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Reductive Bis-addition of Aromatic Aldehydes to α,β-Unsaturated Esters via the Use of Sm/Cu(I) in Air: A Route to the Construction of Furofuran Lignans

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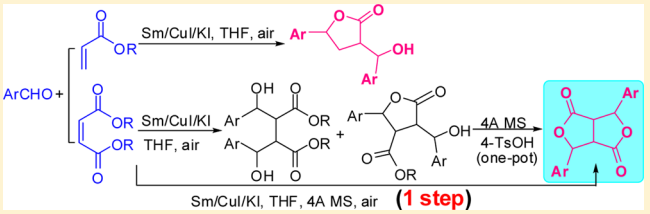
Supporting Information

ABSTRACT: The novel bis-addition of benzaldehydes to acrylates or maleates was achieved by the direct use of samarium metal with the assistance of CuI under mild conditions under dry air, and the useful 2-hydroxylalkyl-γ-butyrolactons and lignan derivatives were thus constructed with high efficiency. The key factors that influence the reaction efficiency were investigated. The use of potassium iodide and molecular sieves as additives can improve the reaction efficiency remarkably.



Samarium reagents in the past three decades have emerged as one of the reagents extensively exploited in a variety of synthetic strategies.[1−3] In contrast to the ever-increasing explorations of SmI_2 owing to its powerful reducing reactivity,[1,2] however, the direct use of samarium metal draws relatively fewer attention and in most cases acts as a moderate reductive agent in organic synthesis.[3] Nevertheless, the direct use of samarium metal as a reducing agent showed certain advantages as being more practical and electron-economical than the use of SmI_2.[3a]

The chemical skeleton **I** (Figure 1) is found in natural products and other widespread compounds of biomedical relevance.[4]

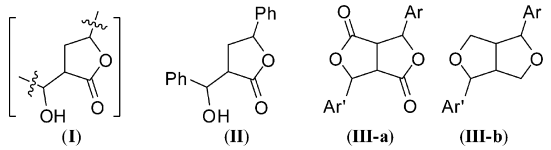


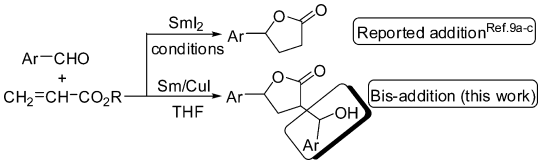
Figure 1. 2-Hydroxylbenzyl-γ-butyrolactons and furofuran lignans.

For example, 2-hydroxylbenzyl-γ-butyrolacton **II** (also see product **3a** in this article) is a natural product existing in smoking compositions as one of the main components of tobacco flavorant-release.[4a] Dilactons **III-a** (also see products **7** herein)[5] containing the moiety of **I** can readily transform to 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes (**III-b**)[6] via a facile reduction.[5a] Both of them are actually the furofuran lignans[7] which have exhibited diverse range of biological activities of particular importance in antitumor, antihypertensive, anti-inflammatory, insecticidal, platelet-activating factor antagonist activities, as well as in treating immunopathy, in the improvement of cerebral circulation, metabolism, and function.[5−7]

So far, the efficient syntheses for such compounds were usually involved with long reaction routes and harsh operation conditions, such as KHMDS (−70 °C, starting from *syn*-aldols, 3 steps),[4b] LDA (−78 °C, from α-benzoylsuccinic ester, 4 steps),[4c,5a] LDA (−78 °C, photochemistry, from cyclic ketene silyl acetals, 2 steps),[4d] LHMDS (−78 °C, from β-ketoesters, 6 steps),[5d] DIBALH (−78 °C, from TC-1 and selectfluor, 2 steps),[6a] and so on.

On the other hand, the incorporation of copper salts into other metals for the achievement of specific purposes is impressive.[8] These metals mainly includes lithium, palladium,[8a] magnesium,[8b] zinc,[8c,d] titanium,[8e] and so on, which exhibit particular reactivity in the presence of copper. By virtue of copper's strong coupling ability, samarium reagents incorporated with copper may exhibit exceptional reactivity. Herein the Sm/Cu(I) combination was applied in the coupling of aldehydes to acrylates and thus afforded a facile synthesis of 2-hydroxylalkyl-γ-butyrolactons (Scheme 1),

Scheme 1. Addition between Aldehydes and Acrylates



which is fundamentally different from the known reports which mainly involved a reductive conjugate addition promoted by SmI_2.[9a−e]

A series of conditions were screened to optimize the reaction (Table 1). First of all, the presence of copper salts proved to be crucial to establishing the reactions (entry 1). Room temperature was sufficient to realize the coupling reaction while higher temperature led to lower yields (entries 1−2). By the addition of KI, the reaction can be remarkably accelerated and even

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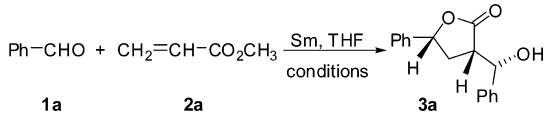
Table 1. Screening on the Conditions for the Coupling Reaction between Benzaldehyde and Methyl Acrylate



1a 2a 3a

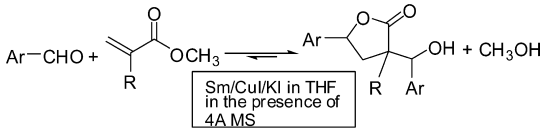
entry[a]	metal salt	additive	T (°C)	t (h)	yield (%)[b]
1	CuI		rt	5	42[c]
2	CuI		reflux	3	31
3	CuI	KI	rt	3	61
4	CuI	KI	rt	10	67[d,e]
5	CuCl	KI	rt	3	60[d]
6	$CuCl_2$	KI	reflux	10	13[d]
7	$AgNO_3$	KI	reflux	10	16[d]
8	$Cu(OAc)_2$	KI	reflux	10	[f]
9	$CuSO_4$	KI	reflux	10	[f]
10	$NiCl_2$	KI	reflux	10	[f]
11	CuI	1,10-phen	rt	3	57
12	CuI	HMPA	rt	4	54
13	CuI	TMSCl	rt	2.5	48
14	CuI	I_2	rt	2.5	49[g]
15	CuI	KI/4A MS	rt	10	81[e,h]
16	CuI	KI/4A MS	rt	3	78[h]
17	SmI_2/CuI		rt	0.5	14[i]
18	SmI_2		rt	0.5	[f,i]
19	CuI	KI/4A MS	rt	12	57[h,j]

[a]Sm (2 mmol), **1a** (2 mmol), **2a** (4 mmol), metal salt (2 mmol), additive (4 mmol), N_2, unless otherwise specified. [b]Isolated yields. [c]No reactions occur in the absence of CuI. [d]No reactions occur in the absence of KI. [e]In dry air. [f]Product **3a** was not observed. [g]A grain of I_2 was added. [h]4A molecular sieves and KI were added at the beginning. [i]Complicated mixture observed. [j]Open flask without preventing moisture.

proceed with better efficiency in dry air despite the longer reaction time, while no reaction could be detected at all without the addition of KI in dry air (entries 3−4). Although CuCl, $CuCl_2$, or $AgNO_3$ alone hardly promote the reaction, the combination of either of them with KI could facilitate the reaction (entries 5−7), instead, no product was obtained in the presence of $Cu(OAc)_2$, $CuSO_4$, or $NiCl_2$ (entries 8−10). Certain additives such as 1,10-phenanthroline or HMPA can accelerate the reaction (entries 11−12), due probably to the efficient coordination with copper or samarium. On the other hand, TMSCl or I_2 may accelerate the reaction by activation to samarium metal (entries 13−14). In almost all these cases, the addition efficiency was mainly influenced by the byproduct of benzoin which was formed via the self-coupling of benzaldehyde.[9f] A significant improvement of the yield was observed when 4A molecular sieves were added together with KI at the beginning of the reaction (entry 15−16). For comparison, a complicated reaction mixture containing **3a** was obtained when SmI_2 was used in the same reaction although the starting materials were consumed very soon (entry 17), while no **3a** was observed at all when only SmI_2 was used in the absence of CuI (entry 18).

According to the results, although moisture impeded the coupling reaction significantly (entry 19), the reaction can be carried out with better efficiency in dry air, and the use of KI proved necessary in establishing and improving the reactions. Although 1,10-phenanthroline can also improve the reaction efficiency to a certain extent, it was not introduced into the optimal conditions considering the simplicity of the reagents.

Scheme 2. Promotion of the Formation of 3 by 4A Molecular Sieves



The reaction efficiency was remarkably improved by 4A molecular sieves which were proposed to be able to deprive methanol[10] thereby promoting the cyclization process (Scheme 2).

At this stage, the scope and limitation of this reaction were investigated under the optimal conditions. A variety of benzaldehydes and acrylates were compatible with the conditions to afford products **3** in good yields (Table 2). The results showed the reaction efficiency decreased obviously when the reaction was carried out in the absence of 4A MS (entries 2, 11, 19), or when bulky-alkyl acrylates were used as the bis-addition acceptor (entries 3−9, 11). These results further support the promotion effect of 4A MS in Scheme 2. Besides, the influences of the steric hindrance were observed from the acrylates with different alkoxy groups (entries 2−9, 11, 19). The acrylates with bulky leaving groups, such as *tert*-butyl (**2c**), *iso*-octyl (**2d**), and octadecyl (**2e**), all underwent the reaction sluggishly in moderate yields (entries 4−6), while better results were brought out when aryl acrylates (**2f**, **2g**) were used, probably due to the better leaving ability of phenolate than that of alkoxy (entries 6, 7, 10). Interestingly, no obvious differences were observed from α-methyl acrylate (**2h**) and other acrylates (**2a**−**2e**). The functional group tolerance to Br and NO_2 is also interesting (entries 7, 8), the resulting tribromophenol and dinitrophenol from the cyclization can be recovered, without the debromination and NH_2 reduction products observed.

The bis-addition exhibited excellent diastereoselectivity in most cases (entries 1−11, 13−17). However, lower diastereoselectivity of the reaction was observed for the acrylates with an α-methyl (entries 18−21). The results also showed that better yields were obtained for the benzaldehydes with electron-donating groups (entries 10−15 and 20−21) than those with electron-withdrawing groups (entries 16−17). Nevertheless, strong electron-withdrawing groups led to the simple reduction of aldehydes into benzyl alcohols rather than the bis-addition (entries 22−23). Attempts to expand the coupling reaction to ketones and aliphatic aldehydes were not successful, where only complicated products were afforded.

Single-crystal structures of **3a** and **3j** show unambiguously that the products have a hydroxybenzyl group in the α-position of the carbonyl, indicating the occurrence of the bis-addition.[11] The stereochemistry shows a syn-configuration between α-R and γ-H of the butyrolacton ring. Probably due to the steric hindrance between α-CH_3 and γ-H, the diastereoselectivity decreased (entries 18−21).

Maleates **4** contain the moiety of acrylates and are proven to be more reactive in the reaction (Table 3). However, probably due to the hindrance, either products **5** or the monocyclic products **6** were obtained in different cases. No good regularity of the ratio between **5** and **6** can be observed (entries 1−5 compared with entries 6−8). Notably, no desired product was formed from fumarate, which may be contributed to the trans-configuration that impede the bis-addition and/or the cyclization process.

Encouraging results were also obtained when 4A MS were added right before the reaction start. Single bicyclic products **7**

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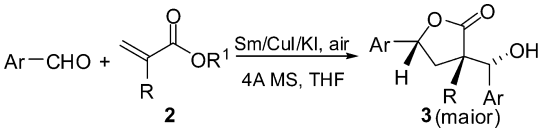
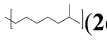
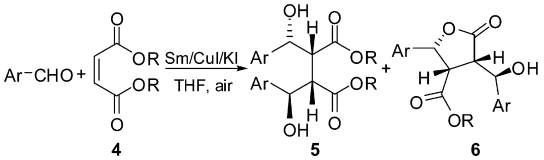
Table 2. Bis-Addition of Benzaldehydes to Acrylates



Entry[a]	Ar	R	R^1	Yield (%)[b]	*dr* Ratio[c]
1	Ph	H	Me (**2a**)	81 (**3a**)	>99:1
2	Ph	H	Me	67[d]	>99:1
3	Ph	H	Et (**2b**)	71	>99:1
4	Ph	H	*t*-Bu (**2c**)	56	>99:1
5	Ph	H	 (**2d**)	59	>99:1
6	Ph	H	 (**2e**)	61	>99:1
7	Ph	H	 (**2f**)	76	>99:1
8	Ph	H	 (**2g**)	73	>99:1
9	4-Me-C_6H_4	H	**2f**	70 (**3b**)	>99:1
10	4-Me-C_6H_4	H	Me	86	>99:1
11	4-Me-C_6H_4	H	Et	69[d]	>99:1
12	4-Et-C_6H_4	H	Me	80 (**3c**)	88:12
13	3,4-*di*Me-C_6H_3	H	Me	87 (**3d**)	>99:1
14	4-MeO-C_6H_4	H	Me	82 (**3e**)	>99:1
15	3-Me-C_6H_4	H	Me	81 (**3f**)	>99:1
16	3-F-C_6H_4-	H	Me	73 (**3g**)	>99:1
17	3-Cl-C_6H_4	H	Me	68 (**3h**)	>99:1
18	Ph	Me	Me (**2h**)	81 (**3i**)	67:33
19	Ph	Me	Me	58 (**3i**)[d]	67:33
20	4-MeO-C_6H_4	Me	Me	76 (**3j**)	95:5
21	3,4-*di*Me-C_6H_3	Me	Me	82 (**3k**)	80:20
22	3-pyridinyl	H	Me	71[e]	
23	4-NO_2-C_6H_4	H	Me	67[e]	

[a]Benzaldehydes (2 mmol), **2** (4 mmol), Sm (2 mmol), CuI (2 mmol), KI (4 mmol), and 4A MS in THF (15 mL) at r.t. in air. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]In the absence of 4A MS. [e]Reduction products (benzyl alcohols).

Table 3. Bis-Addition of Benzaldehydes to Maleates



entry[a]	Ar	R	yield (**5** and **6**) (%)[b]
1	Ph	Et	70 (**5a**)
2	4-Me-C_6H_4	Me	73 (**5b**:**6b** = 43:30)
3	4-Et-C_6H_4	Me	75 (**5c**)
4	4−Cl-C_6H_4	Me	68 (**5d**)
5	2−Cl-C_6H_4	Me	66 (**5e**)
6	Ph	Me	72 (**6a**)
7	4-Me-C_6H_4	Et	65 (**6c**)
8	4-MeO-C_6H_4	Me	68 (**6d**)

[a]Benzaldehydes (2 mmol), **4** (4 mmol), Sm (2 mmol), CuI (2 mmol), KI (4 mmol) at r. t. in air. [b]Isolated yields.

were afforded in better efficiency in one step with the assistance of 4A MS (Table 4). It is also found that the resulting products **5** and **6** from Table 3 can be transformed to **7** provided 4A MS were added together with 4-TsOH to the final reaction mixture in a one-pot manner (Table 4, entries 3−4). No diastereomers observed by ^{1}H NMR indicate the excellent diastereoselectivity of the reaction.

The relative stereochemistry of product **7** was identified by single crystal.[11] Products **5** and **6** are the precursors of **7**, so there is stereochemical similarity between compounds **5** (or **6**) and **7**.

The reaction mechanism is not clear yet at current stage. As it is well-known, olefins can coordinate efficiently with copper which affects the reactivity of olefins significantly,[12] and various reactions have been documented,[13] such as reduction,[13a] oxidation,[13b−d] and the C−H bond activation.[13e−g] Besides, catalyzed by copper a single-electron oxidative addition[13b,c] often occurs during the ATRP process in which olefins are polymerized controllably.[14] Such reactivity of copper may play important roles during the bis-addition.

In summary, a new application of Sm/Cu(I) was demonstrated. The bis-addition between benzaldehydes and acrylates or maleates provides an efficient method for the synthesis of

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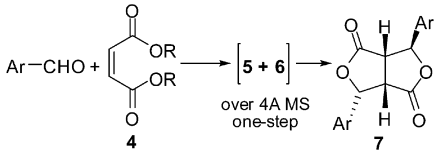
Table 4. Bis-Addition of Benzaldehydes to Maleates in the Presence of 4A MS



entry	Ar	R	yield (%)[a]
1	Ph	Me	84 (**7a**)
2	Ph	Me	78 (**7a**)[b]
3	Ph	Et	76 (**7a**)[c]
4	Ph	*n*-Bu	65 (**7a**)[c]
5	3,4-*di*Me-C_6H_3	Me	86 (**7b**)
6	4-MeO-C_6H_4	Me	82 (**7c**)
7	3—Cl-C_6H_4	Me	77 (**7d**)
8	1-Naphthaldehyde	Me	80 (**7e**)

[a]Isolated yields. [b]N_2 atmosphere. [c]4-Toluenesulfonic acid was added.

2-hydroxylbenzyl-γ-butyrolacton and lignans derivatives from readily available materials in a facile and novel way in short steps.

EXPERIMENTAL SECTION

General. All NMR spectra were measured in $CDCl_3$ and recorded on Bruker Avance-500 spectrometer (^{1}H NMR 500 MHz and ^{13}C NMR 125 MHz) with TMS or the residual signals of the solvent (δ 7.26 for ^{1}H NMR and δ 77.16 for ^{13}C NMR) as the internal standard. Chemical shifts are expressed in δ values (ppm) and coupling constants are given in J values (Hz). IR spectra were recorded on a Bruker Tensor-27 spectrometer. High-resolution mass spectra (HRMS) were measured on Thermo Scientific LTQ Orbitrap XL mass spectrometer usingelectrospray ionization (ESI) and electron impact (EI) methods. Melting points were measured on RY-1 melting point apparatus, and the values are uncorrected. All chemical reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified. Before use, THF was refluxed and redistilled over sodium and benzophenone. Flash column chromatography was performed over silica gel (100—200 mesh). All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography using silica gel precoated glass plates, which were visualized with UV light and then developed using either iodine or a solution of anisaldehyde.

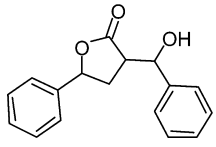
Typical Procedure for the Synthesis of 2-Hydroxylphenylmethyl-4-phenyl-γ-butyrolacton (3a). To a mixture of samarium powder (0.3 g, 2 mmol), cuprous iodide (0.39 g, 2 mmol); potassium iodide (0.68 g, 4 mmol) in anhydrous tetrahydrofuran (15 mL), benzaldehyde (2 mmol, 0.21 mL), methyl acrylate (4 mmol, 0.36 mL); and 4A molecular sieves (1 g) were added at room temperature with magnetic stirring under dry air. Then the flask was sealed with rubber stoppers to prevent moisture, and the reaction mixture turned dark in 2 h. After the reaction proceeded overnight, dilute hydrochloric acid (2 mol·L^{-1}, 5 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and saturated sodium thiosulfate solution successively, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified with flash chromatography (over silica, hexane:ethyl acetate = 7:1 v/v) to afford 217 mg of **3a** with 81% yield.

Typical Procedure for the Synthesis of Diethyl 2,3-Bis(hydroxy(phenyl)methyl)succinate (5a). To a mixture of samarium powder (0.3 g, 2 mmol), cuprous iodide (0.39 g, 2 mmol); potassium iodide (0.68 g, 4 mmol) in anhydrous tetrahydrofuran (15 mL), benzaldehyde (2 mmol, 0.21 mL), diethyl maleate (4 mmol, 0.63 mL); and 4A molecular sieves (1 g) were added at room temperature with magnetic stirring under dry air. Then the flask was sealed with rubber stoppers to prevent moisture, and the reaction mixture turned dark in 2 h. After the reaction proceeded overnight, dilute hydrochloric acid (2 mol·L^{-1}, 5 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and saturated sodium thiosulfate solution successively, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified with flash chromatography (over silica, hexane:ethyl acetate = 2:1 v/v) to afford 270 mg of **5a** with 70% yield.

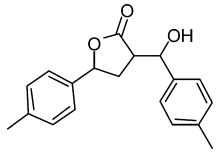
Typical Procedure for the Synthesis of Methyl 4-(hydroxy(phenyl)methyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (6a). To a mixture of samarium powder (0.3 g, 2 mmol), cuprous iodide (0.39 g, 2 mmol); potassium iodide (0.68 g, 4 mmol) in anhydrous tetrahydrofuran (15 mL), benzaldehyde (2 mmol, 0.21 mL), dimethyl maleate (4 mmol, 0.50 mL); and 4A molecular sieves (1 g) were added at room temperature with magnetic stirring under dry air. Then the flask was sealed with rubber stoppers to prevent moisture, and the reaction mixture turned dark in 2 h. After the reaction proceeded overnight, dilute hydrochloric acid (2 mol·L^{-1}, 5 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and saturated sodium thiosulfate solution successively, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified with flash chromatography (over silica, hexane:ethyl acetate = 5:1 v/v) to afford 235 mg of **6a** with 72% yield.

Typical Procedure for the Synthesis of Methyl 3,6-Diphenyltetrahydrofuro[3,4-*c*]furan-1,4-dione (7a). To a mixture of samarium powder (0.3 g, 2 mmol), cuprous iodide (0.39 g, 2 mmol); potassium iodide (0.68 g, 4 mmol) in anhydrous tetrahydrofuran (15 mL), benzaldehyde (2 mmol, 0.21 mL), dimethyl maleate (4 mmol, 0.50 mL); and 4A molecular sieves (1 g) were added at room temperature with magnetic stirring under dry air. Then the flask was sealed with rubber stoppers to prevent moisture, and the reaction mixture turned dark in 2 h. After the reaction proceeded overnight, dilute hydrochloric acid (2 mol·L^{-1}, 5 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and saturated sodium thiosulfate solution successively, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified with flash chromatography (over silica, hexane:ethyl acetate = 7:1 v/v) to afford 247 mg of **7a** with 84% yield.

3-(Hydroxy(phenyl)methyl)-5-phenyldihydrofuran-2(3H)-one (3a). White solid. mp 217 mg (81%). 184—186 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.40—7.28 (m, 10 H), 5.49 (s, 1 H), 5.35—5.31 (m, 1 H), 3.20—3.16 (m, 1 H), 2.50—2.43 (m, 2 H), 2.33—2.27 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.0, 141.4, 139.1, 128.8, 128.7, 127.9, 125.9, 125.5, 125.0, 80.0, 70.3, 49.9, 30.7; IR (KBr/cm^{-1}) ν 3432, 3055, 2900, 1678, 1596, 1580, 1446; HRMS m/z calcd for $C_{17}H_{17}O_3^+$ $[M+H]^+$ 269.1178, found 269.1185.



3-(Hydroxy(p-tolyl)methyl)-5-*p*-tolyldihydrofuran-2(3H)-one (3b). White solid. 255 mg (86%). mp 164—167 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.26—7.15 (m, 8 H), 5.44 (m, 1 H), 5.30—5.27 (m, 1 H), 3.14 (m, 1 H), 2.46 (m, 2 H), 2.49 (s, 3H), 2.43 (s, 3H), 2.36 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.0, 138.5, 137.5, 136.1, 129.4, 129.3, 126.0, 125.4, 80.0, 70.3, 49.9, 30.8, 21.3, 21.2. IR (KBr/cm^{-1}) ν 3457, 3036, 2912, 1677, 1588, 1581, 1432; HRMS m/z calcd for $C_{19}H_{21}O_3^+$ $[M+H]^+$ 297.1491, found 297.1485.



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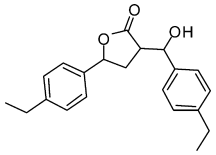
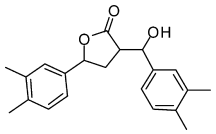
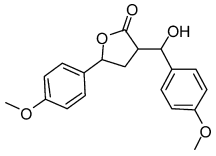
5-(4-Ethylphenyl)-3-((4-ethylphenyl)(hydroxy)methyl)-dihydrofuran-2(3H)-one (3c). White solid. 259 mg (80%). mp 144−146 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.28−7.17 (m, 8 H), 5.44 (s, 1 H), 5.30−5.27 (m, 1 H), 3.16−3.12 (m, 1 H), 2.66−2.63 (m, 4 H), 2.50−2.43 (m, 2 H), 2.32−2.26 (m, 1 H), 1.25−1.19(m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.2, 145.0, 144.0, 138.8, 136.3, 128.2, 128.1, 126.1, 125.5, 80.1, 70.3, 49.9, 30.7, 28.6, 15.7; IR (KBr/cm^{-1}) ν 3464, 3076, 2956, 1677, 1575, 1565, 1466; HRMS m/z calcd for $C_{21}H_{25}O_3^+$ $[M+H]^+$ 325.1804, found 325.1810.



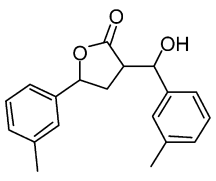
5-(3,4-Dimethylphenyl)-3-((3,4-dimethylphenyl)(hydroxy)-methyl)dihydrofuran-2(3H)-one (3d). White solid. 282 mg (87%). mp 134−136 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.14−7.10 (m, 6 H), 5.39 (s, 1 H), 5.27−5.24 (m, 1 H), 3.13 (m, 1 H), 2.46−2.43 (m, 2 H), 2.30−2.29 (t, 1 H), 2.28 (s, 3 H), 2.27 (s, 3 H), 2.26 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.1, 139.0, 137.2, 137.1, 136.9, 136.5, 136.1, 129.9, 127.2, 126.7, 123.5, 122.9, 80.1, 70.4, 49.9, 30.9, 19.8, 19.4. IR (KBr/cm^{-1}) ν 3435, 3045, 2943, 1676, 1576, 1534, 1454; HRMS m/z calcd for $C_{21}H_{25}O_3^+$ $[M+H]^+$ 325.1804, found 325.1802.



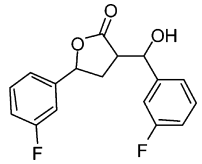
3-(Hydroxy(4-methoxyphenyl)methyl)-5-(4-methoxyphenyl)-dihydrofuran-2(3H)-one (3e). White solid. 269 mg (82%). mp 162−164 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.30−7.26 (m, 4 H), 6.91−6.88 (m,4 H), 5.43−5.41 (m, 1 H), 5.29−5.26 (m, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.15−3.10 (m, 1 H), 2.48−2.41 (m, 2 H), 2.30−2.25 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.0, 160.0, 159.2, 133.5, 130.9, 127.6, 126.7, 114.1, 114.0, 79.9, 70.2, 55.3, 49.9, 30.7; IR (KBr/cm^{-1}) ν 3389, 3023, 2956, 1674, 1574, 1517, 1422; HRMS m/z calcd for $C_{19}H_{21}O_5^+$ $[M+H]^+$ 329.1389, found 329.1379.



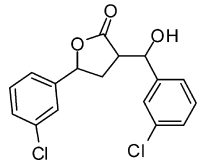
3-(Hydroxy(m-tolyl)methyl)-5-*m*-tolyldihydrofuran-2(3H)-one (3f). White solid. 239 mg (81%). mp 164−167 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.26−7.15 (m, 8 H), 5.44 (m, 1 H), 5.30−5.27 (m, 1 H), 3.14 (m, 1 H), 2.46 (m, 2 H), 2.49 (s, 3 H), 2.43 (s, 3 H), 2.36 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.4, 140.9, 138.5, 138.0, 137.8, 128.8, 128.0, 124.9, 125.5, 122.4, 122.0,79.5, 69.8, 49.3, 30.2, 20.9, 20.8; IR (KBr/cm^{-1}) ν 3434, 3074, 2937, 1676, 1585, 1531, 1454; HRMS m/z calcd for $C_{19}H_{21}O_3^+$ $[M+H]^+$ 297.1491, found 297.1487.



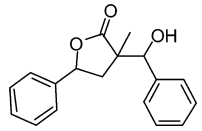
5-(3-Fluorophenyl)-3-((3-fluorophenyl)(hydroxy)methyl)-dihydrofuran-2(3H)-one (3g). White solid. 222 mg (73%). mp 156−158 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.31−7.03 (m, 8 H), 5.75−5.74 (m, 1 H), 5.64−5.62 (m, 1 H), 3.36 (m, 1 H), 2.56−2.55 (m, 1 H), 2.36−2.32 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.4, 160.6 (158.7, J_{C-F} = 246.6 Hz), 159.9 (158.0 J_{C-F} = 242.8), 129.9, 129.3, 128.4, 127.1, 126.8, 126.3, 124.6, 124.4, 115.5, 115.3, 74.1, 64.7, 47.8, 29.9; IR (KBr/cm^{-1}) ν 3461, 3045, 2924, 1681, 1557, 1543, 1445; ν HRMS m/z calcd for $C_{17}H_{15}F_2O_3^+$ $[M+H]^+$ 305.0989, found 305.0992.



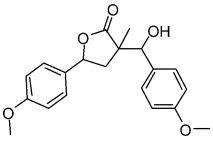
5-(3-Chlorophenyl)-3-((3-chlorophenyl)(hydroxy)methyl)-dihydrofuran-2(3H)-one (3h). White solid. 228 mg (68%). mp 166−168 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.33−7.21 (m, 8 H), 5.47−5.45 (m, 1 H), 5.31−5.28 (m, 1 H), 3.18−3.13 (m, 1 H), 2.55−2.54 (m, 1 H), 2.41−2.28 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.2, 143.4, 140.9, 134.8, 130.1, 130.0, 128.8, 128.0, 125.9, 125.6, 123.8, 123.6, 114.8, 78.9, 69.5, 49.6, 30.3; IR (KBr/cm^{-1}) ν 3457, 3047, 2968, 1681, 1578, 1523, 1436; HRMS m/z calcd for $C_{17}H_{15}Cl_2O_3^+$ $[M+H]^+$ 337.0398, found 337.0389.



3-(Hydroxy(phenyl)methyl)-3-methyl-5-phenyldihydrofuran-2(3H)-one (3i). White solid. 228 mg (68%). Obtained together with its diastereomer (67:33). mp 130−136 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm7.40−7.27 (m, 10 H), 5.40−5.37 (m, 1 H), 5.02−5.01 (m, 1 H), 2.87−2.82 (m, 1 H), 2.72−2.70 (m, 1 H), 1.96−1.92 (m, 1 H), 1.21 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 180.6, 139.7, 128.7, 128.6, 128.2, 128.0, 127.1, 125.9, 78.5, 75.8, 51.3, 37.5, 20.5; IR (KBr/cm^{-1}) ν 3457, 3047, 2968, 1681, 1578, 1523, 1436; HRMS m/z calcd for $C_{18}H_{19}O_3^+$ $[M+H]^+$ 283.1334, found 283.1339.



3-(Hydroxy(4-methoxyphenyl)methyl)-5-(4-methoxyphenyl)-3-methyldihydrofuran-2(3H)-one (3j). White solid. 260 mg (76%). Obtained together with its diastereomer (95:5). mp 160−162 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm7.32−7.24 (m, 4 H), 6.92−6.86 (m, 4 H), 5.36−5.32 (m, 1 H), 4.98−4.95 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.86−2.81 (m, 1 H), 2.60−2.59 (m, 1 H), 1.92−1.88 (m, 1 H), 1.18(s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 180.7, 159.9, 159.6, 131.9, 131.3, 128.3, 127.6, 114.1, 113.7, 78.4, 76.0, 55.3, 51.4, 37.5, 20.6; IR (KBr/cm^{-1}) ν 3402, 3033, 2954, 1676, 1566, 1542, 1443; HRMS m/z calcd for $C_{20}H_{23}O_5^+$ $[M+H]^+$ 343.1545, found 343.1549.



5-(3,4-Dimethylphenyl)-3-((3,4-dimethylphenyl) (hydroxy)-methyl)-3-methyldihydrofuran-2(3H)-one (3k). White solid. 277 mg (82%). Obtained together with its diastereomer (80:20). mp 164−168 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm7.26−7.03 (m, 6 H), 5.45−5.32 (m, 1 H), 4.95−4.90 (s, 1 H), 3.09−2.82 (m, 1 H), 2.60−2.53 (d, 1 H), 2.30 (s, 3 H), 2.28 (s, 3 H), 2.26 (s, 3 H), 2.22 (s, 3 H), 1.95−1.71 (m, 1 H), 1.21−1.15 (s, 3 H); ^{13}C NMR

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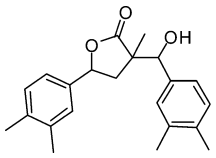
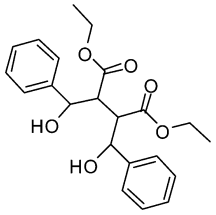
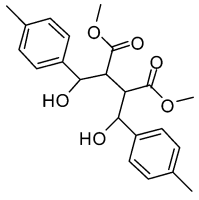
(125 MHz, $CDCl_3$) δppm 181.0, 137.3, 137.0, 136.8, 136.5, 136.4, 129.8, 129.5, 128.3, 127.3, 126.5, 124.7, 123.6, 79.0, 75.9, 51.3, 37.8, 20.6, 20.5, 19.8, 19.5; IR (KBr/cm^{-1}) ν 3412, 3045, 2945, 1676, 1578, 1532, 1412; HRMS *m/z* calcd for $C_{22}H_{27}O_3^+$ $[M+H]^+$ 339.1960, found 339.1956.



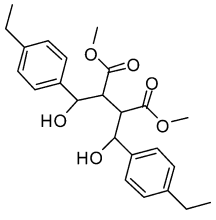
Diethyl 2,3-bis(hydroxy(phenyl)methyl)succinate (5a). White solid. 270 mg (70%). mp 255−257 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.40−7.34 (m, 10 H), 5.68−5.67 (m, 2 H), 4.31−4.29 (m, 2 H), 3.76−3.70 (m, 2 H), 3.68−3.66 (m, 2 H), 3.65−3.56 (m, 2 H), 0.73−0.71 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.8, 169.6, 134.4, 128.8, 128.4, 125.5, 81.0, 61.1, 51.2, 41.6, 31.1, 29.7, 13.4; IR (KBr/cm^{-1}) ν 3501, 3302, 3045, 2934, 1761, 1739, 1567, 1487, 1455; HRMS *m/z* calcd for $C_{22}H_{27}O_6^+$ $[M+H]^+$ 387.1808, found 387.1801.



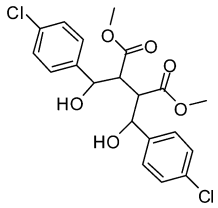
Dimethyl 2,3-Bis(hydroxy(p-tolyl)methyl)succinate (5b). White solid. 166 mg (43%). mp 252−253 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.17−7.15 (m, 4 H), 7.08−7.06 (m,4 H), 5.79−5.77 (m, 2 H), 3.83−3.78 (m, 2 H), 3.75−3.71 (m, 2 H), 3.40 (s, 6 H), 2.33 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.5, 168.9, 139.2, 131.7, 129.3, 125.8, 79.1, 52.3, 49.4, 40.1, 21.2; IR (KBr/cm^{-1}) ν 3498, 3302, 3057, 2958, 1759, 1743, 1589, 1467, 1422; HRMS *m/z* calcd for $C_{22}H_{27}O_6^+$ $[M+H]^+$ 387.1808, found 387.1807.



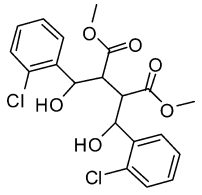
Dimethyl 2,3-Bis((4-ethylphenyl) (hydroxy)methyl)succinate (5c). White solid. 311 mg (75%). mp 254−256 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.17−7.15 (d, 4 H, *J* = 6.5 Hz), 7.08 (d, 4 H, *J* = 6.5 Hz), 5.93−5.91 (m, 2 H), 4.59−4.55 (m, 2 H), 3.56−3.53 (m, 2 H), 3.40 (s, 6 H), 2.62 (q, 4 H, *J* = 6.0 Hz), 1.20 (t, 6 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 175.6, 168.9, 145.4, 132.6, 128.0, 126.0, 79.2, 52.3, 49.5, 39.5, 28.5, 15.5; IR (KBr/cm^{-1}) ν 3498, 3303, 3065, 2967, 1760, 1744, 1566, 1476, 1423; HRMS *m/z* calcd for $C_{24}H_{31}O_6^+$ $[M+H]^+$ 415.2121, found 415.2116.



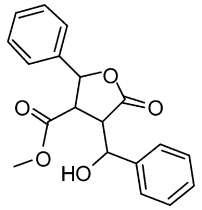
Dimethyl 2,3-Bis((4-chlorophenyl) (hydroxy)methyl)-succinate (5d). White solid. 290 mg (68%). mp 262−263 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.36 (d, 4 H, *J* = 6.5 Hz), 7.15 (d, 4 H, *J* = 6.5 Hz), 5.81−5.79 (m, 2 H), 3.88−3.78 (m, 2 H), 3.70−3.66 (m, 2 H), 3.44 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.2, 169.5, 132.7, 132.3, 130.3, 129.7, 127.2, 127.0, 52.4, 48.3, 42.0; IR (KBr/cm^{-1}) ν 3517, 3308, 3049, 2954, 1769,1744, 1597, 1495, 1443; HRMS *m/z* calcd for $C_{20}H_{21}Cl_2O_6^+$ $[M+H]^+$ 427.0715, found 427.0709.



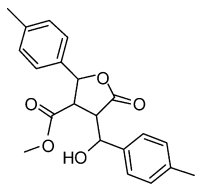
Dimethyl 2,3-Bis((2-chlorophenyl) (hydroxy)methyl)-succinate (5e). White solid. 281 mg (66%). mp 255−257 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.40−7.39 (m, 2 H), 7.32−7.31 (m, 6 H), 6.26−6.24 (m, 2 H), 4.14 (m, 2 H), 3.64−3.63 (m, 2 H), 3.32 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 173.8, 170.5, 140.2, 135.4, 135.3, 134.8, 130.7, 130.0, 129.5, 129.4, 125.8, 124.8, 123.7, 122.8, 80.1, 79.3, 50.6, 44.9; IR (KBr/cm^{-1}) ν 3522, 3313, 3045, 2946, 1770, 1746, 1597, 1498, 1445; HRMS *m/z* calcd for $C_{20}H_{21}Cl_2O_6^+$ $[M+H]^+$ 427.0715, found 427.0711.



Methyl 4-(Hydroxy(phenyl)methyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (6a). White solid. 235 mg (72%). mp 199−201 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm7.36−7.32 (m, 5 H), 7.30−7.24 (m, 5 H), 5.57 (d, 1 H, *J* = 6.0 Hz), 5.19 (d, 1 H, *J* = 9.0 Hz), 4.30 (s, 1 H), 3.30 (dd, 1 H, *J* = 7.5 Hz, *J* = 9.0 Hz), 3.20 (s, 3 H), 3.12 (dd, 1 H, *J* = 6.0 Hz, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.7, 168.8, 139.6, 133.8, 128.8, 128.4, 126.5, 125.2, 80.1, 71.3, 58.5, 51.8, 51.6, 50.9; IR (KBr/cm^{-1}) ν 3455, 3036, 2933, 1767, 1722, 1515, 1453; HRMS *m/z* calcd for $C_{19}H_{19}O_5^+$ $[M+H]^+$ 327.1232, found 327.1233.



Methyl 4-(Hydroxy(p-tolyl)methyl)-5-oxo-2-p-tolyltetrahydrofuran-3-carboxylate (6b). White solid. 98 mg (30%). mp 211−213 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.15−7.10 (m, 8 H), 5.54−5.53 (d, 1 H, *J* = 6.0 Hz), 5.13 (d, 1 H, *J* = 9.0 Hz), 4.28 (s, 1 H), 3.27 (dd, 1 H, *J* = 7.5 Hz, *J* = 9.0 Hz), 3.21 (s, 3 H), 3.09 (dd, 1 H, *J* = 6.0 Hz, *J* = 7.5 Hz), 2.33 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.0, 168.9, 138.7, 138.6, 136.8, 130.9, 129.9, 129.1, 126.5, 125.2, 80.4, 71.2, 51.9, 51.7, 51.0, 21.2; IR (KBr/cm^{-1}) ν 3452, 3033, 2920, 1768, 1721, 1514, 1441; HRMS *m/z* calcd for $C_{21}H_{23}O_5^+$ $[M+H]^+$ 355.1545, found 355.1541.



Ethyl 4-(Hydroxy(*p*-tolyl)methyl)-5-oxo-2-p-tolyltetrahydrofuran-3-carboxylate (6c). White solid. 239 mg (65%). mp 209−211 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.25−6.99 (m, 8 H), 5.51−5.49 (m, 1 H), 5.02−5.00 (m, 1 H), 3.73−3.72 (m, 1 H), 3.66−3.63 (m, 1 H), 3.55 (q, 2 H, *J* = 7.0 Hz), 3.46−3.43 (m, 1 H),

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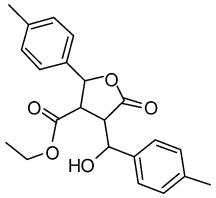
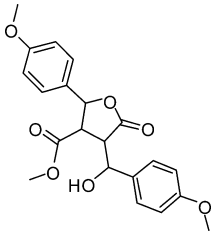
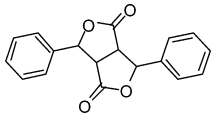
2.31 (s, 3 H), 2.30 (s, 3 H), 0.79−0.77 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.7, 168.3, 136.2, 132.2, 130.9, 129.2, 129.0, 126.4, 126.2, 125.7, 79.6, 73.7, 61.2, 49.1, 48.5, 22.7, 21.1, 14.1 ; IR (KBr/cm^{-1}) ν 3447, 3027, 2944, 1767, 1719, 1532, 1435; HRMS m/z calcd for $C_{22}H_{25}O_5^+$ $[M+H]^+$ 369.1702, found 369.1701.



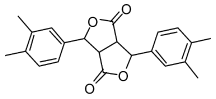
Methyl 4-(Hydroxy(4-methoxyphenyl)methyl)-2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (6d). White solid. 262 mg (68%). mp 196−198 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.20−7.15 (m, 4 H), 6.87−6.84 (m, 4 H), 5.53 (d, 1 H, J = 6.0 Hz), 5.12 (d, 1 H, J = 9.0 Hz), 4.25 (s, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.28 (dd, 1 H, J = 7.5 Hz, J = 9.0 Hz), 3.24 (s, 3 H), 3.08 (dd, 1 H, J = 6.0 Hz, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.8, 168.9, 159.9, 159.8, 131.9, 127.8, 126.7, 125.9, 114.2, 113.8, 80.2, 70.9, 55.3, 51.9, 51.6, 51.1; IR (KBr/cm^{-1}) ν 3444 3025, 2956, 1766, 1721, 1534, 1429; HRMS m/z calcd for $C_{21}H_{23}O_7^+$ $[M+H]^+$ 387.1444, found 387.1441.



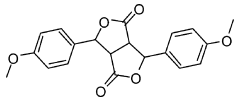
3,6-Diphenyltetrahydrofuro[3,4-*c*]furan-1,4-dione (7a). White solid. 247 mg (84%). mp 184−186 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.46−7.33 (m, 10 H), 5.90−5.89 (m, 1 H), 5.84 (m, 1 H), 3.89−3.86 (m, 1 H), 3.70−3.68 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.5, 171.1, 138.5, 133.6, 129.3, 129.2, 129.1, 128.7, 125.6, 124.6, 81.1, 80.3, 50.9, 45.4; IR (KBr/cm^{-1}) ν 3046, 2922, 1775, 1767, 1510, 1449; HRMS m/z calcd for $C_{18}H_{15}O_4^+$ $[M+H]^+$ 295.0970, found 295.0966.



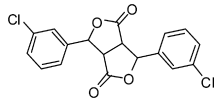
3,6-Bis(3,4-dimethylphenyl)tetrahydrofuro[3,4-*c*]furan-1,4-dione (7b). White solid. 301 mg (86%). mp 172−173 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.19−7.04 (m, 6 H), 5.83−5.82 (m, 1 H), 5.77 (m, 1 H), 3.86−3.83 (m, 1 H), 3.67−3.64 (m, 1 H), 2.28 (s, 3 H), 2.27 (s, 3 H), 2.26 (s, 3 H), 2.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.8, 171.4, 137.8, 137.6, 137.0, 135.9, 130.9, 130.3, 129.9, 126.8, 125.9, 123.1, 122.1, 81.2, 80.4, 50.9, 45.6, 19.9, 19.7, 19.5; IR (KBr/cm^{-1}) ν 3040, 2952, 1774, 1768, 1506, 1450; HRMS m/z calcd for $C_{22}H_{23}O_4^+$ $[M+H]^+$ 351.1596, found 351.1596.



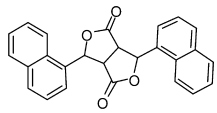
3,6-Bis(4-methoxyphenyl)tetrahydrofuro[3,4-*c*]furan-1,4-dione (7c). White solid. 290 mg (82%). mp 158−160 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.23 (d, 4 H, J = 8.5 Hz), 6.92 (d, 4 H, J = 8.5 Hz), 5.88 (s, 2 H), 3.80 (s, 6 H), 3.56 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.9, 160.2, 130.0, 126.2, 114.6, 81.9, 55.4, 48.3; IR (KBr/cm^{-1}) ν 3055, 2947, 1772, 1763, 1510, 1448; HRMS m/z calcd for $C_{20}H_{19}O_6^+$ $[M+H]^+$ 355.1182, found 355.1178.



3,6-Bis(3-chlorophenyl)tetrahydrofuro[3,4-*c*]furan-1,4-dione (7d). White solid. 279 mg (77%). mp 177−178 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.39−7.21 (m, 8 H), 5.85−5.84 (m, 1 H), 5.80 (m, 1 H), 3.87−3.84 (m, 1 H), 3.69−3.67 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 173.8, 170.5, 140.2, 135.4, 135.3, 134.8, 130.6, 130.0, 129.5, 129.4, 125.8, 124.8, 123.7, 122.8, 80.1, 79.3, 50.6, 44.9; IR (KBr/cm^{-1}) ν 3037, 2945, 1775, 1769, 1512, 1447; HRMS m/z calcd for $C_{18}H_{13}Cl_2O_4^+$ $[M+H]^+$ 363.0191, found 363.0189.



3,6-Di(naphthalen-1-yl)tetrahydrofuro[3,4-*c*]furan-1,4-dione (7e). White solid. 236 mg (60%). mp 252−254 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 8.28−8.26 (m, 1 H), 7.97−7.87 (m, 4 H), 7.74−7.67 (m, 2 H), 7.63−7.52 (m, 5 H), 7.44−7.35 (m, 2 H), 6.63 (m, 1 H), 6.55 (m, 1 H), 4.02−3.97 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.7, 170.9, 133.9, 129.8, 129.6, 129.3, 127.6, 126.9, 126.6, 1256.0, 125.5, 122.8, 122.2, 121.2, 121.0, 78.8, 78.1, 52.5, 46.9; IR (KBr/cm^{-1}) ν 3064, 2945, 1785, 1771, 1639, 1558, 1540, 1507; HRMS m/z calcd for $C_{26}H_{19}O_4^+$ $[M+H]^+$ 395.1283, found 395.1282.



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00278.

NMR data for products (PDF)

X-ray crystallographic data for compounds **3a**, **3j**, and **7b** (CIF)

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Notes

The authors declare no competing financial interest.

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