FULL PAPER

Furanyl Alcohols as Alkylating Reagents in *Friedel–Crafts* Reaction of Arenes

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Furanyl alcohols react with arenes by a variant of the *Friedel–Crafts* reaction to give benzyl furans with fairly satisfying yields. The reaction is mediated by Tf_2O and occurs with reduced times in the presence of Ph_3PO. Some prepared compounds exhibit a lignan-like backbone.

Keywords: *Friedel–Crafts* alkylation, Furan, Triflic anhydride, Triphenylphosphine oxide, Lignans

Introduction

The importance of *Friedel–Crafts* (*FC*) reactions both on laboratory and industrial scale inspires ongoing research in this field [1], mainly in order to avoid the use of the required stoichiometric metal salts/acids in unfavorable conditions and increase the regioselectivity [2]. Currently, triflic anhydride (Tf_2O) is one of the most studied and applied catalysts. It has been used in *FC* acylation starting from hetero- [3] and carbocyclic [4] acids with reduction of steps and without the use of acid catalysts. More recently, Tf_2O-mediated *FC* alkylation reactions of arenes with alkenyl substrates [5] and benzyl alcohols [6] have also been described. We have applied Tf_2O-mediated *FC* acylation of aryl compounds for the first time to opportunely substituted furoic acids with the aim of obtaining aroylfurans [3] with a C_6C_3–C_3C_6 backbone typical of lignans that are widespread plant secondary metabolites holding a large series of bioactivities [7]. The introduction of the heterocyclic system in the lignan scaffold was inspired by the easy preparation and high versatility of furans that are efficiently converted into reduced forms as dihydro- and tetrahydrofurans or to oxidized forms as furanones or enediones [8]. As part of our ongoing studies on the preparation of lignan-like compounds, we have applied the Tf_2O-mediated *FC* alkylation of aryls to 2-aryl-4-(hydroxymethyl)furans to verify the possibility to synthesize furan lignan analogs as shown in *Fig. 1*. To our knowledge, this procedure has not been previously applied to heterocyclic derivatives.

Results and Discussion

Starting 4-(hydroxymethyl)furans **1a**, **1c**, and **1d** (*Scheme*) were prepared by $NaBH_4$ reduction of the corresponding dimethyl furan-3,4-dicarboxylates [9]. The reaction was carried out in the mixed solvent system ^{t}BuOH/MeOH [10] and stopped at *ca.* 50% conversion to avoid a high amount of the corresponding dialcohols. It is significant that under these controlled conditions the reduction leads selectively to **1a** and **1c**, most likely for steric reasons as previously observed in other reactions [3][11]. The attempt to prepare furanyl alcohol **1b** using this procedure failed and **1b** was prepared differently (*Scheme*). The corresponding dimethyl ester [9] was selectively hydrolyzed to 4-(methoxycarbonyl)-5-(4-methoxyphenyl) furan-3-carboxylic acid [11] that was first converted to a mixed anhydride using ClCOOMe in the presence of *N*-methylmorpholine (NMM) and then reduced with $NaBH_4$ in H_2O [12].

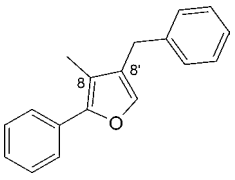

Fig. 1. Lignan-like furans.

Scheme. Synthesis of furanyl alcohols **1**.

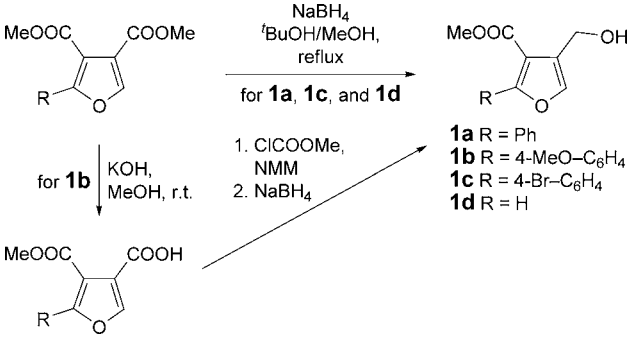

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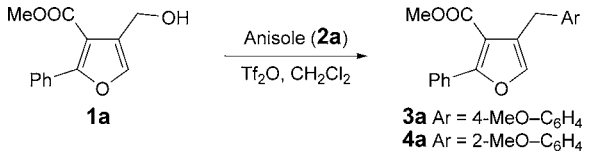
Table 1. *Friedel–Crafts* alkylation of anisole (**2a**) with furanyl alcohol **1a**



1a

3a Ar = 4-MeO–C_6H_4
4a Ar = 2-MeO–C_6H_4

Entry	Conditions	*T* [°C]/*t* [h]	Yield [%][a])	**3a**/**4a**
1	Tf_2O	−20/20	61	68:32
2	Tf_2O	r.t./4	30	83:17
3	Tf_2O/2,6-lutidine	−20/20	62	68:32
4	Tf_2O/Ph_3PO	r.t./1	61	60:40
5	Tf_2O/Ph_3PO	0/5	56	71:29

[a]) Yield of isolated product after preparative TLC.

In initial experiments, the reaction of methyl 4-(hydroxymethyl)-2-phenylfuran-3-carboxylate (**1a**) in the presence of Tf_2O was examined with anisole (**2a**) under different conditions (*Table 1*). As shown in *Table 1*, the *FC* alkylation occurs in all cases regioselectively in favor of the *para*-isomer. The reaction in the presence of only Tf_2O occurs with appreciable yield, mainly at low temperature.

In an attempt to improve the yield, considering that triflic acid (TfOH) is generated, the reaction was also performed in the presence of a non-nucleophilic base, 2,6-lutidine. No effect in total yield or in the regioisomeric ratio was observed. Previously, these conditions were found particularly useful in Tf_2O-mediated acylations [13] [14]. The combination of Tf_2O and Ph_3PO with the resulting triphenylphosphine ditriflate (TPPD) was then used at 0 °C to room temperature [6]. Under these conditions, the reaction time was significantly reduced. We then decided to apply the reaction of anisole (**2a**) under the *Khodaei–Nazari* procedure [6] (furanyl alcohol, arene, and TPPD in 1:1:1.2 molar ratio, room temperature) to differently substituted furanyl alcohols **1b** – **1d** and to dialcohol **1e** (*Table 2*, *Entries 2 – 5*). In addition, to extend the scope for preparation of lignan-like compounds, starting from furans **1a** and **1b** the alkylation was performed using other aromatic substrates, with lignan-typical aryl substitution [7], such as phenol (**2b**) and 1,2-dimethoxybenzene (**2c**). Pure isomers were isolated by preparative silica gel thin-layer chromatography using hexane/AcOEt. The data in *Table 2* evidence that the reaction occurs except for dialcohol **1e** (*Table 2*, *Entry 5*). The aryl substitution of furan ring appears not essential (compare *Entries 1 – 3* and *4*). In these cases, the ratio of regioisomers is in favor of **3** due to the lower steric crowding of the corresponding diaryl furan products. A different position selectivity is observed in the alkylation of 1,2-dimethoxybenzene (**2c**) probably since the electronic effect of the donating substituent is also of importance (compare *Entries 1/2* and *7/8*) [15]. The alkylation works, although with low yield, even with phenol (**2b**) that gives no reaction starting from benzyl alcohols [6]. High regioselectivity at the *ortho* position of the phenol is observed, as also reported in similar cases [16].

In conclusion, Tf_2O has proved to be a promoting agent in *FC* alkylation of arenes with furyl alcohols, mainly in the presence of Ph_3PO. We used this environmentally conscious reaction as a simple tool for access to diaryl furans with a lignan backbone. The presence of furan system highlights manifold elaborations of the heterocyclic ring to a variety of product types [8].

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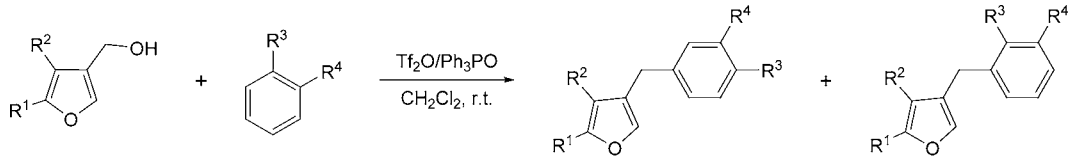
Table 2. Tf_2O/Ph_3PO-Promoted *Friedel–Crafts* alkylation of arenes **2** with furanyl alcohols **1**



1 **2** **3** **4**

Entry		R^1	R^2		R^3	R^4	Products	Yield [%][a])	**3**/**4**
1	**1a**	Ph	COOMe	**2a**	MeO	H	**3a**/**4a**	61	60:40
2	**1b**	4-MeO–C_6H_4	COOMe	**2a**	MeO	H	**3b**/**4b**	58	62:38
3	**1c**	4-Br–C_6H_4	COOMe	**2a**	MeO	H	**3c**/**4c**	55	61:39
4	**1d**	H	COOMe	**2a**	MeO	H	**3d**/**4d**	41	58:42
5	**1e**	Ph	CH_2OH	**2a**	MeO	H	No reaction		
6	**1a**	Ph	COOMe	**2b**	OH	H	**3e**/**4e**	14	10:90
7	**1a**	Ph	COOMe	**2c**	MeO	MeO	**3f**/**4f**	53	100:0
8	**1b**	4-MeO–C_6H_4	COOMe	**2c**	MeO	MeO	**3g**/**4g**	62	42:58

[a]) Yield of isolated product after preparative TLC.

Experimental Part

General

All reagents and solvents were obtained from commercial suppliers and used without further purification. Dimethyl 2-arylfuran-3,4-dicarboxylates were synthesized according to the literature [9]; dimethyl furan-3,4-dicarboxylate was commercially available. Prep. thin layer chromatography (TLC): silica gel (SiO_2). IR Spectra: *Jasco FT/IR-430* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-400* (400 and 100 MHz, resp.) or *INOVA 500* (500 and 126 MHz, resp.) spectrometers; at r.t.; δ in ppm rel. to Me_4Si as internal standard, J in Hz. The C-multiplicity was evidenced by DEPT experiments. The H-atom couplings were evidenced by $^1H,^1H$-COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences. EI-MS: *GC-MS QP5050A* (*Shimadzu*) equipped with a 70 eV EI detector; in m/z.

Synthesis of Furanyl Alcohols **1a** and **1c** – **1e**

MeOH (4 ml) was added over a period of 1 h to a boiling mixture of $NaBH_4$ (175 mg, 4.6 mmol) and dimethyl 2-phenylfuran-3,4-dicarboxylate [9] (1.2 g, 4.6 mmol) in ^{t}BuOH (18 ml). The resultant mixture was heated under reflux for 2 h. The reaction was quenched by addition of H_2O (12 ml). Most of the org. solvents were evaporated on a rotary evaporator, and the residue was extracted with CH_2Cl_2. The combined org. extracts were dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by prep. TLC (SiO_2; hexane/AcOEt 9:1) and gave starting diester (520 mg), **1a** (530 mg), and diol **1e** (139 mg).

Methyl 4-(Hydroxymethyl)-2-phenylfuran-3-carboxylate (**1a**). Yield: 530 mg (50%). Yellow oil. IR (CH_2Cl_2): 3655, 3065, 2990, 1717, 1600, 1282. ^1H-NMR (500 MHz, $CDCl_3$): 7.71 – 7.69 (*m*, H–C(2′,6′)); 7.45 (*s*, H–C(5)); 7.44 – 7.42 (*m*, H–C(3′,4′,5′)); 4.63 (*s*, CH_2); 3.81(*s*, Me). ^{13}C-NMR (126 MHz, $CDCl_3$): 165.2 (*C*OOMe); 159.3 (C(2)); 139.8 (C(5)); 130.0 (C(1′)); 129.5 (C(3′,5′)); 128.8 (C(4′)); 128.0 (C(2′,6′)); 127.3 (C(3)); 112.5 (C(4)); 55.9 (CH_2); 51.8 (Me). EI-MS: 232.07 (M^+).

(2-Phenylfuran-3,4-diyl)dimethanol (**1e**). Yield: 139 mg (13%). Oil. IR (CH_2Cl_2): 3695, 3560, 3065, 2990, 1600, 1282. ^1H-NMR (500 MHz, $CDCl_3$): 7.59 (*m*, H–C(2′,6′)); 7.41 (*t*, *J* = 7.7, H–C(3′,5′)); 7.38 (*s*, H–C(5)); 7.32 (*dd*, *J* = 10.8, 4.0, H–C(4′)); 4.70 (*s*, CH_2); 4.56 (*s*, CH_2). ^{13}C-NMR (126 MHz, $CDCl_3$): 153.1 (C(2)); 139.3 (C(5)); 130.5 (C(1′)); 128.7 (C(3′,5′)); 128.1 (C(4′)); 126.7 (C(2′,6′)); 126.5 (C(3)); 119.5 (C(4)); 55.3 (CH_2); 54.5 (CH_2). EI-MS: 204.08 (M^+).

Methyl 2-(4-Bromophenyl)-4-(hydroxymethyl)furan-3-carboxylate (**1c**). Furan **1c** was prepared using the same procedure of **1a** starting from dimethyl 2-(4-bromophenyl)furan-3,4-dicarboxylate (676 mg, 2 mmol) [9]. Yield: 266 mg (43%). Oil. IR (CH_2Cl_2): 3617, 2947, 2918, 3040, 1694, 1476, 1129, 912, 835. ^1H-NMR (400 MHz, $CDCl_3$): 7.58 (*d*, *J* = 8.3, H–C(2′,6′)); 7.55 (*d*, *J* = 8.5, H–C(3′,5′)); 7.44 (*s*, H–C(5)); 4.61 (*s*, CH_2); 3.80 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 165.1 (*C*OOMe); 157.0 (C(2)); 140.0 (C(5)); 131.2 (C(3′,5′)); 130.3 (C(2′,6′)); 128.8 (C(4′)); 127.4 (C(3)); 123.9 (C(1′)); 112.8(C(4)); 55.8 (CH_2O); 51.9 (COO*Me*). EI-MS: 309.88 (M^+).

Methyl 4-(Hydroxymethyl)furan-3-carboxylate (**1d**). Furan **1d** was prepared using the same procedure of **1a** starting from commercially available dimethyl furan-3,4-dicarboxylate (368 mg, 2 mmol). Yield: 125 mg (40%). Oil. IR (CH_2Cl_2): 1708, 1543, 1315, 1143, 1107, 1019. ^1H-NMR (400 MHz, $CDCl_3$): 7.97 (*s*, H–C(2)); 7.39 (*s*, H–C(5)); 4.61 (*s*, CH_2O); 3.86 (*s*, MeO). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.9 (*C*OOMe); 149.3 (C(2)); 141.1 (C(5)); 125.2 (C(3)); 117.8 (C(4)); 55.3 (CH_2O); 51.9 (COO*Me*). EI-MS: 156.07 (M^+).

Methyl 4-(Hydroxymethyl)-2-(4-methoxyphenyl)furan-3-carboxylate (**1b**). To a soln. of 4-(methoxycarbonyl)-5-(4-methoxyphenyl)furan-3-carboxylic acid (735 mg, 2.7 mmol), prepared as reported [11], and NMM (391 l, 3.5 mmol) in THF (8.8 ml), methyl chloroformate (270 l, 3.5 mmol) was added dropwise at 0° under stirring. After 2 h, the mixture was filtered, and the salt was washed with THF (3 2.5 ml). A suspension of $NaBH_4$ (147 mg, 3.89 mmol) in H_2O (1 ml) was then added dropwise to the filtrate in an ice bath under stirring. After 2 h the temperature was allowed to increase to r.t. After 20 min, the solvent was evaporated under reduced pressure and the residue was dissolved in AcOEt (15 ml). The soln. was washed with brine until neutral. The org. layer was separated, dried (Na_2SO_4), filtered, and concentrated to give the crude alcohol that was purified by prep. TLC (SiO_2; hexane/AcOEt, gradient). Yield: 282 mg (40%). Oil. IR (CH_2Cl_2): 3700, 3060, 3040, 1717, 1600, 1282. ^1H-NMR (500 MHz, $CDCl_3$): 7.67 (br. *d*, *J* = 8.8, H–C(2′,6′)); 7.41 (*s*, H–C(5)); 6.95 (*d*, *J* = 8.9, H–C(3′,5′)); 4.62 (*s*, CH_2); 3.86 (*s*, Me); 3.81 (*s*, Me). ^{13}C-NMR (126 MHz, $CDCl_3$): 165.3 (*C*OOMe); 160.5 (C(4′)); 159.5 (C(2)); 139.3 (C(5)); 130.3 (C(2′,6′)); 128.2 (C(3)); 122.5 (C(1′)); 113.5 (C(3′,5′)); 111.5 (C(4)); 55.9 (CH_2); 55.3 (Me); 51.7 (COO*Me*). EI-MS: 262.28 (M^+).

Experiments of Furanyl Alcohol **1a** (*Table 1*)

Entries 1 and *2*: Pure **1a** (58 mg, 0.25 mmol) was dissolved in 2 ml of anh. solvent (CH_2Cl_2) and then 5 equiv. of anisole (**2a**) were added (*Table 1*). The mixture was cooled to 20° and Tf_2O (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*. On completion of the reaction (controlled by TLC), the mixture was washed with sat. $NaHCO_3$ soln. and extracted twice with Et_2O. The org. layer was collected, dried (Na_2SO_4), filtered, and concentrated to give a residue that was separated by prep. TLC (SiO_2; hexane/

CH_2Cl_2 9:1). *Entry 3*: Pure **1a** (58 mg, 0.25 mmol) was dissolved in 2 ml of anh. CH_2Cl_2 and then 5 equiv. of anisole were added. The mixture was cooled to 20° and Tf_2O (2.5 equiv.) was added dropwise at this temperature. Then 2,6-lutidine (2.5 equiv.) was added at the same temperature. The resulting mixture was stirred under N_2 atmosphere at 20° for 20 h. Work-up and purification were performed as described above.

General Procedure for Tf_2O/Ph_3PO-Mediated Friedel–Crafts Alkylation of Furans **1**

To a soln. of Ph_3PO (0.6 mmol) in anh. CH_2Cl_2 (1 ml), Tf_2O (0.1 ml, 0.6 mmol) was added at 0° and the mixture was stirred for 15 min at room temperature. (*Table 2*). Then, arene (0.5 mmol) and furanyl alcohol (0.5 mmol in 1 ml of anh. CH_2Cl_2) were added and the mixture was stirred. Upon completion of the reaction (1 h), the org. solvent was evaporated and the residue was separated by prep. TLC (SiO_2; hexane/AcOEt).

Methyl 4-(4-Methoxybenzyl)-2-phenylfuran-3-carboxylate (**3a**) and **Methyl 4-(2-Methoxybenzyl)-2-phenylfuran-3-carboxylate** (**4a**). Compounds **3a** and **4a** were prepared according to the general procedure using furanyl alcohol **1a** (116 mg) and anisole (54 mg, 55 l). Purification was achieved by prep. TLC (SiO_2; hexane/AcOEt 9:1). **3a**. Yield: 60 mg (37%). Oil. IR (CH_2Cl_2): 1715, 1547, 1493, 1441, 1213, 1086, 1030. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 7.9, H–C(2′,6′)); 7.46 – 7.36 (*m*, H–C(3′ – 5′)); 7.18 (*d*, *J* = 8.4, H–C(2″,6″)); 7.04 (*s*, H–C(5)); 6.86 (*d*, *J* = 8.5, H–C(3″,5″)); 3.93 (*s*, CH_2); 3.81 (*s*, Me); 3.75 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.8 (*C*OOMe); 158.2 (C(4″)); 157.9 (C(2)); 140.1 (C(5)); 131.6 (C(1′)); 130.1 (C(1″)); 129.7 (C(2″,6″)); 129.0 (C(4′)); 128.5 (C(3′ – 5′)); 128.1 (C(2′,6′)); 122.3 (C(3)); 113.7 (C(3″,5″)); 110.4 (C(4)); 55.2 (Me); 51.3 (COO*Me*); 30.3 (CH_2). EI-MS: 322.12 (M^+). **4a**. Yield: 38 mg (24%). Oil. IR (CH_2Cl_2): 1715, 1547, 1493, 1440, 1215, 1076. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.77 (br. *d*, *J* = 7.8, H–C(2′,6′)); 7.43 – 7.35 (*m*, H–C(3′ – 5′)); 7.23 (*t*, *J* = 8.0, H–C(4″)); 7.17 (*d*, *J* = 7.5, H–C(6″)); 7.00 (*s*, H–C(5)); 6.90 (*d* and *t*, *J* = 7.4, H–C(3″,5″)); 3.99 (*s*, CH_2); 3.84 (*s*, Me); 3.76 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 165.8 (*C*OOMe); 157.7 (C(2)); 157.5 (C(2″)); 140.2 (C(5)); 130.8 (C(1′)); 130.0 (C(6″)); 129.0 (C(4′)); 128.7 (C(3)); 128.2 (C(3′,5′)); 128.0 (C(2′,6′)); 127.5 (C(4″)); 126.2 (C(1″)); 120.4 (C(5″)); 110.3 (C(3″,4)); 55.3 (Me); 51.2 (COO*Me*); 25.2 (CH_2). EI-MS: 322.10 (M^+).

Methyl 4-(4-Methoxybenzyl)-2-(4-methoxyphenyl) furan-3-carboxylate (**3b**) and **Methyl 4-(2-Methoxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate** (**4b**). Compounds **3b** and **4b** were prepared according to the general procedure using furanyl alcohol **1b** (131 mg) and anisole (54 mg, 55 l). Purification was achieved by prep. TLC (SiO_2; hexane/AcOEt 9:1). **3b**. Yield: 62 mg (35%). Oil. IR (CH_2Cl_2): 1716, 1535, 1493, 1439, 1213, 1070. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 8.6, H–C(2′,6′)); 7.19 (*d*, *J* = 8.4, H–C(2″,6″)); 7.01 (*s*, H–C(5)); 6.97, 6.96 (*d*, *J* = 8.4, H–C(3′,5′)); 6.87 (*d*, *J* = 8.5, H–C(3″,5″)); 3.94 (*s*, CH_2); 3.87 (*s*, Me); 3.82 (*s*, Me); 3.76 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.8 (*C*OOMe); 160.3 (C(4′)); 158.6 (C(4″)); 158.0 (C(1)); 139.5 (C(5)); 131.9 (C(1′)); 129.9 (C(2′,6′)); 129.7 (C(2″,6″)); 127.2 (C(3)); 122.9 (C(1″)); 113.8 (C(3′,5′)); 113.5 (C(3″,5″)); 55.3 (Me); 55.3 (Me); 51.2 (COO*Me*); 30.5 (CH_2). EI-MS: 352.15 (M^+). **4b**. Yield: 39 mg (22%). Oil. IR (CH_2Cl_2): 1716, 1530, 1491, 1439, 1213, 1054, 1019. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 9.0, H–C(2′,6′)); 7.24 (*td*, *J* = 7.8, 1.7, H–C(4″)); 7.19 (br. *d*, *J* = 7.9, H–C(6″)); 6.98 – 6.93 (*m*, H–C(3′,5,5′,5″)); 6.91 (*d*, *J* = 7.9, H–C(3″)); 4.00 (*s*, CH_2); 3.87 (*s*, Me); 3.86 (*s*, Me); 3.77 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 165.0 (*C*OOMe); 160.2 (C(4′)); 158.3 (C(2)); 157.4 (C(2″)); 139.7 (C(5)); 130.1 (C(6″)); 129.9 (C(2′,6′)); 129.7 (C(1′)); 128.3 (C(3)); 127.5 (C(4″)); 126.1 (C(1″)); 120.5 (C(5″)); 113.8 (C(4)); 113.5 (C(3′,5′)); 110.4 (C(3″)); 55.4 (Me); 55.3 (Me); 51.2 (COO*Me*); 25.4 (CH_2). EI-MS: 352.09 (M^+).

Methyl 2-(4-Bromophenyl)-4-(4-methoxybenzyl)furan-3-carboxylate (**3c**) and **Methyl 2-(4-Bromophenyl)-4-(2-methoxybenzyl)furan-3-carboxylate** (**4c**). Compounds **3c** and **4c** were prepared according to the general procedure using furanyl alcohol **1c** (155 mg) and anisole (54 mg, 55 l). Purification was achieved by prep. TLC (SiO_2; hexane/AcOEt 85:15). **3c**. Yield: 66 mg (33%). Oil. IR (CH_2Cl_2): 1716, 1611, 1512, 1176, 1078. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.66 (*d*, *J* = 7.3, H–C(2′,6′)); 7.54 (*d*, *J* = 7.3, H–C(3′,5′)); 7.16 (*d*, *J* = 7.6, H–C(2″,6″)); 7.03 (*s*, H–C(5)); 6.85 (*d*, *J* = 7.3, H–C(3″,5″)); 3.91 (*s*, CH_2); 3.80 (*s*, Me); 3.75 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.5 (*C*OOMe); 158.0 (C(4″)); 157.0 (C(1)); 140.3 (C(5)); 131.5 (C(1′)); 131.2 (C(3′,5′)); 129.8 (C(2″,6″)); 129.6 (C(2′,6′)); 129.0 (C(1″)); 127.5 (C(2)); 123.4 (C(4′)); 113.8 (C(3″,4,5″)); 55.2 (Me); 51.4 (COO*Me*); 30.3 (CH_2). EI-MS: 400.06 (M^+). **4c**. Yield: 42 mg (21%). Oil. IR (CH_2Cl_2): 1716, 1605, 1522, 1175, 1080. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.67 (*d*, *J* = 7.1, H–C(3′,5′)); 7.53 (*d*, *J* = 7.1, H–C(2′,6′)); 7.23 (*m*, H–C(4″)); 7.16 (*d*, *J* = 7.4, H–C(6″)); 6.99 (*s*, H–C(5)); 6.90 (br. *t*, *J* = 7.6, H–C(3″,5″)); 3.97 (*s*, CH_2); 3.84 (*s*, Me); 3.77 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.7 (*C*OOMe); 157.2 (C(2″)); 156.7 (C(1)); 140.5 (C(5)); 131.2 (C(3′,5′)); 130.0 (C(6″)); 129.9 (C(2′,6′)); 129.2 (C(1′)); 127.9 (C(3)); 127.6 (C(4″)); 126.4 (C(1″)); 123.3 (C(4′)); 120.5 (C(5″)); 113.8 (C(4)); 110.3 (C(3″)); 55.3 (Me); 51.4 (COO*Me*); 25.3 (CH_2). EI-MS: 400.04 (M^+).

Methyl 4-(4-Methoxybenzyl)furan-3-carboxylate (**3d**) and **Methyl 4-(2-Methoxybenzyl)furan-3-carboxylate** (**4d**). Compounds **3d** and **4d** were prepared according to the general procedure using furanyl alcohol **1d** (78 mg) and anisole (54 mg, 55 l). Purification was achieved by prep. TLC (SiO_2; hexane/AcOEt 9:1, two runs). **3d**. Yield: 29 mg (24%). Oil. IR (CH_2Cl_2): 1722, 1600, 1588, 1494, 1091. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.99 (*d*, *J* = 1.7, H–C(2)); 7.18 (*d*, *J* = 8.6, H–C(2′,6′)); 7.03 (*d*, *J* = 1.7, H–

C(5)); 6.86 (*d*, *J* = 8.6, H–C(3′,5′)); 3.95 (*s*, CH_2); 3.82 (*s*, Me); 3.81 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.0 (*C*OOMe); 158.0 (C(4′)); 149.0 (C(2)); 141.7 (C(5)); 131.6 (C(1′)); 129.6 (C(2′,6′)); 125.6 (C(3)); 118.0 (C(4)); 113.7 (C(3′,5′)); 55.1 (Me); 51.1 (COO*Me*); 29.4 (CH_2). EI-MS: 246.08 (M^+). **4d**. Yield: 20 mg (17%). Oil. IR (CH_2Cl_2): 1720, 1599, 1585, 1490, 1091. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.98 (*s*, H–C(2)); 7.23 (*t*, *J* = 7.8, H–C(4′)); 7.19 (*d*, *J* = 7.1, H–C(6′)); 7.00 (*s*, H–C(5)); 6.92 – 6.89 (*m*, H–C(3′,5′)); 4.01 (*s*, CH_2); 3.84 (Me); 3.83 (Me). ^{13}C-NMR (126 MHz, $CDCl_3$): 164.1 (*C*OOMe); 157.3 (C(2′)); 148.7 (C(2)); 142.1 (C(5)); 130.1 (C(6′)); 128.3 (C(1′)); 127.6 (C(4′)); 124.4 (C(3)); 120.4 (C(5′)); 118.2 (C(4)); 110.4 (C(3′)); 55.3 (Me); 51.2 (COO*Me*); 24.4 (CH_2). EI-MS: 246.11 (M^+).

Methyl 4-(4-Hydroxybenzyl)-2-phenylfuran-3-carboxylate (**3e**) and **Methyl 4-(2-Hydroxybenzyl)-2-phenylfuran-3-carboxylate** (**4e**). Compounds **3e** and **4e** were prepared according to the general procedure using furanyl alcohol **1a** (116 mg) and phenol (**2b**, 47 mg). Prep. TLC (SiO_2; CH_2Cl_2/AcOEt 9:1) gave pure **4e** and isomer **3e** in trace. **3e**. Yield: 2 mg (1%). Oil. IR (CH_2Cl_2): 3200, 1718, 1589, 1492, 1324, 1085. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.75 (*dd*, *J* = 8.0, 1.6, H–C(2′,6′)); 7.45 – 7.35 (*m*, H–C(3′ – 5′)); 7.12 (*d*, *J* = 8.5, H–C(2″,6″)); 7.03 (*s*, *J* = 7.5, H–C(5)); 6.78 (*d*, *J* = 8.5, H–C(3″,5″)); 3.91 (*s*, CH_2); 3.74 (*s*, Me). EI-MS: 308.07 (M^+). **4e**. Yield: 20 mg (13%). Oil. IR (CH_2Cl_2): 3201, 1719, 1589, 1482, 1328, 1080. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.66 (*dd*, *J* = 6.6, 3.1, H–C(2′,6′)); 7.44 – 7.38 (*m*, H–C(3′ – 5′)); 7.20 (*d*, *J* = 7.6, H–C(6″)); 7.15 (*t*, *J* = 7.5, H–C(5″)); 6.92 – 6.86 (*m*, H–C(2″,3″)); 6.84 (*s*, H–C(5)); 3.98 (*s*, CH_2); 3.79 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 162.0 (*C*OOMe); 154.4 (C(2)); 150.0 (C(2″)); 136.6 (C(5)); 126.5 (C(6″)); 126.2 (C(1′)); 125.3 (C(4′)); 124.6 (C(2′,6′)); 124.2 (C(5″)); 124.0 (C(3′,5′)); 122.1 (C(1″,4″)); 121.8 (C(3)); 116.7 (C(3″)); 112.6 (C(4)); 47.8 (COO*Me*); 20.9 (CH_2). EI-MS: 308.11 (M^+).

Methyl 4-(3,4-Dimethoxybenzyl)-2-phenylfuran-3-carboxylate (**3f**). Compound **3f** was prepared according to the general procedure using furanyl alcohol **1a** (116 mg) and 1,2-dimethoxybenzene (**2c**; 69 mg). Prep. TLC (SiO_2; hexane/AcOEt 4:1) gave only isomer **3f**. Yield: 93 mg (53%). Oil. IR (CH_2Cl_2): 1715, 1514, 1214, 1139, 1028. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.78 (*dd*, *J* = 7.8, 1.4, H–C(2′,6′)); 7.46 – 7.38 (*m*, H–C(3′ – 5′)); 7.06 (*s*, H–C(5)); 6.87 – 6.78 (*m*, H–C(2″,5″,6″)); 3.96 (*s*, CH_2); 3.90 (*s*, Me); 3.88 (*s*, Me); 3.78 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.7 (*C*OOMe); 158.2 (C(1)); 148.9 (C(3″)); 147.5 (C(4″)); 140.1 (C(5)); 132.2 (C(1′)); 130.3 (C(1″)); 129.2 (C(4′)); 128.3 (C(3′,5′)); 128.1 (C(2′,6′)); 127.3 (C(3)); 120.7 (C(6″)); 112.1 (C(2″)); 111.4 (C(4)); 111.2 (C(5″)); 55.9 (Me); 55.9 (Me); 51.3 (COO*Me*); 30.9 (CH_2). EI-MS: 352.08 (M^+).

Methyl 4-(3,4-Dimethoxybenzyl)-2-(4-methoxyphenyl) furan-3-carboxylate (**3g**) and **Methyl 4-(2,3-Dimethoxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate** (**4g**). Compounds **3g** and **4g** were prepared according to the general procedure using furanyl alcohol **1b** (131 mg) and 1,2-dimethoxybenzene (**2c**; 69 mg). Purification was achieved by prep. TLC (SiO_2; hexane/AcOEt 8:2). **3g**. Yield: 50 mg (26%). Oil. IR (CH_2Cl_2): 1714, 1500, 1177, 1076, 1029. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 9.1, H–C(2′,6′)); 7.01 (*s*, H–C(5)); 6.96 (*d*, *J* = 9.1, H–C(3′,5′)); 6.86 – 6.77 (*m*, H–C(2″,5″,6″)); 3.95 (*s*, CH_2); 3.89 (*s*, Me); 3.88 (*s*, Me); 3.87 (*s*, Me); 3.77 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 164.4 (*C*OOMe); 160.3 (C(4′)); 158.4 (C(2)); 148.8 (C(4″)); 147.8 (C(3″)); 139.5 (C(5)); 132.2 (C(1′)); 129.9 (C(2′,6′)); 129.8 (C(1″)); 127.1 (C(3)); 120.7 (C(6″)); 113.4 (C(3′,5′)); 112.1 (C(2″)); 111.2 (C(5″)); 111.1 (C(4)); 55.9 (Me); 55.8 (Me); 55.3 (Me); 51.2 (COO*Me*); 31.0 (CH_2). EI-MS: 382.07 (M^+). **4g**. Yield: 68 mg (36%). Oil. IR (CH_2Cl_2): 1715, 1580, 1170, 1076, 1025. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 9.1, H–C(2′,6′)); 7.03 (*t*, *J* = 7.8, H–C(5″)); 6.98 – 6.93 (*s*,*d*, H–C(3′,5,5′); 6.84 (*dd*, *J* = 8.2, 1.5, H–C(6″)); 6.81 (*dd*, *J* = 7.7, 1.5, H–C(4″)); 4.03 (*s*, CH_2); 3.90 (*s*, Me); 3.87 (*s*, Me); 3.84 (*s*, Me); 3.78 (*s*, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 167.7 (*C*OOMe); 160.4 (C(4′)); 158.3 (C(2)); 152.9 (C(2″,3″)); 139.7 (C(3)); 133.8 (C(2)); 130.1 (C(2′,6′)); 123.7 (C(6″)); 122.9 (C(1′)); 122.2 (C(5″)); 113.4 (C(3′,5′)); 110.8 (C(4″)); 60.6 (Me); 55.7 (Me); 55.2 (Me); 51.3 (COO*Me*); 25.4 (CH_2). EI-MS: 382.10 (M^+).

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