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Note

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 16 May 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

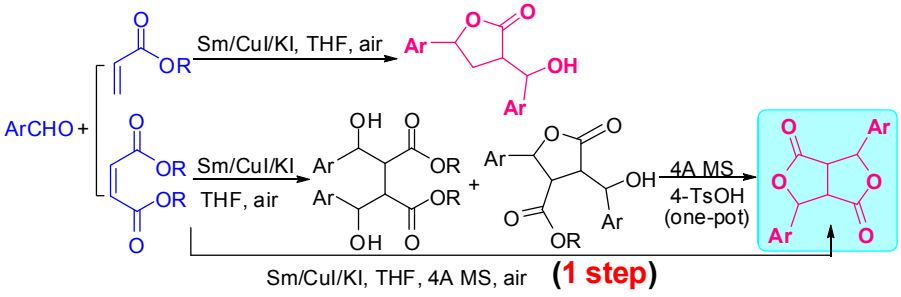
Reductive Bis-addition of Aromatic Aldehydes to α,β-Unsaturated Esters *via* the Use of Sm/Cu(I) in Air: A Route to the Construction of Furofuran Lignans

Yongjun Liu,* Guang Tian, Jingjing Li, Yan Qi, Yonghong Wen, Feng Du

State Key Laboratory Base of Eco-chemical Engineering; Key Laboratory of Eco-chemical Engineering, Ministry of Education; College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P. R. China.

yongjunliu@qust.edu.cn

ABSTRACT GRAPHIC



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 of 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] For example, 2-hydroxylbenzyl-γ-butyrolacton **II** (also see product **3a** in this paper) 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]

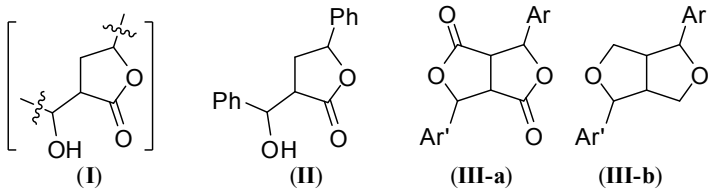


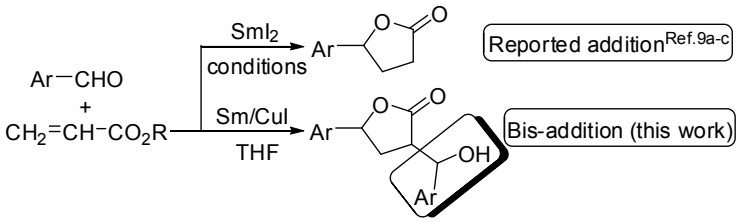
Figure 1. 2-Hydroxylbenzyl-γ-butyrolactons and furofuran lignans.

So far, the efficient syntheses for such compounds were usually involved with long reaction routes

and harsh operation conditions, such as KHMDS (-70 ºC, starting from *syn*-aldols, 3 steps),[4b] LDA (-78 ºC, from α-benzoylsuccinic ester, 4 steps),[4c,5a] LDA (-78 ºC, photochemistry, from cyclic ketene silyl acetals, 2 steps),[4d] LHMDS (-78 ºC, from β-ketoesters, 6 steps),[5d] DIBALH (-78 ºC, 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), which is fundamentally different from the known reports which mainly involved with a reductive conjugate addition promoted by SmI_2.[9a-e]

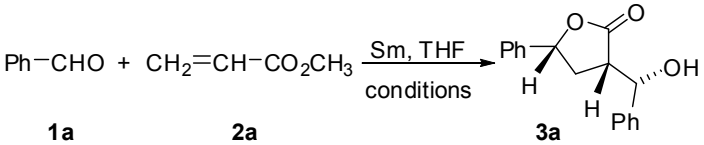
Scheme 1. Addition between Aldehydes and Acrylates



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 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 out very soon (entry 17), while no **3a** was observed at all when only SmI_2 was used in the absence of CuI (entry 18).

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



1a **2a** **3a**

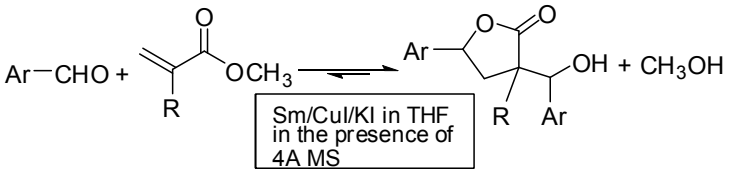
Entry[a]	Metal salt	Additive	T (ºC)	t (h)	Yield (%)[b]
1	CuI		rt	5	42[c]
2	CuI		reflux	3	31
3	CuI	KI	rt	3	61
4	CuI	KI	rt	10	67[d,e]
5	CuCl	KI	rt	3	60[d]
6	$CuCl_2$	KI	reflux	10	13[d]
7	$AgNO_3$	KI	reflux	10	16[d]
8	$Cu(OAc)_2$	KI	reflux	10	--[f]

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.

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. 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).

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

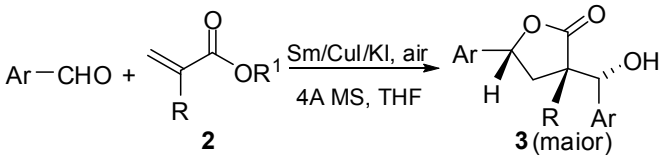


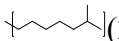
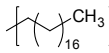
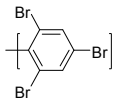
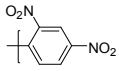
At the stage, the scope and limitation of this reaction were investigated under the optimal conditions. A variety of benzaldehydes and acrylates were compatible with the conditions to afford

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-methylacrylate (**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.

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]	

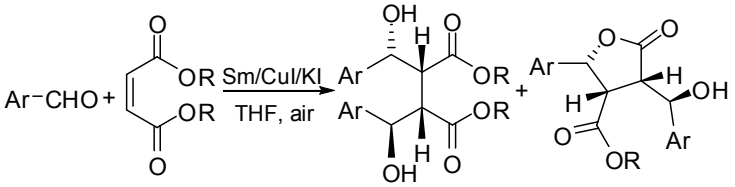
[a]Benzaldehydes (2 mmol), **2** (4 mmol), Sm (2 mmol), CuI (2 mmol), KI (4 mmol) and 4A MS in THF (15 mL) at r.t. in air. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]In the absence of 4A MS. [e]Reduction products (benzyl alcohols).

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 proved 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.

Table 3. Bis-Addition of Benzaldehydes to Maleates



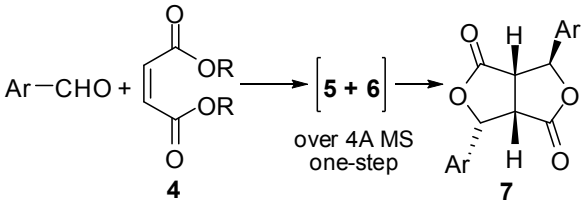
Entry[a]	Ar	R	Yield (**5** and **6**) (%)[b]
1	Ph	Et	70 (**5a**)
2	4-Me-C_6H_4	Me	73 (**5b**:**6b** = 43:30)
3	4-Et-C_6H_4	Me	75 (**5c**)
4	4-Cl-C_6H_4	Me	68 (**5d**)
5	2-Cl-C_6H_4	Me	66 (**5e**)
6	Ph	Me	72 (**6a**)
7	4-Me-C_6H_4	Et	65 (**6c**)
8	4-MeO-C_6H_4	Me	68 (**6d**)

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

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

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



Entry	Ar	R	Yield (**5** and **6**) (%)[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]Benzaldehydes (2 mmol), **4** (4 mmol), Sm (2 mmol), CuI (2 mmol), KI (4 mmol) at r. t. in dry air. [b]N_2 atmosphere. [c]4-Toluenesulfonic acid was added.

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 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 using Electrospray 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 pre-coated 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.

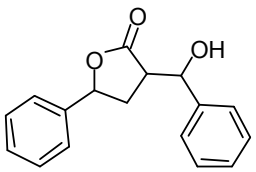
Typical procedure for the synthesis of methyl 4-(hydroxy(phenyl)methyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (6a):

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.

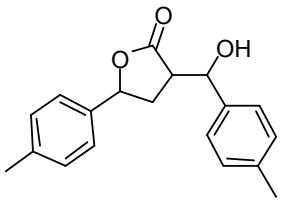
Typical procedure for the synthesis of methyl 3,6-diphenyltetrahydrofuro[3,4-c]furan-1,4-dione (7a): To a mixture of samarium powder (0.3 g, 2 mmol), cuprous iodide (0.39 g, 2 mmol), potassium iodide (0.68 g, 4 mmol) in anhydrous tetrahydrofuran (15 mL), benzaldehyde (2 mmol, 0.21 mL), dimethyl maleate (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)



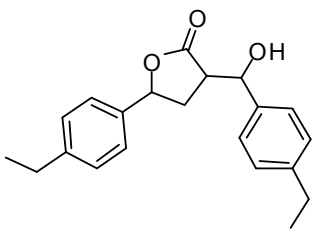
White solid. m.p. 217 mg (81 %). 184-186 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.40-7.28 (m, 10 H), 5.49 (s, 1 H), 5.35-5.31 (m, 1 H), 3.20-3.16 (m, 1 H), 2.50-2.43 (m, 2 H), 2.33-2.27 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.0, 141.4, 139.1, 128.8, 128.7, 127.9, 125.9, 125.5, 125.0, 80.0, 70.3, 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)



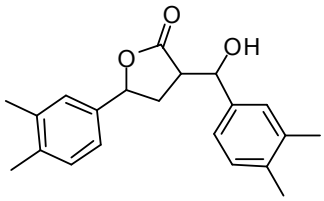
White solid. 255 mg (86 %). m.p. 164-167 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.26-7.15 (m, 8 H), 5.44 (m, 1 H), 5.30-5.27 (m, 1 H), 3.14 (m, 1 H), 2.46 (m, 2 H), 2.49 (s, 3H), 2.43 (s, 3H), 2.36 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.0, 138.5, 137.5, 136.1, 129.4, 129.3, 126.0, 125.4, 80.0, 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.

5-(4-Ethylphenyl)-3-((4-ethylphenyl)(hydroxy)methyl)dihydrofuran-2(3H)-one (3c)



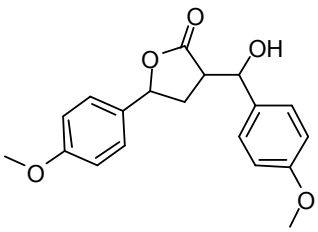
White solid. 259 mg (80 %). m.p. 144-146 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.28-7.17 (m, 8 H), 5.44 (s, 1 H), 5.30-5.27 (m, 1 H), 3.16-3.12 (m, 1 H), 2.66-2.63 (m, 4 H), 2.50-2.43 (m, 2 H), 2.32-2.26 (m, 1 H), 1.25-1.19(m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.2, 145.0, 144.0, 138.8, 136.3, 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)



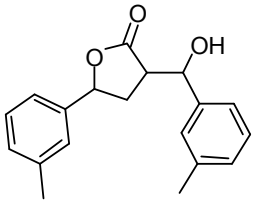
White solid. 282 mg (87 %). m.p. 134-136 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.14-7.10 (m, 6 H), 5.39 (s, 1 H), 5.27-5.24 (m, 1 H), 3.13 (m, 1 H), 2.46-2.43 (m, 2 H), 2.30-2.29 (t, 1 H), 2.28 (s, 3 H), 2.27 (s, 3 H), 2.26 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 177.1, 139.0, 137.2, 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 %). m.p. 162-164 ºC. ^{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.

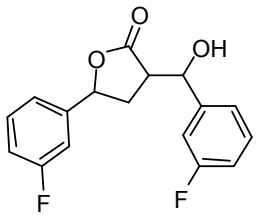
3-(Hydroxy(m-tolyl)methyl)-5-m-tolyldihydrofuran-2(3H)-one (3f)



White solid. 239 mg (81 %). m.p. 164-167 ºC. ^{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,

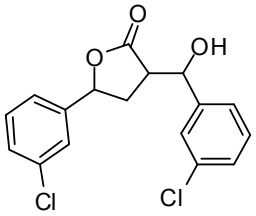
30.2, 20.9, 20.8; IR (KBr/cm^{-1}) *v* 3434, 3074, 2937, 1676, 1585, 1531, 1454; HRMS m/z calcd for $C_{19}H_{21}O_3^+$ $[M + H]^+$ 297.1491, found 297.1487.

5-(3-Fluorophenyl)-3-((3-fluorophenyl)(hydroxy)methyl)dihydrofuran-2(3H)-one (3g)



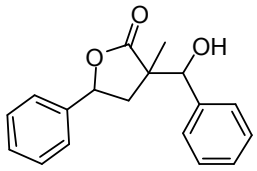
White solid. 222 mg (73 %). m.p. 156-158 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.31-7.03 (m, 8 H), 5.75-5.74 (m, 1 H), 5.64-5.62 (m, 1 H), 3.36 (m, 1 H), 2.56-2.55 (m, 1 H), 2.36-2.32 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.4, 160.6 (158.7, $J_{C\text{-}F}$ = 246.6 Hz), 159.9 (158.0 $J_{C\text{-}F}$ = 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}) *v* 3461, 3045, 2924, 1681, 1557, 1543, 1445; *v* 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)



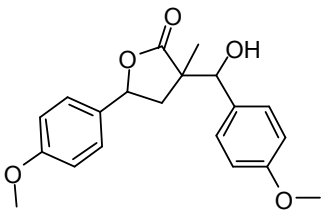
White solid. 228 mg (68 %). m.p. 166-168 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.33-7.21 (m, 8 H), 5.47-5.45 (m, 1 H), 5.31-5.28 (m, 1 H), 3.18-3.13 (m, 1 H), 2.55-2.54 (m, 1 H), 2.41-2.28 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.2, 143.4, 140.9, 134.8, 130.1, 130.0, 128.8, 128.0, 125.9, 125.6, 123.8, 123.6, 114.8, 78.9, 69.5, 49.6, 30.3; IR (KBr/cm^{-1}) *v* 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). m.p. 130-136 ºC. ^{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}) *v* 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.

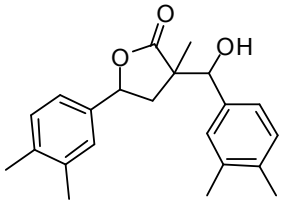
3-(Hydroxy(4-methoxyphenyl)methyl)-5-(4-methoxyphenyl)-3-methyldihydrofuran-2(3H)-one (3j)



White solid. 260 mg (76 %). Obtained together with its diastereomer (95 : 5). m.p. 160-162 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm7.32-7.24 (m, 4 H),

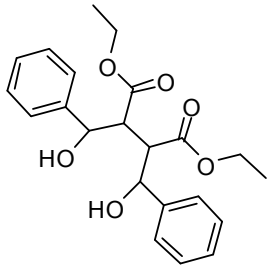
6.92-6.86 (m, 4 H), 5.36-5.32 (m, 1 H), 4.98-4.95 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.86-2.81 (m, 1 H), 2.60-2.59 (m, 1 H), 1.92-1.88 (m, 1 H), 1.18(s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 180.7, 159.9, 159.6, 131.9, 131.3, 128.3, 127.6, 114.1, 113.7, 78.4, 76.0, 55.3, 51.4, 37.5, 20.6; IR (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)



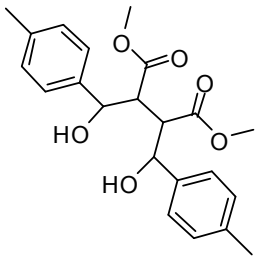
White solid. 277 mg (82 %). Obtained together with its diastereomer (80 : 20). m.p. 164-168 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm7.26-7.03 (m, 6 H), 5.45-5.32 (m, 1 H), 4.95-4.90 (s, 1 H), 3.09-2.82 (m, 1 H), 2.60-2.53 (d, 1 H), 2.30 (s, 3 H), 2.28 (s, 3 H), 2.26 (s, 3 H), 2.22 (s, 3 H), 1.95-1.71 (m, 1 H), 1.21-1.15 (s, 3 H); ^{13}C NMR (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)



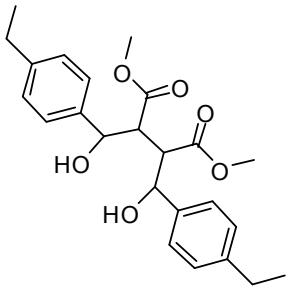
White solid. 270 mg (70 %). m.p. 255-257 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.40-7.34 (m, 10 H), 5.68-5.67 (m, 2 H), 4.31-4.29 (m, 2 H), 3.76-3.70 (m, 2 H), 3.68-3.66 (m, 2 H), 3.65-3.56 (m, 2 H), 0.73-0.71 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.8, 169.6, 134.4, 128.8, 128.4, 125.5, 81.0, 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)



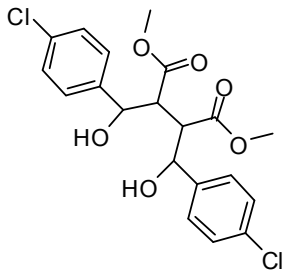
White solid. 166 mg (43 %). m.p. 252-253 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.17-7.15 (m, 4 H), 7.08-7.06 (m,4 H), 5.79-5.77 (m, 2 H), 3.83-3.78 (m, 2 H), 3.75-3.71 (m, 2 H), 3.40 (s, 6 H), 2.33 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.5, 168.9, 139.2, 131.7, 129.3, 125.8, 79.1, 52.3, 49.4, 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)



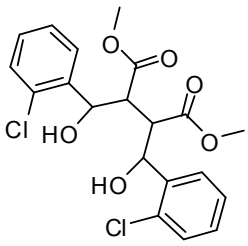
White solid. 311 mg (75 %). m.p. 254-256 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.17-7.15 (d, 4 H, J = 6.5 Hz), 7.08 (d, 4 H, J = 6.5 Hz), 5.93-5.91 (m, 2 H), 4.59-4.55 (m, 2 H), 3.56-3.53 (m, 2 H), 3.40 (s, 6 H), 2.62 (q, 4 H, J = 6.0 Hz), 1.20 (t, 6 H, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 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)



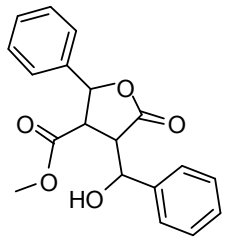
White solid. 290 mg (68 %). m.p. 262-263 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.36 (d, 4 H, J = 6.5 Hz), 7.15 (d, 4 H, J = 6.5 Hz), 5.81-5.79 (m, 2 H), 3.88-3.78 (m, 2 H), 3.70-3.66 (m, 2 H), 3.44 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.2, 169.5, 132.7, 132.3, 130.3, 129.7, 127.2, 127.0, 52.4, 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 %). m.p. 255-257 ºC. ^{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.

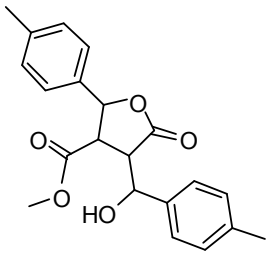
Methyl 4-(hydroxy(phenyl)methyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (6a)



White solid. 235 mg (72 %). m.p. 199-201 ºC. ^{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

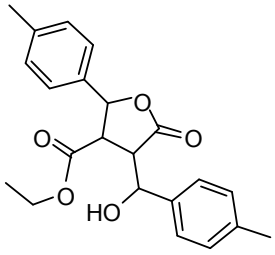
H, J = 6.0 Hz, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 176.7, 168.8, 139.6, 133.8, 128.8, 128.4, 126.5, 125.2, 80.1, 71.3, 58.5, 51.8, 51.6, 50.9; IR (KBr/cm^{-1}) ν 3455, 3036, 2933, 1767, 1722, 1515, 1453; HRMS m/z calcd for $C_{19}H_{19}O_5^+$ $[M + H]^+$ 327.1232, found 327.1233.

Methyl 4-(hydroxy(p-tolyl)methyl)-5-oxo-2-p-tolyltetrahydrofuran-3-carboxylate (6b)



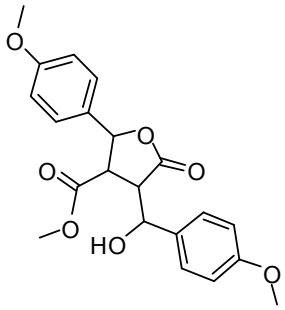
White solid. 98 mg (30 %). m.p. 211-213 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.15-7.10 (m, 8 H), 5.54-5.53 (d, 1 H, J = 6.0 Hz), 5.13 (d, 1 H, J = 9.0 Hz), 4.28 (s, 1 H), 3.27 (dd, 1 H, J = 7.5 Hz, J = 9.0 Hz), 3.21 (s, 3 H), 3.09 (dd, 1 H, J = 6.0 Hz, J = 7.5 Hz), 2.33 (s, 3 H), 2.32 (s, 3 H); ^{13}C 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 %). m.p. 209-211 ºC. ^{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), 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.

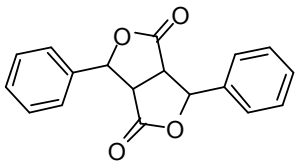
Methyl 4-(hydroxy(4-methoxyphenyl)methyl)-2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (6d)



White solid. 262 mg (68 %). m.p. 196-198 ºC. ^{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,

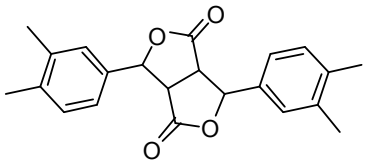
1534, 1429; HRMS m/z calcd for $C_{21}H_{23}O_7^+$ $[M + H]^+$ 387.1444, found 387.1441.

3,6-Diphenyltetrahydrofuro[3,4-c]furan-1,4-dione (7a)



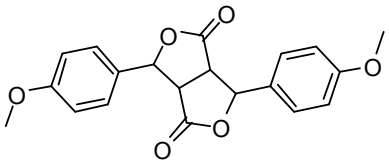
White solid. 247 mg (84 %). m.p. 184-186 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.46-7.33 (m, 10 H), 5.90-5.89 (m, 1 H) , 5.84 (m, 1 H), 3.89-3.86 (m, 1 H), 3.70-3.68 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.5, 171.1, 138.5, 133.6, 129.3, 129.2, 129.1, 128.7, 125.6, 124.6, 81.1, 80.3, 50.9, 45.4; 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)



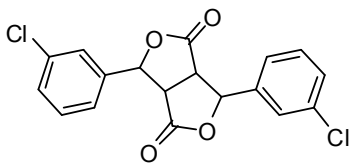
White solid. 301 mg (86 %). m.p. 172-173 ºC. ^{1}HNMR (500 MHz, $CDCl_3$) δppm 7.19-7.04 (m, 6 H), 5.83-5.82 (m, 1 H) , 5.77 (m, 1 H), 3.86-3.83 (m, 1 H), 3.67-3.64 (m, 1 H), 2.28 (s, 3 H) , 2.27 (s, 3 H) , 2.26 (s, 3 H) , 2.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δppm 174.8, 171.4, 137.8, 137.6, 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 %). m.p. 158-160 ºC. ^{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.

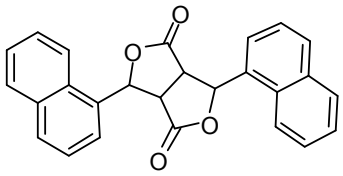
3,6-Bis-(3-chlorophenyl)tetrahydrofuro[3,4-c]furan-1,4-dione (7d)



White solid. 279 mg (77 %). m.p. 177-178 ºC. ^{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 %). m.p. 252-254 ºC. ^{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}) *v* 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.

ACKNOWLEDGMENTS

The project sponsored by the Promotive Research Fund for Excellent Young and Middle-Aged Scientists of Shandong Province (BS2011CL019), and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (Project No. [2007]1108).

Supporting Information Available: CIF files of crystal data, NMR data for products. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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