_2O-mediated FC reaction to a readily accessible furancarboxilic acid, namely 3-methoxycarbonyl-2-phenylfuran-4-carboxylic acid (**1**).[17,18]

The regioselective formation of 4- or 3-aroylderivatives takes advantage of a tautomerism evidenced some decades ago that occurs when a free carboxylic acid is activated in the presence of a neighbouring ester functionality.[19] To the best of our knowledge this behaviour has never been purposely exploited for a regiodivergent synthetic approach.

The obtained aroylfurans are very interesting intermediates; in particular, 4-aroyl-2-phenylfurans show a C6C3–C3C6 backbone, typical of lignans, that are widespread plant secondary metabolites holding a large series of bioactivities.[20,21] For this purpose we attempted the conversion of **1** into an acylating agent of opportunely substituted aryl compounds to obtain aryl ketones suitable for subsequent elaboration to lignan scaffolds.

Results and discussion

In initial experiments reported conditions of classical FC acylation[18] were used, performing the reaction with anisole as the aryl substrate, and acid chloride of **1**, prepared by **1** with stoichiometric $AlCl_3$. Under these conditions the formation of a 1 : 1 regioisomeric mixture of both 3- and 4-aroylfuran was observed at room temperature. Attempts to improve regioselectivity working at lower temperatures failed because of the very sluggish activation of the furan reactant. These disappointing results spurred us to explore different FC conditions reported in the literature. Actually, direct activation of the 2-phenyl-4-furoic acid **1** was contemplated and the use of trifluoromethylsulfonic anhydride emerged as the most promising reagent since it can work within a large range of temperatures (Table 1).

Data in Table 1 show that the regioisomeric ratio of products in favour of 4-aroylfuran **3a** was remarkably improved on using

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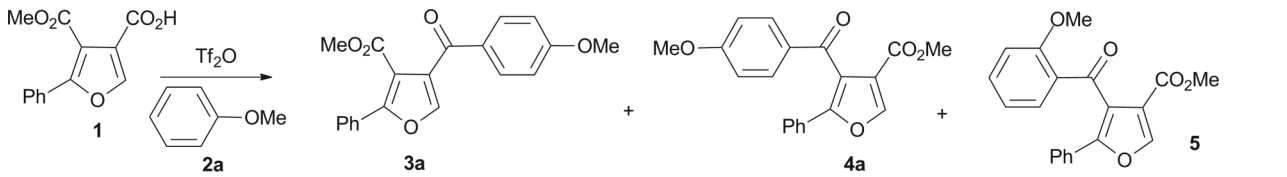
† Electronic supplementary information (ESI) available: 1D and 2D NMR spectra. See DOI: 10.1039/c1ob06560b

Table 1 Tf_2O-promoted FC-acylation of anisole



Entry	Substrate	Solvent	Tf_2O (eq)	T/°C	Time	Products and yields (%)[a]
1	**2a**	CH_2Cl_2	1.1	rt	2 h	**3a** (25), **4a** (35), **5** (10)
2	**2a**	Neat	1.1	rt	2 h	**3a** (50), **4a** (17), **5** (5)
3	**2a**	Neat	2.5	–30	12 h	**3a** (83), **4a** (10), **5** (5)

[a] Isolated compounds from column chromatography.

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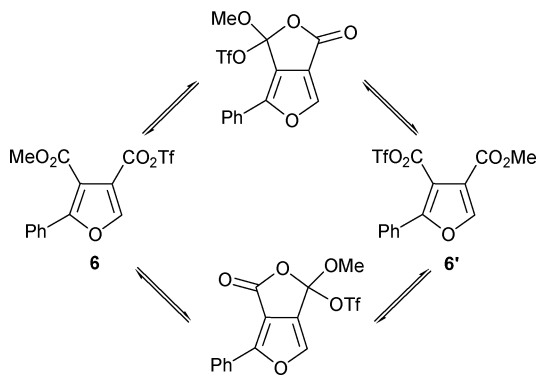
anisole as the solvent under neat conditions (compare entry 1 with entries 2 and 3). An especially satisfying result (Table 1, entry 3) was obtained by performing the reaction at a lower temperature (–30 °C) and increasing both Tf_2O equivalents and reaction time; these conditions (conditions *A*) resulted in a sensibly reduced generation of compound **4a**, likely arising from a rearrangement of the acylating agent prior to the electrophilic attack to anisole. Interestingly, in all cases (Table 1) the only detectable *ortho*-product (**5**) (5–10% yield) was that deriving from the rearrangement of the acylating reagent, despite the apparently higher steric crowding of the corresponding furan product.

Formation of both regioisomers starting from furoic acid **1** can be consistent with a previously proposed mechanism of interchange between the ester function and the leaving group.[19]

Actually, when an acid halide function is sufficiently close to an ester function in a dibasic acid, ring-chain tautomerism can occur leading to the generation of two reactive isomeric open chain forms. Very likely, this also happens when a triflate is used as leaving group, with intermediates **6** and **6′** being the corresponding acylating species (Scheme 1).



Scheme 1 Interchange mechanism between the ester function and the leaving group by a ring-chain tautomerism.

Keeping in mind these mechanistic considerations, the investigation was focused on establishing whether precursor **1**, bearing the activatable carboxyl function at C-4, could provide exclusively 3-aryl ketones, resulting from carboxyl activation at the furan C-3. When the Friedel–Crafts acylation of anisole was performed at higher temperature (refluxing dichloromethane) the corresponding 3-aryl ketone **4a** was indeed the main product (Table 2, entry 1). This result indicated that anhydride **6′** should be a more reactive intermediate than the initially generated anhydride **6**. This indication allowed us to achieve a further regioselectivity improvement through a procedural modification based on the slow addition of anisole to the reaction medium (conditions *B*), which actually led to best isomeric ratio in favour of **4a** (Table 2, entry 2 and Table 3, entry 2). The latter method was effective in reversing the regioselectivity of the acylation even working at room temperature rather than at refluxing conditions. Both procedures were then examined on a range of other aromatic substrates (Table 3). At low temperatures the acylation involved the starting carboxylated position of **1** to give 4-aroylfurans as major products (Table 3, odd entries). Under these conditions a satisfying regioisomeric control was achieved even when neat conditions could not be used (Table 3, entries 3, 7, and 9). On the other hand the slow addition of the arene at room temperature allowed to obtain mainly 3-aroylfurans in all the cases examined (Table 3, even entries). Dichloromethane was the solvent of choice for these conditions, although in the case of 1,2-benzodioxole (Table 3, entry 6) and 1,3,5-trimethoxybenzene (Table 3, entry 8) the best yields were obtained in benzene at 4 °C.

4-Aroyl-2-phenyl-3-methoxycarbonylfurans are very interesting products since they possess a typical lignan scaffold (Fig. 1). Hydrogenation of the furan moieties of the readily obtained 4-aroylfurans **3a–e**, would thus offer a versatile and straightforward route to lignan derivatives or analogues thereof.

To test this synthetic opportunity, model furan **3a** was hydrogenated at high pressure (100 atm) with Pd on carbon, as already reported for 2-arylfuran-3,4-dicarboxylate esters,[22] under different temperature conditions.

Tuning of the temperature was indeed useful for obtaining in high yields furan derivatives with a differentiated profile of functional groups or the corresponding tetrahydrofuran (**9**, Scheme 2) in which the carbonyl function also underwent reduction to methylenic group because of its dibenzylic character.[23]

Performing the hydrogenation reaction at room temperature only reduction of the carbonyl function to hydroxyl group

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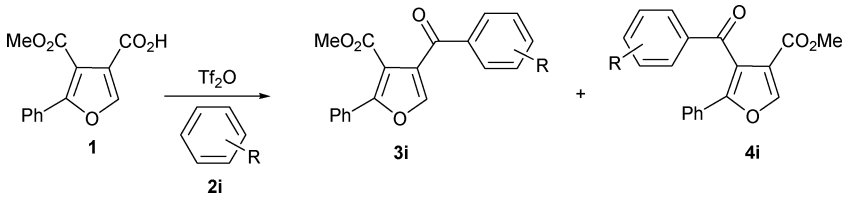
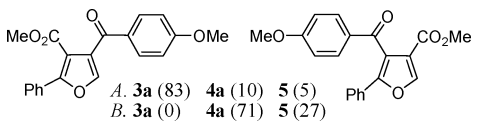
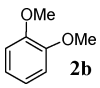
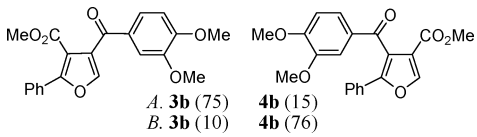
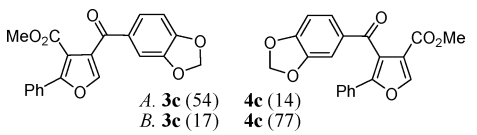
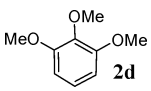
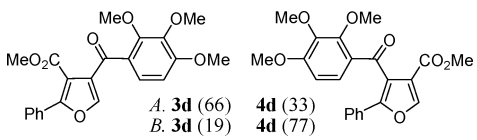
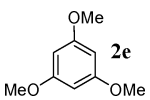
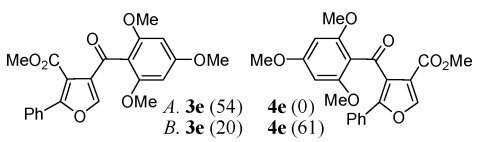
Table 2 Regioselectivity improvement in the synthesis of the 3-aroylfuran **4a**

Entry	Substrate	Solvent	Tf_2O (equiv)	T/°C	Time	Products and yields (%)[a]
1	**2a**	CH_2Cl_2	1.1	Reflux	2 h	**3a** (15), **4a** (47), **5** (12)
2	**2a**[b]	CH_2Cl_2	1.1	rt	2 h	**3a** (0), **4a** (71), **5** (27)

[a] Isolated yields after column chromatography. [b] Slow addition of the arene to the reaction medium.

Table 3 Results of FC-acylation related to the synthesis of 4-aroylfurans **3i** (conditions *A*, even entries) and the synthesis of 3-aroylfurans **4i** (conditions *B*, odd entries)



Entry	Substrate	Conditions	T/°C	Products and yields (%)[a]
1	 **2a**	*A*. Neat, 12 h, 2.5 equiv Tf_2O	−30	 *A*. **3a** (83) **4a** (10) **5** (5) *B*. **3a** (0) **4a** (71) **5** (27)
2	**2a**[b]	*B*. CH_2Cl_2, 4 h, 1.1 equiv Tf_2O	rt	
3	 **2b**	*A*. CH_2Cl_2, 12 h, 2.0 equiv Tf_2O	−30	 *A*. **3b** (75) **4b** (15) *B*. **3b** (10) **4b** (76)
4	**2b**[b]	*B*. CH_2Cl_2, 3 h, 1.5 equiv Tf_2O	rt	
5	 **2c**	*A*. Neat, 12 h, 2.5 equiv Tf_2O	−15	 *A*. **3c** (54) **4c** (14) *B*. **3c** (17) **4c** (77)
6	**2c**[b]	*B*. Benzene, 3 h, 2.0 equiv Tf_2O	4	
7	 **2d**	*A*. CH_2Cl_2, 12 h, 2.0 equiv Tf_2O	−30	 *A*. **3d** (66) **4d** (33) *B*. **3d** (19) **4d** (77)
8	**2d**[b]	*B*. Benzene, 3 h, 2.0 equiv Tf_2O	4	
9	 **2e**	*A*. CH_2Cl_2, 12 h, 2.0 equiv Tf_2O	−30	 *A*. **3e** (54) **4e** (0) *B*. **3e** (20) **4e** (61)
10	**2e**[b]	*B*. CH_2Cl_2, 3 h, 1.1 equiv Tf_2O	rt	

[a] Isolated yields after column chromatography. [b] Slow addition of the arene to the reaction medium.

occurs in very high yield (7, Scheme 2), while, increasing the temperature to 50 °C, the 4-acylfuran **3a** was converted, *via* the intermediate compound **7**, to the 4-alkylfuran **8** in moderate yield likely due to the subsequent hydrogenolysis of the hydroxyl group.[23,24]

Hydrogenation of the furan ring occurs at higher temperature (80 °C) with high stereoselectivity evidencing a non-conjugated hydrogenation mechanism.[22]

This hydrogenation product (**9**) is an analogue of tetrahydrofuran plant lignans with antimicrobial (taxiresinol, Fig. 1) and

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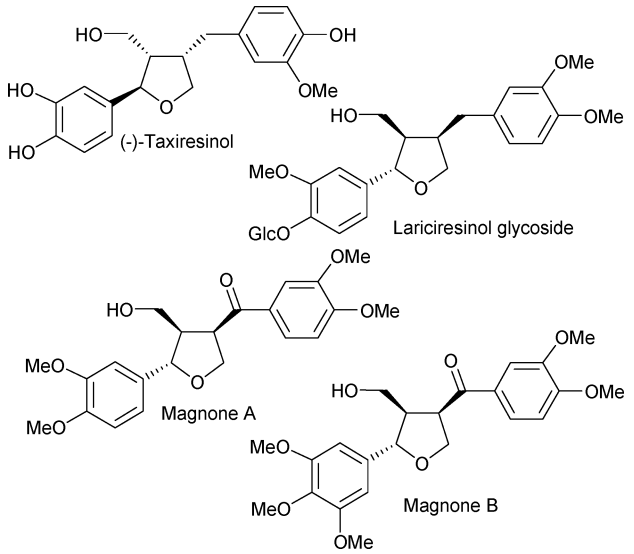
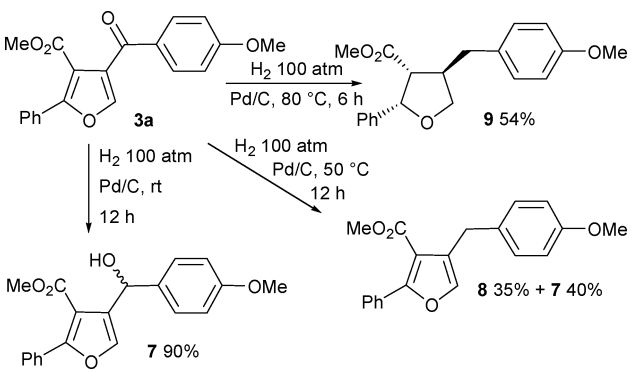


Fig. 1 Some examples of natural tetrahydrofuran lignans with anti-inflammatory and antimicrobial activities.



Scheme 2 Hydrogenation reactions. *Reagents and conditions*: reactions were performed in the presence of 10 mol % Pd/C 10% catalyst at 100 atm of H_2 in 40 mL of MeOH. Isolated yields after column chromatography were reported.

anti-inflammatory (magnone A, magnone B, lariciresinol glycoside, Fig. 1) activities.[21]

Conclusions

In summary, herein we have reported a strategy allowing the preparation of either 3-aroyl-2-phenyl- or 4-aroyl-2-phenylfurans starting from a unique easily accessible mono-acid precursor **1**. This method is based on tunable Tf_2O-mediated FC-acylation and takes advantage of a ring-chain tautomeric interchange occurring on the acylating agent.

4-Aroyl-2-phenylfurans show a suitable scaffold for the elaboration of lignan structures as demonstrated by the hydrogenation of the model compound **methyl 4-(4-methoxybenzoyl)-2-phenyl-3-furoate** (**3a**) which led to tetrahydrofuran analogue of some bioactive natural lignans in useful yield.

Experimental

General procedure for the synthesis of 4-aroyl-2-phenyl-3-methoxycarbonylfurans (conditions *A*)

In a typical experiment 50 mg (0.2 mmol) of **1** were coevaporated three times with toluene, the residue was dried and then mixed under nitrogen with the desired arene and dissolved in 1 mL of CH_2Cl_2, excepted for anisole and 1,2-benzodioxole in which the substrate was directly dissolved (1 mL). The reaction mixture was stirred at the reported temperature (Table 3) for few minutes. Triflic anhydride (84 μL, 0.5 mmol) was then added. After the complete conversion of the reactant the reaction was diluted with diethyl ether (20 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by column chromatography (mixture of petroleum ether/diethyl ether).

General procedure for the synthesis of 3-aroyl-2-phenyl-4-methoxycarbonylfurans (conditions *B*)

Typically, 50 mg (0.2 mmol) of **1** were coevaporated three times with toluene, the residue was dried and dissolved in 1 mL of CH_2Cl_2 (for details, see Table 3). Triflic anhydride (37 μL, 0.22 mmol) was added and a solution of the desired arene (1 mmol) in 2 mL of CH_2Cl_2 was then added dropwise in 2 h by a syringe-pump. The reaction mixture was stirred at room temperature one more hour. The reaction was then diluted with diethyl ether (20 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by column chromatography (mixture of petroleum ether/diethyl ether).

General procedure for hydrogenation

Compound **3a** (0.3 mmol) was dissolved in dry MeOH (40 mL) and 10% Pd/C catalyst (20 mg) was then added under nitrogen atmosphere. Hydrogenation was performed at 100 atm (for details, see Scheme 2). After releasing the pressure, the mixture was filtered and the solvent was removed *in vacuo*. The products were purified by flash chromatography (petroleum ether/diethyl ether).

Methyl 4-(4-methoxybenzoyl)-2-phenyl-3-furoate (3a). IR (CH_2Cl_2): 3010, 2928, 2853, 1727, 1652, 1600, 1205, 1168, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.9 Hz, 2H, ArH), 7.88 (dd, J = 8.4, 1.6 Hz, 2H, ArH), 7.74 (s, 1H, H-5), 7.46-7.44 (m, 3H, ArH), 6.97 (d, J = 9.0 Hz, 2H, ArH), 3.89 (s, 3H, $-OCH_3$), 3.65 (s, 3H, $-COOCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.4, 164.1, 163.7, 156.2, 143.9, 131.5 (× 2), 130.9, 129.7, 128.5 (× 2), 127.8 (× 2), 120.9, 120.6, 113.9 (× 2), 111.7, 55.5, 52.0; MALDI-MS m/z 359.39 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.76; H, 5.12.

Methyl 4-(4-methoxybenzoyl)-5-phenyl-3-furoate (4a). IR (CH_2Cl_2): 3020, 1725, 1660, 1598, 1217, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, H-2), 7.90 (d, J = 8.7 Hz, 2H, ArH), 7.55 (dd, J = 8.0, 1.7 Hz, 2H, ArH), 7.31–7.27 (m, 3H, ArH), 6.91 (d, J = 8.9 Hz, 2H, ArH), 3.85 (s, 3H, $-OCH_3$), 3.66 (s, 3H, $-COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 164.1, 162.4, 152.1, 146.5, 131.8 (× 2), 130.5 (× 2), 128.9 (× 2), 128.8, 125.7 (× 2), 120.9, 119.6, 114.0 (× 2), 55.5, 51.7; MALDI-MS m/z 359.98

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[M+Na]$^+$. Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.85; H, 4.98.

Methyl 4-(2-methoxybenzoyl)-5-phenyl-3-furoate (5). IR (CH_2Cl_2): 3053, 1726, 1657, 1598, 1218, 1048 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H, H-2), 7.79 (dd, J = 9.7, 1.8 Hz, 1H, ArH), 7.61 (dd, J = 9.8, 1.7 Hz, 2H, ArH), 7.54 (t, J = 9.4 Hz, 1H, ArH), 7.45 (t, J = 8.9 Hz, 1H, ArH), 7.31–7.26 (m, 2H, ArH) 6.97 (t, J = 9.4 Hz, 1H, ArH), 6.91 (d, J = 10.4 Hz, 1H, ArH), 3.71 (s, 3H, –OCH_3), 3.60 (s, 3H, –OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 162.6, 159.4, 152.5, 145.9, 134.5, 131.9, 131.3, 128.9, 128.8, 128.6 (× 2), 126.2 (× 2), 120.4, 113.8, 112.0, 79.2, 55.7, 51.5; MALDI-MS m/z 359.16 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.56; H, 5.02.

Methyl 4-(3,4-dimethoxybenzoyl)-2-phenyl-3-furoate (3b). IR (CH_2Cl_2): 3020, 1731, 1658, 1598, 1218, 1048 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, J = 10.1, 2.2 Hz, 2H, ArH), 7.76 (s, 1H, H-5), 7.54–7.44 (m, 5H, ArH), 6.92 (d, J = 10.1 Hz, 1H, ArH), 3.96 (s, 3H, –OCH_3), 3.95 (s, 3H, –OCH_3), 3.66 (s, 3H, -OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 187.4, 164.2, 156.1, 153.5, 149.2, 144.0, 131.0, 129.7, 128.9, 128.5 (× 2), 127.5 (× 3), 124.3, 114.0, 110.8, 110.0, 56.1 (× 2), 52.1; MALDI-MS m/z 389.32 [M+Na]$^+$. Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 69.34; H, 5.44.

Methyl 4-(3,4-dimethoxybenzoyl)-5-phenyl-3-furoate (4b). IR (CH_2Cl_2): 3057, 1726, 1658, 1592, 1218, 1145 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H, H-2), 7.66 (d, J = 3.9 Hz, 1H, ArH), 7.59–7.56 (m, 2H, ArH), 7.40–7.27 (m, 4H, ArH), 6.78 (d, J = 16.8 Hz, 1H, ArH), 3.94 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 3.67 (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 162.3, 153.9, 149.3, 146.5, 144.0, 130.6, 129.7, 128.7 (× 2), 127.5, 125.7 (× 2), 125.3, 120.8, 110.2, 110.1, 110.0, 56.0 (× 2), 51.7; MALDI-MS m/z 389.52 [M+Na]$^+$. Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H 4.95. Found: C, 69.76; H, 5.53.

Methyl 4-(3,4-(benzo[*d*][1,3]dioxole-5-carbonyl)-2-phenyl-3-furoate (3c). IR (CH_2Cl_2): 3052, 1727, 1654, 1605, 1217, 1041 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90–7.88 (m, 2H, ArH), 7.74 (s, 1H, H-5), 7.52–7.43 (m, 5H, ArH), 6.87 (d, J = 8.0 Hz, 1H, ArH), 6.08 (s, 2H, –OCH_2O–), 3.69 (s, 3H, –OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 186.8, 164.2, 156.3, 151.9, 148.2, 143.8, 132.8, 129.7, 128.6, 128.4 (× 2), 127.5 (× 2), 125.9, 118.4, 113.6, 108.6, 107.8, 101.9, 52.1; MALDI-MS m/z 373.62 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03. Found: C, 68.73; H, 4.42.

Methyl 4-(3,4-(benzo[*d*][1,3]dioxole-5-carbonyl)-5-phenyl-3-furoate (4c). IR (CH_2Cl_2): 3050, 1726, 1663, 1489, 1217, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H, H-2), 7.57–7.54 (m, 2H, ArH), 7.49–7.41 (m, 2H, ArH), 7.34–7.27 (m, 3H, ArH), 6.77 (d, J = 8.1 Hz, 1H, ArH), 6.04 (s, 2H, –OCH_2O–), 3.69 (s, 3H, –OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 162.2, 152.5, 152.1, 148.4, 147.4, 146.5, 132.4, 128.6, 128.5 (× 2), 126.7, 125.6 (× 2), 120.6, 119.5, 108.4, 108.2, 102.0, 51.8; MALDI-MS m/z 373.28 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.57; H 4.03. Found: C, 68.97; H 4.35.

Methyl 4-(2,3,4-trimethoxybenzoyl)-2-phenyl-3-furoate (3d). IR (CH_2Cl_2): 3056, 1729, 1656, 1590, 1217, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.2, 1.6 Hz, 2H, ArH), 7.72 (s, 1H, H-5), 7.43 (m, 3H, ArH), 7.36 (d, J = 8.7 Hz, 1H, ArH), 6.72 (d, J = 8.7 Hz, 1H, ArH), 3.92 (s, 3H, –OCH_3), 3.89 (s, 3H, –OCH_3), 3.83 (s, 3H, –OCH_3), 3.70 (s, 3H, –OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 164.5, 157.0, 155.1, 153.3, 145.7, 142.4, 129.6, 128.9, 128.6 (× 2), 127.2 (× 2), 126.5, 125.8, 113.6, 106.8, 106.7, 62.0, 61.0, 56.1, 52.2; MALDI-MS m/z 419.43 [M+Na]$^+$. Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.76; H, 5.54.

Methyl 4-(2,3,4-trimethoxybenzoyl)-5-phenyl-3-furoate (4d). IR (CH_2Cl_2): 3051, 1726, 1657, 1588, 1218, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, H-2), 7.61–7.57 (m, 2H, ArH), 7.30–7.28 (m, 4H, ArH), 6.69 (d, J = 8.9 Hz, 1H, ArH), 3.89 (s, 3H, –OCH_3), 3.80 (s, 3H, –OCH_3), 3.69 (s, 3H, –OCH_3), 3.67 (s, 3H, –OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.6, 162.5, 158.1, 154.8, 151.8, 146.0, 142.3, 129.1, 128.6 (× 2), 127.3, 125.9 (× 2), 125.7, 122.7, 120.6, 106.8 (× 2), 61.2, 60.8, 56.1, 51.6; MALDI-MS m/z 420.55 [M+Na]$^+$. Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.99; H, 5.23.

Methyl 4-(2,4,6-trimethoxybenzoyl)-2-phenyl-3-furoate (3e). IR (CH_2Cl_2): 3055, 1731, 1666, 1606, 1218, 1131 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.4, 1.6 Hz, 2H, ArH), 7.68 (s, 1H, H-5), 7.40 (m, 3H, ArH), 6.14 (s, 2H, ArH), 3.85 (s, 3H, –OCH_3), 3.81 (s, 3H, –OCH_3), 3.74 (s, 6H, –OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 165.4, 162.7, 159.1 (× 2), 153.7, 147.7, 129.9, 129.2 (× 2), 128.6 (× 2), 126.3 (× 2), 113.2, 111.6, 90.6 (× 2), 55.9 (× 2), 55.4, 52.6; MALDI-MS 420.22 [M+Na]$^+$. Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 67.23; H, 5.71.

Methyl 4-(2,4,6-trimethoxybenzoyl)-5-phenyl-3-furoate (4e). IR (CH_2Cl_2): 3056, 1731, 1664, 1604, 1218, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H, H-2), 7.66–7.63 (m, 2H, ArH), 7.29–7.27 (m, 3H, ArH), 6.00 (s, 2H, ArH), 3.77 (s, 3H, –OCH_3), 3.66 (s, 6H, –OCH_3), 3.64 (s, 3H, –OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 163.6, 163.0, 161.0 (× 2), 154.0, 145.8, 129.5, 128.7 (× 2), 128.1 (× 2), 126.9 (× 2), 120.3, 112.8, 90.7 (× 2), 56.0 (× 2), 55.3, 51.5; MALDI-MS m/z 419.27 [M+Na]$^+$. Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 67.11; H, 5.42.

Methyl 4-(hydroxy(4-methoxyphenyl)methyl)-2-phenyl-3-furoate (7). IR (CH_2Cl_2): 3447, 3016, 1692, 1611, 1512, 1214, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (m, 2H, ArH), 7.43–7.38 (m, 5H, ArH), 7.02 (s, 1H, H-5), 6.91 (d, J = 8.7 Hz, 2H, ArH), 5.90 (bs, 1H, -C*H*OH), 4.43 (bs, 1H, –CHO*H*), 3.82 (s, 3H, –OCH_3), 3.73 (s, 3H, –$COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.3, 159.0, 140.6, 133.8, 131.4, 130.0, 129.5 (× 2), 128.7 (× 2), 128.0 (× 2), 127.7 (× 2), 113.6, 112.3, 67.8, 55.2, 51.8; MALDI-MS m/z 361.39 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.43; H, 5.48.

Methyl 4-(4-methoxybenzyl)-2-phenyl-3-furoate (8). IR (CH_2Cl_2): 3021, 2942, 1716, 1612, 1604, 1240, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.2, 1.8 Hz, 2H, ArH), 7.40 (m, 3H, ArH), 7.17 (d, J = 8.6 Hz, 2H, ArH), 7.03 (s, 1H, H-5), 6.86 (d, J = 8.6 Hz, 2H, ArH), 3.93 (s, 2H, CH_2), 3.80 (s, 3H, –OCH_3), 3.74 (s, 3H, –$COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 158.2, 158.0, 140.1, 131.7, 130.2, 129.7 (× 2), 129.1, 128.3 (× 2), 128.0 (× 2), 126.1, 113.8 (× 2), 113.2, 55.2, 51.3, 30.4; MALDI-MS m/z 345.76 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.76; H, 5.83.

Methyl 4-(4-methoxybenzyl)-2-phenyl-tetrahydrofuran-3-carboxylate (9). IR (CH_2Cl_2): 3006, 2951, 1732, 1661, 1512, 1176, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (m, 5H, ArH), 7.11 (d, J = 6.8 Hz, 2H, ArH), 6.84 (d, J = 6.8 Hz, 2H, ArH), 5.26 (d, J = 6.7 Hz, 1H, H-2), 4.34 (t, J = 6.4 Hz, 1H, H-5b), 3.79 (s, 3H, $-OCH_3$), 3.66 (t, J = 6.8 Hz, 1H, H-5a), 3.14 (s, 3H, $-COOCH_3$), 3.12 (m, 1H, H-3), 3.08 (m, 1H, H-4), 2.81 (dd, J = 11.1, 5.1 Hz, 1H, CH_aHAr), 2.67 (dd, J = 11.1, 6.8 Hz, 1H, CHH_bAr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 158.1, 138.9, 131.3, 127.9 (× 2), 127.8, 127.7 (× 2), 126.2 (× 2), 113.9 (× 2), 82.2, 73.7, 55.8, 55.2, 51.2, 43.7, 37.3; MALDI-MS 349.54 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.76; H 6.97.

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