3-Phenyl-5-acyloxymethyl-2*H*,5*H*-furan-2-ones: Synthesis and Biological Activity of a Novel Group of Potential Antifungal Drugs†

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3-(Substituted phenyl)-5-acyloxymethyl-2*H*,5*H*-furan-2-ones related to the natural product (−)-incrustoporine were synthesized and their in vitro antifungal activity evaluated. The compounds with halogen substituents on the phenyl ring displayed much higher antifungal effect against *Aspergillus fumigatus* than selected representatives of azole antifungal drugs. In particular, the activity (1.34 μg/mL) of the most promising derivative, 3-(3,4-dichlorophenyl)-5-pivaloyloxymethyl-2*H*,5*H*-furan-2-one, was comparable to that of amphotericin B (0.5 μg/mL). Preliminary evaluation of the toxicity of the compound was carried out as well. Considering the size and properties of these molecules in comparison with those of amphotericin B, further development of this novel group of antifungals may lead to substances with better pharmacological profiles than that of the standard anti-*Aspergillus* drug.

Clinically, candidiasis and aspergillosis account for between 80% and 90% of systemic fungal infections in immunocompromised patients. While there is a multiple choice of drugs for the treatment of candidiasis, only amphotericin B and itraconazole[1] come into consideration in the case of infections due to *Aspergillus fumigatus*. Although the research toward a new azole continues at an unabated pace, with examples such as TAK-187,[2] ER-30346,[3] Sankyo's amido alcohol,[4] UR-9825,[5] and most notably voriconazole[6] and SCH-56592 (posaconazole)[7] having been reported, the discovery and development of new structural types of antifungal compounds are no less desirable.

We have recently published[8] the synthesis and evaluation of in vitro antifungal activity of a series of 5-methyl-3-phenyl-2*H*,5*H*-furan-2-ones based on a fungal metabolite,[9] (−)incrustoporine, as the lead structure (Figure 1). Our results indicated that this class of compounds is suitable for further development as potential antimycotic agents, as some of the derivatives displayed appreciable fungistatic effect, especially against filamentous fungi. As regards structure−activity relationships (SARs), we found that the antifungal effect is linked to the presence of the double bond conjugated with the carbonyl group of the lactone ring and can be increased by substituting the phenyl moiety at C(3) with halogens, while it seems to be suppressed by electron-donating substituents. In particular, the activity of the most potent 3-(3,4-dichlorophenyl)-5-methyl-2*H*,5*H*-furan-2-one exceeded that of ketoconazole against the strain of *Absidia corymbifera*. Although it might seem that this type of compounds could be a nonspecific class of fungal inhibitors based on its Michael acceptor-like structure, we detected virtually no in vitro activity[8] in the case of 5-methyl-3-(4-nitrophenyl)-*2H*,*5H*-furan-2-one, which is a stronger Michael acceptor than the 3-(halophenyl) compounds. Herein we present the design, synthesis, and preliminary biological evaluation of a novel group of potent antifungal compounds derived from the substances described in our previous study.

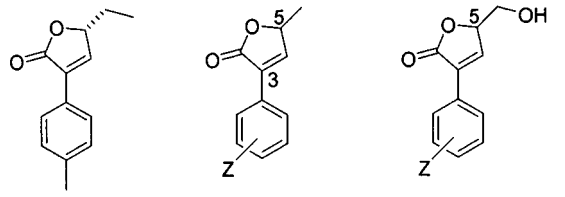

Figure 1.

Results and Discussion

Bearing in mind that the desired biological activity is supported by the substitution of the phenyl moiety at C(3) with halogens, we shifted attention to the substitution at C(5) of the furanone ring. With the mechanism of the antifungal effect being unknown, we assumed that while a certain degree of lipophilicity is necessary for the compound to penetrate the fungal cell wall, the presence of a hydrophilic moiety can play a most vital role in binding to its biological target molecule. Thus, we designed a series of 5-hydroxymethyl

† Dedicated to Professor Karel Waisser on the occasion of his 65th birthday.

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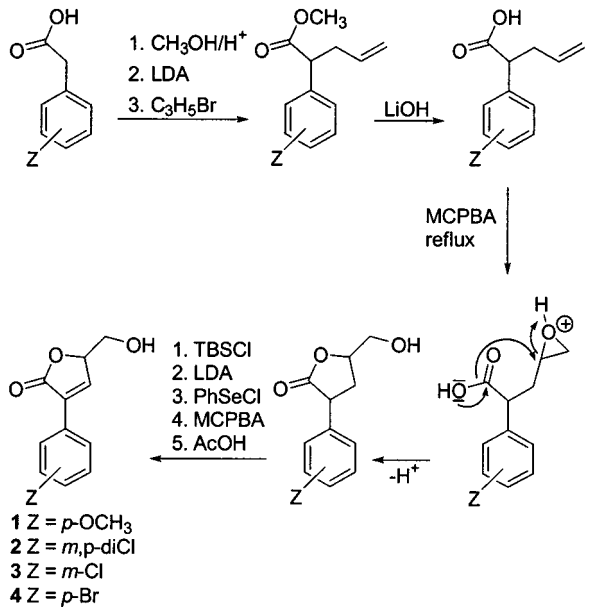
Table 1. Antifungal Activity of Compounds **1**−**4**, **1a**−**c**, **2a**−**c**, **3a**−**c**, and **4a-c**

		strain/MIC [μmol L^{-1}][b]											
no.	time,[a] h	CA1[c]	CA2[d]	CP[e]	CK1[f]	CK2[g]	CT[h]	CG[i]	CL[j]	TB[k]	AF[l]	AC[m]	TM[n]
1	24	15.63	31.25	250	62.5	62.5	125	125	31.25	500	125	31.25	15.63
	48	62.5	62.5	500	125	125	250	250	125	1000	500	62.5	62.5
2	24	62.5	250	250	250	125	250	62.5	125	500	62.5	125	15.63
	48	250	500	500	250	250	500	62.5	250	>1000	250	125	15.63
3	24	31.25	250	500	1000	1000	500	62.5	250	250	31.25	125	15.63
	48	62.5	250	1000	>1000	>1000	>1000	62.5	1000	1000	125	500	15.63
4	24	31.25	250	250	500	500	250	125	250	125	62.5	250	15.63
	48	62.5	250	500	1000	500	500	125	250	500	125	250	15.63
1a	24	1.95	31.25	62.5	31.25	31.25	31.25	62.5	62.5	>125	31.25	31.25	7.81
	48	15.63	62.5	>125	62.5	62.5	125	125	125	>125	125	62.5	15.63
1b	24	<0.98	31.25	31.25	62.5	62.5	31.25	31.25	31.25	62.5	3.91	62.5	7.81
	48	15.63	31.25	62.5	125	125	62.5	31.25	62.5	62.5	31.25	62.5	7.81
1c	24	0.98	31.25	31.25	62.5	62.5	31.25	31.25	31.25	62.5	7.81	62.5	7.81
	48	15.63	31.25	62.5	62.5	125	62.5	31.25	31.25	62.5	31.25	125	7.81
2a	24	0.12	1.95	1.95	3.91	3.91	1.95	0.98	1.95	1.95	0.98	15.63	0.98
	48	1.95	3.91	3.91	7.81	7.81	3.91	0.98	3.91	7.81	3.91	31.25	0.98
2b	24	0.49	3.91	3.91	3.91	3.91	3.91	0.98	1.95	1.95	0.98	15.63	0.98
	48	3.91	3.91	7.81	7.81	3.91	7.81	0.98	1.95	7.81	7.81	15.63	0.98
2c	24	0.49	1.95	3.91	7.81	3.91	3.91	0.49	1.95	1.95	1.95	7.81	0.24
	48	1.95	1.95	3.91	31.25	7.81	7.81	0.98	3.91	7.81	3.91	15.63	0.49
3a	24	1.95	7.81	7.81	7.81	15.63	15.63	1.95	7.81	7.81	1.95	3.91	1.95
	48	3.91	7.81	31.25	15.63	15.63	31.25	1.95	15.63	15.63	3.91	15.63	3.91
3b	24	0.98	3.91	7.81	3.91	7.81	7.81	≤0.98	3.91	3.91	1.95	3.91	1.95
	48	3.91	7.81	7.81	7.81	7.81	15.63	0.98	7.81	15.63	3.91	7.81	1.95
3c	24	≤0.98	3.91	7.81	7.81	7.81	7.81	≤0.98	3.91	3.91	≤0.98	7.81	1.95
	48	3.91	7.81	15.63	7.81	15.63	15.63	≤0.98	7.81	15.63	3.91	15.63	1.95
4a	24	1.95	3.91	7.81	7.81	7.81	7.81	1.95	3.91	3.91	0.98	7.81	1.95
	48	3.91	7.81	15.63	15.63	15.63	15.63	1.95	7.81	15.63	3.91	15.63	3.91
4b	24	≤0.98	1.95	7.81	3.91	3.91	7.81	0.98	1.95	3.91	0.98	7.81	1.95
	48	1.95	3.91	7.81	7.81	7.81	15.63	1.95	3.91	7.81	3.91	15.63	1.95
4c	24	0.49	1.95	3.91	3.91	7.81	7.81	1.95	3.91	7.81	0.98	7.81	1.95
	48	1.95	7.81	15.63	7.81	7.81	7.81	1.95	7.81	7.81	3.91	15.63	3.91

[a] 72 and 120 h for *Trichophyton mentagrophytes* 445. [b] Defined as 80% inhibition of the growth of control. [c] *C. albicans* ATCC44859. [d] *C. albicans* ATCC90028. [e] *C. parapsilosis* ATCC22019. [f] *C. krusei* ATCC 6258. [g] *C. krusei* E28. [h] *C. tropicalis* 156. [i] *C. glabrata* 20/I.[j] *C. lusitaniae* 2446/I. [k] *Trichosporon beigelii* 1188. [l] *Aspergillus fumigatus* 231. [m] *Absidia corymbifera* 272. [n] *Trichophyton mentagrophytes* 445.

Scheme 1



derivatives (Figure 1) because they were easily derived from the epoxidation of 2-phenylpent-4-enoic acids, which had served as intermediates in our synthesis of the 5-methyl series of compounds.

The preparation of the target compounds is outlined in general terms in Scheme 1. A commercially available substituted phenylacetic acid was converted into the corresponding methyl ester, which was enolized with LDA. The enolate was subsequently treated with allyl bromide and the ester group removed by hydrolysis. The resultant 2-(substituted phenyl)pent-4-enoic acid was subjected to epoxidation with MCPBA. Under the reaction conditions (MCPBA, $CHCl_3$, reflux for several hours), the carboxylic function of the initially formed epoxy acid acted as an internal nucleophile, opening the epoxide ring with the formation of a mixture of cis and trans 3-(substituted phenyl)-5-hydroxymethylfuran-2-ones.

To introduce the double bond, the hydroxy group was protected as a TBS ether, the mixture of the protected diastereomeric furanones was enolized with LDA, and the enolate was quenched with PhSeCl. The intermediate 3-phenylselenenyl derivative was, because of its limited stability, oxidized without delay by MCPBA to afford the corresponding selenoxide, which immediately underwent a spontaneous syn elimination introducing the double bond into the desired location. Finally, the acidic removal of the silyl group furnished the target compound. With a view to evaluating SARs on a preliminary basis, we synthesized the *p*-methoxy derivative **1** and three halogenated compounds **2**, **3**, and **4**.

The compounds were evaluated for their in vitro antifungal activity against a set of human pathogenic fungi including the representatives of both yeast and filamentous strains using the microdilution format of the NCCLS M27-A guidelines.[10] The results are sum-

Table 2. Antifungal Activity of Compounds **2c**, (+)**2c**, and (−)**2c** Compared to Drug Standards

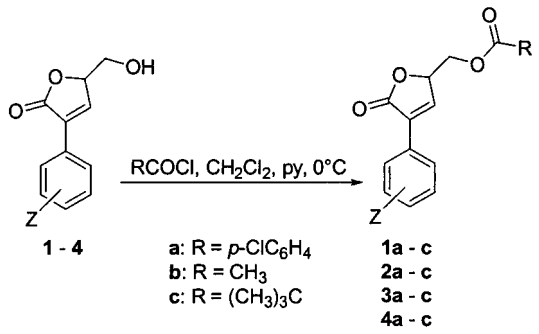
		strain/MIC [μg mL^{-1}][b]											
no.	time,[a] h	CA1[c]	CA2[d]	CP[e]	CK1[f]	CK2[g]	CT[h]	CG[i]	CL[j]	TB[k]	AF[l]	AC[m]	TM[n]
(+)2c	24	0.67	1.34	2.68	5.36	5.36	5.36	0.67	1.34	2.68	1.34	10.73	0.34
	48	1.34	2.68	5.36	10.73	10.73	10.73	1.34	2.68	5.36	2.68	10.73	0.67
(−)2c	24	0.67	1.34	2.68	2.68	2.68	2.68	0.67	1.34	1.34	1.34	5.36	0.34
	48	1.34	2.68	5.36	10.73	5.36	5.36	1.34	2.68	5.36	2.68	21.45	0.34
2c	24	0.17	0.67	1.34	2.67	1.34	1.34	0.17	0.67	0.67	0.67	2.68	0.08
	48	0.67	0.67	1.34	10.73	2.68	2.68	0.34	1.34	2.68	1.34	5.36	1.17
KET[o]	24	0.06	≤0.03	0.06	1.04	2.08	8.31	0.13	0.03	0.06	8.31	16.61	0.52
	48	0.06	≤0.03	0.06	1.04	2.08	8.31	0.26	0.06	0.06	8.31	16.61	1.04
AMP[p]	24	1	2	2	2	2	2	2	2	0.25	0.25	2	1
	48	1	2	2	4	4	2	2	2	0.25	0.5	2	1
FLU[q]	24	0.25	0.25	2	32	16	0.5	4	1	1	>128	>128	8
	48	0.5	1	4	64	32	>128	16	1	2	>128	>128	16

[a] 72 and 120 h for *Trichophyton mentagrophytes* 445. [b] Defined as 80% inhibition of the growth of control. [c] *C. albicans* ATCC44859. [d] *C. albicans* ATCC90028. [e] *C. parapsilosis* ATCC22019. [f] *C. krusei* ATCC 6258. [g] *C. krusei* E28. [h] *C. tropicalis* 156. [i] *C. glabrata* 20/I.[j] *C. lusitaniae* 2446/I. [k] *Trichosporon beigelii* 1188. [l] *Aspergillus fumigatus* 231. [m] *Absidia corymbifera* 272. [n] *Trichophyton mentagrophytes* 445. [o] Ketoconazole. [p] Amphotericin B. [q] Fluconazole.

marized in Table 1. In general, the antifungal effect (expressed as the minimum inhibitory concentration (MIC) in μmol/L) of the 5-hydroxymethyl derivatives is moderate to low, and there appear to be no significant differences between the activity of the *p*-methoxyphenyl derivative **1** and the three halophenyl compounds **2**, **3** and **4**.

The next step was increasing lipophilicity of the alcohols by conversion to esters. The compounds were treated with several acyl chlorides under carefully controlled conditions in CH_2Cl_2 with 1.5 equiv of pyridine at 0 °C to yield the corresponding esters **1a**−**c**, **2a**−**c**, **3a**−**c**, and **4a**−**c** (Scheme 2).

Scheme 2



As shown in Table 1, this subtle change in structure had a profound effect on in vitro antifungal activity. MICs of all esters are generally much lower than those of the parent hydroxy compounds, which seems to indicate that one of the reasons for low activity of the parent hydroxy compounds could be the hydrophilic character of the primary OH group leading to a decreased ability of the substances to penetrate the fungal cell wall. In the case of esters derived from 3-(halophenyl)-2*H*,5*H*-furan-2-ones, the decrease of MIC is quite dramatic, which supports the previously made conclusion[8] that halogenation of the phenyl ring at C(3) of the lactone moiety is important for the antifungal effect. MIC profiles show that all esters have a broad spectrum of activity displaying a fungistatic effect against both yeast and filamentous strains.

A comparison of one of the most promising compounds, ester **2c**, to selected drug standards in μg/mL is presented in Table 2. Compared to ketoconazole, a representative of azole antifungals, **2c** possesses comparable activity against *Candida krusei* and *Candida glabrata* and is superior to the drug against *Candida tropicalis*. Most importantly, compound **2c** (as well as all other esters) exhibits a remarkable in vitro antifungal effect against *Aspergillus fumigatus* (1.34 μg/mL), which is a clear indication that this type of substances is worthy of further development.

Because all compounds were applied in the form of racemic mixtures, we separated alcohol **2** into (+) and (−) enantiomers on an ID Chiralcel OD-R column with a cellulose derivative as the chiral selector. Both isomers were converted to the corresponding pivaloyl esters **(+)-2c** and **(−)2c** and the compounds subjected to evaluation of antifungal activity (Table 2). Surprisingly, there are no significant differences in MICs of the optical isomers, suggesting that there is probably no relationship between chirality at C(5) and the antifungal effect. The racemic mixture also seems to be more potent than either enantiomer.

To obtain an idea of the toxic properties of the new compounds, we carried out a preliminary assessment of the toxicity of the most promising ester **2c**. The value of LD_{50} (mice, intraperitoneal administration) was determined to be 54 mg/kg with the compound having been very well absorbed through the peritoneum.

In conclusion, we have discovered a novel group of potential antifungal compounds that are comparable to amphotericin B as regards their in vitro efficacy against *Aspergillus fumigatus*. Unlike amphotericin B, 5-acyloxymethyl-3-aryl-2*H*,5*H*-furan-2-ones are relatively lipophilic, small, rigid molecules of low structural complexity, which renders them possible targets for further investigation and development as potential antimycotics, the pharmacological profile of which may be better than that of this standard antifungal drug. A full account of our work, including further biological studies, will be published in due course.

Experimental Section

General Procedures. THF was distilled from benzophenone ketyl and diisopropylamine from CaH_2. Substituted phenylacetic acids were obtained from Sigma-Aldrich and used as received. All anhydrous reactions were performed in flame-dried Schlenk tubes under Ar atmosphere. Analytical thin-layer chromatography (TLC) was conducted on E. Merck TLC plates (silica gel 60 F_{254}, aluminum back). Silica gel 60 (230−400 mesh) for column chromatography was purchased from

E. Merck. Melting points were determined on a Kofler block and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz for ^{1}H. Chemical shifts were recorded as δ values in parts per million (ppm) and were indirectly referenced to tetramethylsilane (TMS) via the solvent signal (7.26 for ^{1}H, 77.0 for ^{13}C in $CDCl_3$). All assignments were made on the basis of gCOSY, gHSQC, and gHMBC experiments. Infrared spectra were recorded in $CDCl_3$ on a Nicolet Impact 400 spectrophotometer. Low-resolution mass spectra were measured on a Magnum Finnigan Mat apparatus.

In Vitro Biological Studies. In vitro antifungal activities of the compounds, ketoconazole (Janssen-Cilag), fluconazole (Pfizer), and amphotericin B (Sigma-Aldrich), were evaluated on a panel of four ATCC (*Candida albicans* ATCC 44859, *C. albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*C. krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon beigelii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. Three of the above ATCC strains (*C. albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) also served as the quality control strains. All the isolates were maintained on Sabouraud dextrose agar prior to being tested.

Minimum inhibitory concentrations (MICs) were determined by the microdilution format of the NCCLS M27-A guidelines.[10] Dimethyl sulfoxide (100%) served as a diluent for all compounds; the final concentration did not exceed 2%. RPMI 1640 (Sevapharma, Prague) medium supplemented with L-glutamine and buffered with 0.165 M morpholinepropanesulfonic acid (Serva) to pH 7.0 by 10 N NaOH was used as the test medium. The wells of the microdilution tray contained 100 μL of the RPMI 1640 medium with 2-fold serial dilutions of the compounds (1000−0.24 μmol/L for the new compounds) and 100 μL of inoculum suspension. Fungal inoculum in RPMI 1640 was prepared to give a final concentration of $5 \times 10^3 \pm 0.2$ cfu mL^{-1}. The trays were incubated at 35 °C, and MICs were read visually for filamentous fungi and photometrically for yeasts as an optical density (OD) at 540 nm after 24 and 48 h. The MIC values for the dermatophytic strain (*T. mentagrophytes*) were determined after 72 and 120 h. The MICs were defined as 80% inhibition of the growth of control. MICs were determined twice and in duplicate, with the exception of **2c**, the activity of which was evaluated in five independent measurements. The deviations from the usually obtained values given in Tables 1 and 2 were no higher than the nearest concentration value up and down the dilution scale.

General Procedure for the Preparation of the Methyl Esters of 2-Phenylpent-4-enoic Acids. A substituted phenylacetic acid (10 mmol) dissolved in methanol saturated with hydrogen chloride (100 mL) was heated under reflux for 3 h. Methanol was removed in vacuo, and the residue was redissolved in ethyl acetate. The solution was washed with 5% Na_2CO_3 and dried over Na_2SO_4, and the solvent was evaporated to give the corresponding methyl ester in a quantitative yield.

Butyllithium (11.0 mmol) was added to a solution of diisopropylamine (10.5 mmol) in dry THF (50 mL) at 0 °C under argon. After 10 min at 0 °C, the LDA solution was cooled to −60 °C, and a solution of the methyl phenylacetate (10 mmol) in THF (5 mL) was added. The reaction temperature was maintained at −60 °C for 30 min, and allyl bromide (10.5 mmol) was subsequently added dropwise. The reaction mixture was slowly allowed to warm to room temperature (over 1 h) in order to drive the reaction to completion. The solution was then diluted with ethyl acetate (100 mL), washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, and concentrated in vacuo to yield the crude methyl ester of the corresponding 2-phenylpent-4-enoic acid. Purification by column chromatography (petroleum ether/ether 95:5) afforded the pure product (yields in the range 80−90%).

General Procedure for the Preparation of the Precursor 5-Hydroxymethyl-3-(substituted phenyl)tetrahydrofuran-2-ones. The methyl ester of a 2-phenylpent-4-enoic acid (8 mmol) was dissolved in a mixture of MeOH/H_2O 3:1 (40 mL), and LiOH (10.4 mmol) was added to the solution. After 20 h at ambient temperature, the reaction mixture was concentrated in vacuo, diluted with H_2O, and acidified with concentrated HCl to pH 1. The mixture was extracted with ethyl acetate (3×), the combined extracts dried over Na_2SO_4, and the solvent evaporated to afford the corresponding acid.

A sample of 57% MCPBA (8.8 mmol) was added to a solution of the 2-phenylpent-4-enoic acid (8 mmol) in $CHCl_3$ (20 mL), and the mixture was heated under reflux for 3 h. The solution was then diluted with ethyl acetate and washed with 5% Na_2CO_3 (3×). The organic phase was dried over Na_2SO_4, and the solvent was removed. Column chromatography (petroleum ether/ethyl acetate 9:1) afforded the 3,5-disubstituted tetrahydrofuran-2-one as a mixture of trans and cis isomers (yields are about 80%).

General Procedure for the Preparation of the Unsaturated Lactones 1−4. The 3,5-disubstituted tetrahydrofuran-2-one (6.4 mmol) was dissolved in dry DMF (10 mL), and imidazole (7.7 mmol) and TBDMSCl (7.1 mmol) were added to this solution. After 12 h at ambient temperature, the reaction mixture was diluted with ethyl acetate (30 mL), washed with 5% HCl, dried over Na_2SO_4, and concentrated in vacuo. The TBS-protected tetrahydrofuran-2-one was purified by column chromatography (petroleum ether). The yields of the compounds were in the range 95−97%.

Butyllithium (6.6 mmol) was added to a solution of diisopropylamine (6.3 mmol) in dry THF (10 mL) at 0 °C under argon. After 10 min at 0 °C, the LDA solution was cooled to −60 °C, and a solution of the protected tetrahydrofuran-2-one (6 mmol) in THF (2 mL) was added. The reaction temperature was maintained at −60 °C for 30 min, and a solution of phenylselenenyl chloride (9 mmol) in THF (5 mL) was added. The resultant mixture was slowly allowed to warm to room temperature (over 2 h), diluted with ethyl acetate (50 mL), washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, and concentrated in vacuo. The crude phenylselenenyl derivative was rapidly purified by column chromatography (petroleum ether/ether 98:2) and was dissolved in $CHCl_3$ (10 mL), and MCPBA (9 mmol) was added to the solution at 0 °C. The reaction mixture was then stirred for 2 h at ambient temperature. A further portion of $CHCl_3$ (10 mL) was added along with 5% aqueous Na_2CO_3 (20 mL). The layers were separated, the organic phase was washed with 5% aqueous Na_2CO_3 (20 mL) and dried over Na_2SO_4, and the solvent was evaporated. The TBS-protected product was purified by column chromatography (petroleum ether/ether 9:1); TBS-protected compounds **1−4** were obtained with yields in the range 50−60%.

The TBS-protected compound (3 mmol) was dissolved in a mixture of AcOH/H_2O/THF 3:1:1 (10 mL), and the solution was maintained at 40 °C for 20 h. The reaction mixture was then diluted with ethyl acetate (20 mL), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/ethyl acetate 8:2) afforded the pure product (yields of compounds **1−4** were in the range 95−97%).

General Procedure for the Preparation of the Esters 1a−c, 2a−c, 3a−c, and 4a−c. Pyridine (1.5 mmol) and acyl chloride (1.5 mmol) were added dropwise to a solution (0 °C) of the alcohol (**1−4**) (1 mmol) in dry CH_2Cl_2 at 0 °C. The reaction mixture was maintained at 0 °C for 20 h and then diluted with ethyl acetate (20 mL), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resultant ester was purified by column chromatography (petroleum ether/ether 9:1). The yields of the esters were in the range 80−90%.

3-(4-Methoxyphenyl)-5-hydroxymethyl-2*H*,5*H*-furan-2-one (1). White crystals, mp 116−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.78 (2H, m, AA′BB′), 7.42 (1H, d, J = 1.9 Hz, H4), 6.95−6.89 (2H, m, AA′BB′), 5.13 (1H, ddd, J_1 = 1.9 Hz,

J_2 = 3.8 Hz, J_3 = 5.5 Hz, H5), 4.05−3.96 (1H, m, −CH_2O−), 3.85−3.75 (1H, m overlapped, −CH_2O−), 3.83 (3H, s overlapped, −OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.94, 160.51, 142.24, 132.37, 128.45, 121.83, 114.02, 81.13, 63.10, 55.31; IR ($CDCl_3$) ν_{max} 1256, 1308, 1465, 1512, 1608, 1756, 2936, 2959 cm^{-1}; LRMS 219($M^{\bullet+}$ − H, 1), 202(100), 187(1), 171(9), 159(3), 146(25), 132(32), 131(15), 115(9), 103(12), 89(15), 77(8), 63(14), 51(8); Anal. ($C_{12}H_{12}O_4$) C, H.

3-(4-Methoxyphenyl)-5-(4-chlorobenzoyloxymethyl)-2*H*,5*H*-furan-2-one (1a). White crystals, mp 150−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96−7.90 (2H, m, AA′BB′), 7.83−7.77 (2H, m, AA′BB′), 7.43 (1H, d, J = 1.9 Hz, H4), 7.42−7.37 (2H, m, AA′BB′), 6.96−6.90 (2H, m, AA′BB′), 5.35 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.7 Hz, J_3 = 5.5 Hz, H5), 4.68 (1H, dd, J_1 = 3.7 Hz, J_2 = 12.1 Hz, −CH_2O−), 4.54 (1H, dd, J_1 = 5.5 Hz, J_2 = 12.1 Hz, −CH_2O−), 3.83 (3H, s, −OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.26, 165.27, 160.72, 140.74, 140.01, 132.90, 131.10, 128.89, 128.53, 127.54, 121.53, 114.11, 78.04, 63.86, 55.32; IR ($CDCl_3$) ν_{max} 1270, 1307, 1403, 1489, 1512, 1596, 1608, 1724, 1766, 2937, 2959 cm^{-1}; LRMS 362($M^{\bullet+}$ + 3H, 1), 315(3), 255-(1), 213(1), 202(100), 187(1), 175(11), 171(18), 159(4), 146(58), 132(68), 117(19), 115(18), 103(24), 89(32), 77(13), 63(27), 51-(13); Anal. ($C_{19}H_{15}ClO_5$) C, H.

3-(4-Methoxyphenyl)-5-acetyloxymethyl-2*H*,5*H*-furan-2-one (1b). White crystals, mp 59−60 °C; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.85−7.79 (2H, m, AA′BB′), 7.37 (1H, d, J = 1.9 Hz, H4), 6.96−6.91 (2H, m, AA′BB′), 5.22 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.9 Hz, J_3 = 5.5 Hz, H5), 4.40 (1H, dd, J_1 = 3.9 Hz, J_2 = 12.0 Hz, −CH_2O−), 4.32 (1H, dd, J_1 = 5.5 Hz, J_2 = 12.0 Hz, −CH_2O−), 3.84 (3H, s, −OCH_3), 2.06 (3H, s, −CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.25, 170.62, 160.68, 140.92, 132.61, 128.51, 121.60, 114.09, 77.94, 63.22, 55.32, 20.62; IR ($CDCl_3$) ν_{max} 1256, 1307, 1367, 1465, 1512, 1609, 1747, 1758, 2840, 2937, 2959 cm^{-1}; LRMS 263($M^{\bullet+}$ + H, 1), 249(1), 202(100), 185-(1), 171(7), 159(2), 146(18), 132(16), 131(10), 117(6), 115(7), 103(9), 89(9), 77(3), 63(8), 51(4); Anal. ($C_{14}H_{14}O_5$) C, H.

3-(4-Methoxyphenyl)-5-pivaloyloxymethyl-2*H*,5*H*-furan-2-one (1c). White crystals, mp 92−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.77 (2H, m, AA′BB′), 7.34 (1H, d, J = 1.9 Hz, H4), 6.95−6.90 (2H, m, AA′BB′), 5.21 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.6 Hz, J_3 = 4.4 Hz, H5), 4.47 (1H, dd, J_1 = 4.4 Hz, J_2 = 12.0 Hz, −CH_2O−), 4.38 (1H, dd, J_1 = 3.6 Hz, J_2 = 12.0 Hz, −CH_2O−), 3.83 (3H, s, −OCH_3), 1.13 (9H, s, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.14, 171.36, 160.60, 141.14, 132.52, 128.47, 121.64, 114.07, 78.34, 62.34, 55.29, 38.85, 27.00; IR ($CDCl_3$) ν_{max} 1257, 1281, 1463, 1480, 1512, 1609, 1729, 1766, 2937, 2973 cm^{-1}; LRMS 303($M^{\bullet+}$ − H, 1), 255(1), 238(1), 213-(1), 202(100), 187(1), 171(9), 159(2), 146(28), 132(33), 117(10), 115(8), 103(12), 89(15), 77(5), 63(12), 50(7); Anal. ($C_{17}H_{20}O_5$) C, H.

3-(3,4-Dichlorophenyl)-5-hydroxymethyl-2*H*,5*H*-furan-2-one (2). White crystals, mp 102−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (1H, d, J = 2.2 Hz, Ar), 7.71 (1H, dd, J_1 = 2.2 Hz, J_2 = 8.5 Hz, Ar), 7.62 (1H, d, J = 1.9 Hz, H4), 7.47 (1H, d, J = 8.5 Hz, Ar), 5.17 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.8 Hz, J_3 = 5.0 Hz, H5), 4.10−4.00 (1H, m, −CH_2O−), 3.91−3.82 (1H, m, −CH_2O−); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.02, 146.07, 133.75, 133.00, 130.98, 130.66, 129.01, 128.86, 126.22, 81.27, 62.56; IR ($CDCl_3$) ν_{max} 1328, 1393, 1472, 1553, 1763, 2935, 3611 cm^{-1}; LRMS 259($M^{\bullet+}$, 1), 240(100), 205(37), 184(4), 170(14), 149(22), 134(4), 113(4), 99(7), 86(3), 74(8), 62(5), 50(8); Anal. ($C_{11}H_8$-Cl_2O_3) C, H.

(+)3-(3,4-Dichlorophenyl)-5-hydroxymethyl-2*H*,5*H*-furan-2-one ((+)2). $[\alpha]_D$ +16.3° (*c* 1.4, $CHCl_3$); all other data are identical with those of the racemate.

(−)3-(3,4-Dichlorophenyl)-5-hydroxymethyl-2*H*,5*H*-furan-2-one ((−)2). $[\alpha]_D$ −16.8° (*c* 1.0, $CHCl_3$); all other data are identical with those of the racemate.

3-(3,4-Dichlorophenyl)-5-(4-chlorobenzoyloxymethyl)-2*H*,5*H*-furan-2-one (2a). White crystals, mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, J = 2.1 Hz, Ar), 7.95−7.89 (2H, m, AA′BB′), 7.69 (1H, dd, J_1 = 2.1 Hz. J_2 = 8.4 Hz, Ar), 7.62 (1H, d, J = 1.9 Hz, H4), 7.48 (1H, d, J = 8.4 Hz, Ar), 7.44−7.38 (2H, m, AA′BB′), 5.40 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.9 Hz, J_3 = 5.0 Hz, H5), 4.68 (1H, dd, J_1 = 3.9 Hz, J_2 = 12.0 Hz, −CH_2O−), 4.61 (1H, dd, J_1 = 5.0 Hz, J_2 = 12.0 Hz, −CH_2O−); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.21, 165.24, 144.51, 140.22, 134.10, 133.15, 131.54, 131.42, 131.07, 130.77, 128.97, 128.91, 127.30, 126.23, 78.27, 63.36; IR ($CDCl_3$) ν_{max} 1269, 1335, 1403, 1472, 1489, 1596, 1725, 1768, 2927 cm^{-1}; LRMS 392($M^{\bullet+}$ − 6H, 7), 378(19), 362(2), 315(10), 285(1), 255(5), 242-(71), 240(100), 207(38), 205(98), 184(12), 170(61), 149(60), 135-(27), 113(9), 99(22), 87(11), 74(25), 61(13), 50(22); Anal. ($C_{18}H_{11}Cl_3O_4$) C, H.

3-(3,4-Dichlorophenyl)-5-acetyloxymethyl-2*H*,5*H*-furan-2-one (2b). White crystals, mp 83−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, d, J = 2.1 Hz, Ar), 7.71 (1H, dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, Ar), 7.57 (1H, d, J = 1.9 Hz, H4), 7.49 (1H, d, J = 8.4 Hz, Ar), 5.26 (1H, td, J_1 = 1.9 Hz, J_2 = 4.6 Hz, H5), 4.42 (1H, dd, J_1 = 4.6 Hz, J_2 = 12.1 Hz, −CH_2O−), 4.37 (1H, dd, J_1 = 4.6 Hz, J_2 = 12.1 Hz, −CH_2O−), 2.06 (3H, s, −CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.53, 170.23, 144.73, 133.99, 133.11, 131.13, 130.73, 128.88, 128.79, 126.24, 78.13, 62.73, 20.58; IR ($CDCl_3$) ν_{max} 1336, 1367, 1384, 1472, 1553, 1747, 1765, 2928, 2958 cm^{-1}; LRMS 299($M^{\bullet+}$ − 2H, 1), 285(1), 267-(1), 242(63), 240(100), 205(55), 184(7), 170(25), 149(31), 135-(8), 113(5), 99(12), 86(6), 74(12), 62(8), 50(10); Anal. ($C_{13}H_{10}$-Cl_2O_4) C, H.

3-(3,4-Dichlorophenyl)-5-pivaloyloxymethyl-2*H*,5*H*-furan-2-one (2c). White crystals, mp 89−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, d, J = 2.1 Hz, Ar), 7.70 (1H, dd, J_1 = 2.1 Hz, J_2 = 8.5 Hz, Ar), 7.53 (1H, d, J = 1.9 Hz, H4), 7.49 (1H, d, J = 8.5 Hz, Ar), 5.26 (1H, td, J_1 = 1.9 Hz, J_2 = 3.8 Hz, H5), 4.51 (1H, dd, J_1 = 3.8 Hz, J_2 = 12.0 Hz, −CH_2O−), 4.40 (1H, dd, J_1 = 3.8 Hz, J_2 = 12.0 Hz, −CH_2O−), 1.12 (9H, s, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.14, 170.31, 144.84, 133.97, 133.16, 131.03, 130.77, 128.86, 128.82, 126.21, 78.56, 61.92, 38.98 26.99; IR ($CDCl_3$) ν_{max} 1281, 1367, 1335, 1399, 1472, 1479, 1731, 1768, 2755, 2929, 2959, 2973 cm^{-1}; LRMS 342($M^{\bullet+}$ − H, 1), 327(2), 315(8), 285(1), 253(4), 242(76), 240-(100), 205(91), 184(12), 170(54), 149(52), 135(13), 114(8), 99-(19), 85(9), 74(23), 62(12), 50(20); Anal. ($C_{16}H_{16}Cl_2O_4$) C, H.

(+)3-(3,4-Dichlorophenyl)-5-pivaloyloxymethyl-2*H*,5*H*-furan-2-one ((+)2c). $[\alpha]_D$ +12.8° (*c* 0.7, $CHCl_3$); all other data are identical with those of the racemate.

(−)3-(3,4-Dichlorophenyl)-5-pivaloyloxymethyl-2*H*,5*H*-furan-2-one ((−)2c). $[\alpha]_D$ −12.2° (*c* 0.3, $CHCl_3$); all other data are identical with those of the racemate.

3-(3-Chlorophenyl)-5-hydroxymethyl-2*H*,5*H*-furan-2-one (3). White crystals, mp 75−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.83 (1H, m, Ar), 7.76−7.72 (1H, m, Ar), 7.61 (1H, d, J = 1.9 Hz, H4), 7.36−7.33 (2H, m, Ar), 5.16 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.8 Hz, J_3 = 4.9 Hz, H5), 4.04 (1H, dd, J_1 = 3.8 Hz, J_2 = 12.2 Hz, −CH_2O−), 3.84 (1H, dd, J_1 = 4.9 Hz, J_2 = 12.2 Hz −CH_2O−); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.30, 146.02, 134.63, 131.83, 130.84, 129.93, 129.54, 127.09, 125.16, 81.31, 62.62; IR ($CDCl_3$) ν_{max} 1329, 1419, 1476, 1568, 1595, 1762, 2933, 3604 cm^{-1}; LRMS 225($M^{\bullet+}$, 1), 208(32), 206(100), 189(2), 171(46), 150(4), 133(13), 126(2), 115(30), 101(8), 87(4), 75(7), 63(5), 50(6); Anal. ($C_{11}H_9ClO_3$) C, H.

3-(3-Chlorophenyl)-5-(4-chlorobenzoyloxymethyl)-2*H*,5*H*-furan-2-one (3a). White crystals, mp 190−191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.90 (2H, m, AA′BB′), 7.84−7.81 (1H, m, Ar), 7.75−7.69 (1H, m, Ar), 7.60 (1H, d, J = 1.9 Hz, H4), 7.43−7.38 (2H, m, AA′BB′), 7.38−7.34 (2H, m, Ar), 5.39 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.8 Hz, J_3 = 5.2 Hz, H5), 4.69 (1H, dd, J_1 = 3.8 Hz, J_2 = 12.0 Hz, −CH_2O−), 4.60 (1H, dd, J_1 = 5.2 Hz, J_2 = 12.0 Hz, −CH_2O−); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.44, 165.25, 144.40, 140.16, 134.78, 132.37, 131.54, 131.09, 130.92, 130.04, 129.85, 128.94, 127.16, 125.21, 78.21, 63.47; IR ($CDCl_3$) ν_{max} 1270, 1335, 1370, 1403, 1489, 1595, 1726, 1773, 2927, 3073 cm^{-1}; LRMS 331(1), 307(1), 244(1), 208-(33), 206(100), 189(1), 171(63), 150(7), 136(29), 115(42), 101-(15), 87(5), 75(14), 63(6), 50(11); Anal. ($C_{18}H_{12}Cl_2O_4$) C, H.

3-(3-Chlorophenyl)-5-acetyloxymethyl-2*H*,5*H*-furan-2-one (3b). White crystals, mp 71−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.83 (1H, m, Ar), 7.77−7.73 (1H, m, Ar), 7.55 (1H, d, J = 1.9 Hz, H4), 7.39−7.35 (2H, m, Ar), 5.28−5.24 (1H,

m, H5), 4.45−4.33 (2H, m, −CH_2O−), 2.06 (3H, s, −CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.37, 170.26, 144.48, 134.62, 131.94, 130.52, 129.90, 129.65, 127.01, 125.10, 78.07, 62.84, 20.69; IR ($CDCl_3$) ν_{max} 1336, 1367, 1385, 1476, 1567, 1595, 1746, 1763, 2927 cm^{-1}; LRMS 265($M^{\bullet+}$ − 2H, 1), 244(2), 208-(100), 206(100), 189(4), 171(100), 150(15), 136(81), 126(7), 115-(100), 101(39), 87(14), 75(40), 63(19), 50(31); Anal. ($C_{13}H_{11}ClO_4$) C, H.

3-(3-Chlorophenyl)-5-pivaloyloxymethyl-2*H*,5*H*-furan-2-one (3c). White crystals, mp 59−60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.81 (1H, m, Ar), 7.75−7.70 (1H, m, Ar), 7.52 (1H, d, J = 1.9 Hz, H4), 7.40−7.35 (2H, m, Ar), 5.26 (1H, td, J_1 = 1.9 Hz, J_2 = 3.9 Hz, H5), 4.50 (1H, dd, J_1 = 3.9 Hz, J_2 = 12.0 Hz, −CH_2O−), 4.40 (1H, dd, J_1 = 3.9 Hz, J_2 = 12.0 Hz, −CH_2O−), 1.13 (9H, s, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.13, 170.52, 144.72, 134.77, 131.99, 130.67, 130.02, 129.74, 127.10, 125.18, 78.49, 62.04, 38.87 26.99; IR ($CDCl_3$) ν_{max} 1281, 1335, 1369, 1399, 1462, 1480, 1568, 1595, 1731, 1767, 2874, 2910, 2937, 2976 cm^{-1}; LRMS 307($M^{\bullet+}$ − 2H, 1), 293(1), 279-(1), 257(1), 208(33), 206(100), 171(75), 150(7), 136(41), 115-(49), 101(17), 87(5), 75(17), 63(8), 50(14); Anal. ($C_{16}H_{17}ClO_4$) C, H.

3-(4-Bromophenyl)-5-hydroxymethyl-2*H*,5*H*-furan-2-one (4). White crystals, mp 104−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.71 (2H, m, AA′BB′), 7.58 (1H, d, J = 1.9 Hz, H4), 7.57−7.52 (2H, m, AA′BB′), 5.15 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.8 Hz, J_3 = 5.2 Hz, H5), 4.08−3.99 (1H, m, −CH_2O−), 3.89−3.80 (1H, m, −CH_2O−); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.29, 144.99, 132.08, 131.89, 128.58, 128.06, 123.93, 81.19, 62.77; IR ($CDCl_3$) ν_{max} 1297, 1328, 1403, 1488, 1590, 1764, 2878, 2934, 3606 cm^{-1}; LRMS 269($M^{\bullet+}$, 1), 252(100), 250(100), 222(4), 194(11), 182(59), 180(58), 171(96), 143(3), 126(7), 115-(100), 101(56), 87(14), 75(51), 63(21), 50(37); Anal. ($C_{11}H_9BrO_3$) C, H.

3-(4-Bromophenyl)-5-(4-chlorobenzoyloxymethyl)-2*H*,5*H*-furan-2-one (4a). White crystals, mp 211−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.89 (2H, m, AA′BB′), 7.74−7.69 (2H, m, AA′BB′), 7.58 (1H, d, J = 1.9 Hz, H4), 7.57−7.51 (2H, m, AA′BB′), 7.42−7.37 (2H, m, AA′BB′), 5.37 (1H, ddd, J_1 = 1.9 Hz, J_2 = 3.9 Hz, J_3 = 5.2 Hz, H5), 4.68 (1H, dd, J_1 = 3.9 Hz, J_2 = 12.0 Hz, −CH_2O−), 4.59 (1H, dd, J_1 = 5.2 Hz, J_2 = 12.0 Hz, −CH_2O−); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.59, 165.23, 143.58, 140.13, 132.49, 131.97, 131.06, 128.92, 128.59, 127.77, 127.37, 124.22, 78.21, 63.47; IR ($CDCl_3$) ν_{max} 1270, 1335, 1403, 1489, 1489, 1529, 1595, 1724, 1769, 2955, 3088 cm^{-1}; LRMS 405($M^{\bullet+}$ − 3H, 1), 377(3), 315(2), 252(100), 250-(92), 194(5), 185(31), 171(47), 115(61), 101(27), 87(7), 75(26), 63(10), 50(18); Anal. ($C_{18}H_{12}BrClO_4$) C, H.

3-(4-Bromophenyl)-5-acetyloxymethyl-2*H*,5*H*-furan-2-one (4b). White crystals, mp 70−71 °C; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.76−7.71 (2H, m, AA′BB′), 7.57−7.52 (2H, m overlapped, AA′BB′), 7.53 (1H, d overlapped, J = 1.9 Hz, H4), 5.26−5.21 (1H, m, H5), 4.44−4.32 (2H, m, −CH_2O−), 2.05 (3H, s, −CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.60, 170.56, 143.81, 132.16, 131.91, 128.58, 127.84, 124.10, 78.09, 62.84, 20.57; IR ($CDCl_3$) ν_{max} 1336, 1367, 1385, 1403, 1488, 1590, 1649, 1747, 1766, 2957, 3089 cm^{-1}; LRMS 315($M^{\bullet+}$ + 4H, 1), 272(1), 252-(100), 250(99), 233(2), 194(4), 180(12), 171(42), 143(1), 126(3), 115(55), 101(22), 87(5), 75(18), 63(8), 50(13); Anal. ($C_{13}H_{11}BrO_4$) C, H.

3-(4-Bromophenyl)-5-pivaloyloxymethyl-2*H*,5*H*-furan-2-one (4c). White crystals, mp 140−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.69 (2H, m, AA′BB′), 7.58−7.53 (2H, m, AA′BB′), 7.49 (1H, d, J = 1.9 Hz, H4), 5.24 (1H, td, J_1 = 1.9 Hz, J_2 = 3.8 Hz, H5), 4.51 (1H, dd, J_1 = 3.8 Hz, J_2 = 12.1 Hz, −CH_2O−), 4.40 (1H, dd, J_1 = 3.8 Hz, J_2 = 12.1 Hz, −CH_2O−), 1.12 (9H, s, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.14, 170.69, 143.92, 132.12, 131.97, 128.57, 127.88, 124.08, 78.52, 61.99, 38.87, 26.99; IR ($CDCl_3$) ν_{max} 1281, 1335, 1401, 1462, 1480, 1488, 1590, 1730, 1768, 2937, 2976 cm^{-1}; LRMS 353($M^{\bullet+}$, 1), 315(1), 272(1), 252(100), 250(98), 222(2), 194(4), 180(23), 171-(47), 143(1), 126(3), 115(58), 101(26), 87(6), 75(22), 63(11), 50-(17); Anal. ($C_{16}H_{17}BrO_4$) C, H.

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