Multisubstituted α,β-Unsaturated γ-Lactones from 1-Chlorovinyl *p*-Tolyl Sulfoxides and *tert*-Butyl Carboxylates Using Pummerer-Type Cyclization as the Key Reaction

Takashi Katae, Shimpei Sugiyama, Tsuyoshi Satoh*

Graduate School of Chemical Sciences and Technology, Tokyo University of Science, Ichigaya-Funagawara-machi 12, Shinjuku-ku, Tokyo 162-0826, Japan
Fax +81(3)52614631; E-mail: tsatoh@rs.kagu.tus.ac.jp
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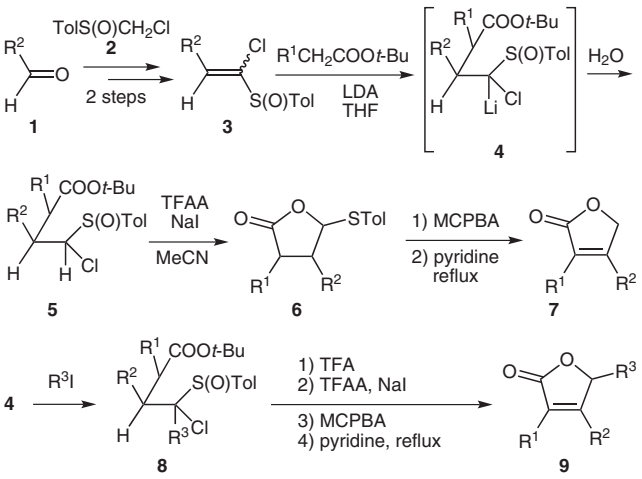
Abstract: The addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides, derived from aldehydes and chloromethyl *p*-tolyl sulfoxide, with the lithium enolate of *tert*-butyl carboxylates gave adducts in quantitative yields. Treatment of the adducts with trifluoroacetic anhydride in the presence of sodium iodide resulted in the formation of γ-lactones bearing a *p*-tolylsulfanyl group at the γ-position through Pummerer-type cyclization. Oxidation of the sulfanyl group to the sulfinyl group followed by thermal *syn*-elimination gave α,β-unsaturated γ-lactones (γ-butenolides) in moderate to good yields. Trapping the intermediates of the addition reaction with iodoalkanes gave alkylated adducts, from which α,γ- and β,γ-disubstituted γ-butenolides were obtained. These procedures provide a good way to synthesize multisubstituted γ-butenolides from aldehydes.

Key words: γ-butenolide, γ-lactones, α,β-unsaturated γ-lactones, sulfoxides, Pummerer reaction

α,β-Unsaturated γ-lactone (γ-butenolide) is a skeletal structure that is quite often found in biologically active natural products.[1] γ-Butenolides are also very important compounds in synthetic organic chemistry. Although a few methods for the synthesis of γ-butenolides and natural products having the γ-butenolide skeletal structure have been reported,[2] development of new methods for the synthesis of such compounds is still an important subject in organic synthesis. In previous studies, we reported a new synthesis, including an asymmetric synthesis, of γ-lactones from 1-chlorovinyl *p*-tolyl sulfoxides and *tert*-butyl carboxylates using Pummerer-type cyclization as the key reaction.[3] In a continuation of our interest in developing new methods for the synthesis of γ-lactones, we recently established a method for the synthesis of multisubstituted γ-butenolides from aldehydes by using our methods.

Thus, as shown in Scheme 1, 1-chlorovinyl *p*-tolyl sulfoxides **3** were synthesized from aldehydes **1** with chloromethyl *p*-tolyl sulfoxide **2** in two steps in almost quantitative yields.[3d] Addition reaction of **3** with the lithium enolate of *tert*-butyl carboxylates gave adducts **5** through lithium α-sulfinyl carbanion intermediates **4**. Treatment of adducts **5** with trifluoroacetic anhydride (TFAA) in the presence of NaI resulted in the formation of γ-lactones **6**, bearing a *p*-tolylsulfanyl group at the γ-position, in good to high yields by using Pummerer-type cyclization.[3] γ-Sulfanyl γ-lactones **6** were oxidized with *m*-chloroperbenzoic acid (MCPBA)[4] and the resulting sulfoxides were heated under reflux in pyridine[5] to afford α-, β-substituted and α,β-disubstituted γ-butenolides **7** in moderate to good yields. When the intermediates **4** were trapped with iodoalkanes,[6] alkylated adducts **8** were obtained. From **8**, α,γ- and β,γ-disubstituted γ-butenolides **9** were obtained. In this paper, the results described above are presented in detail.



Scheme 1

A representative result illustrating this study starting from 3-phenylpropanal is reported as follows (Scheme 2). 1-Chlorovinyl *p*-tolyl sulfoxide **10** was synthesized from 3-phenylpropanal and chloromethyl *p*-tolyl sulfoxide in quantitative yield as a mixture of two geometrical isomers.[3d] Treatment of the mixture of **10** with the lithium enolate of *tert*-butyl acetate resulted in the formation of adduct **11** in quantitative yield as a mixture of two diastereomers. The mixture of adduct **11** was treated with TFAA (5 equiv) in the presence of NaI (5 equiv) in acetonitrile at –40 °C to give γ-lactones **12**, bearing a *p*-tolyl sulfanyl group at the γ-position, in 93% yield through Pummerer-type cyclization.[3] The product **12** was found to be a 10:1 mixture of two separable diastereomers, and the main product was shown to have *trans* configuration by ^{1}H NMR analysis.

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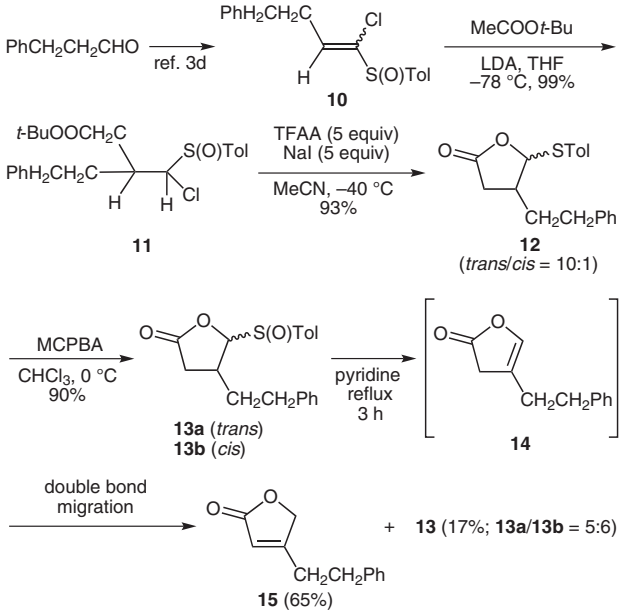


Scheme 2

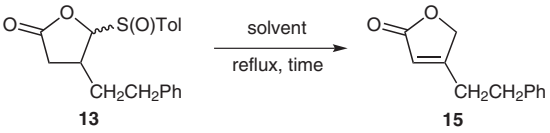
Without separation of the two diastereomers, the sulfanyl group in **12** was oxidized with MCPBA in chloroform at 0 °C to give sulfoxide **13** in 90% yield as a mixture of two configurational isomers (**13a** and **13b**). Thermal *syn*-elimination of sulfoxide **13** in refluxing pyridine[5] resulted in the formation of γ-butenolide **15**, having a 2-phenylethyl group at the β-position, in 65% yield, and a mixture of sulfoxide **13** was recovered in 17% yield. Clearly, the thermal *syn*-elimination of **13** was not complete. In this reaction, the initially produced β,γ-unsaturated γ-lactone **14** was not observed at all. Moreover, separation of **15** and **13** by silica gel column chromatography was found to be straightforward.

We further investigated the conditions for the thermal *syn*-elimination of **13**; the results are summarized in Table 1. Thus, **13** was heated under reflux for three hours in either pyridine, toluene, *N*,*N*-dimethylformamide (DMF) or dimethylsulfoxide (DMSO) (entries 1–4), and toluene was found to be the only unsuitable solvent. Compound **13** was then heated at reflux for 12 hours in *N*,*N*-dimethylformamide or pyridine (entries 5 and 6), and it was found that the best yield (76%) was obtained by using the conditions given in entry 6. The yield of **15** was not affected by prolonging the heating to 24 hours (entry 7). As a result, the conditions shown in entry 6 were found to be the conditions of choice and these conditions were thus used throughout this study.

With optimized conditions for the thermal *syn*-elimination in hand, the substrate scope of this procedure was investigated; the results are summarized in Table 2.

γ-Sulfinyl γ-lactones **16** used in entries 1 and 2 were synthesized from methyl formate[7] and *tert*-butyl 4-phenylbutyrate and ethyl phenylacetate, respectively. α-Substituted γ-butenolides **17a** and **17b** were obtained in good to high yields. γ-Sulfinyl γ-lactones **16** used in entries 3–5 were synthesized from benzaldehyde, 2-thiophenecarboxaldehyde and 2-furaldehyde, respectively, with *tert*-butyl acetate. The yields of β-substituted γ-butenolides **17c–e** were good, however, because of the unstable nature of the furan ring, the yield of **17e** was found to be somewhat low (entry 5). By applying this procedure, α,β-disubstituted γ-butenolides **17f–h** were obtained in up to 94% yield (entries 6–8).

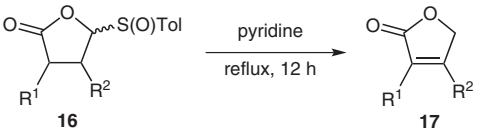
Table 1 Conditions for the Thermal Elimination of Sulfoxide **13**



Entry	Solvent	Time (h)	Yield of **15** (%)[a]
1	pyridine	3	65
2	toluene	3	40
3	DMF	3	69
4	DMSO	3	67
5	DMF	12	61
6	pyridine	12	76
7	pyridine	24	75

[a] Isolated yield.

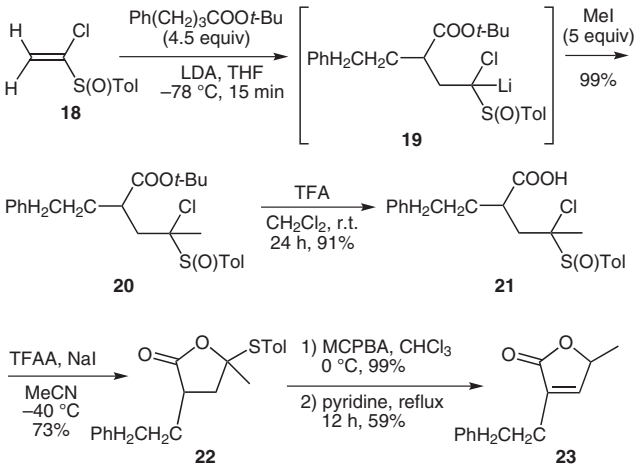
Table 2 Synthesis of α-, β-, and α,β-Disubstituted γ-Butenolide **17** from **16**



Entry	**16**		**17**	Yield (%)[a]
	R^1	R^2		
1	$PhCH_2CH_2$	H	**17a**	90
2	Ph	H	**17b**	78[b]
3	H	Ph (*trans*/*cis* = 4:1)	**17c**	82
4	H	2-thienyl (*trans*/*cis* = 3.1:1)	**17d**	76
5	H	2-furyl (*trans*/*cis* = 2:1)	**17e**	65
6	$PhCH_2CH_2$	$PhCH_2CH_2$	**17f**	72
7	$PhCH_2CH_2$	2-thienyl	**17g**	94
8	$PhCH_2CH_2$	2-furyl	**17h**	56

[a] Isolated yield.
[b] Ethyl phenylacetate was used as the ester and the adduct was hydrolyzed to a carboxylic acid by treatment with KOH in methanol before applying TFAA/NaI.

Next, we planned for the synthesis of γ-substituted γ-butenolides. A representative example is reported starting from 1-chlorovinyl *p*-tolyl sulfoxide (**18**)[7] (Scheme 3). Thus, the reaction of the lithium enolate of *tert*-butyl 4-phenylacetate (4.5 equiv) with **18** at –78 °C resulted in the formation of the lithium α-sulfinyl carbanion intermediate **19**. Addition of iodomethane (5 equiv) to the carbanion gave methylated adduct **20** in quantitative yield.[6] Initially, **20** was treated with TFAA/NaI; however, no lactone formation reaction was observed. To overcome this problem, the *tert*-butyl ester group in **20** was converted into the corresponding carboxylic acid under conventional conditions to give **21** in 91% yield. Carboxylic acid **21** was then treated with TFAA/NaI in acetonitrile to afford the desired γ-methylated γ-lactone **22** in 73% yield. Methylated γ-lactone **22** was oxidized with MCPBA and the resultant sulfoxide (99% yield) was heated under reflux in pyridine to afford the desired γ-substituted γ-butenolide **23** in 59% yield.

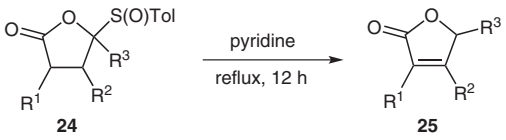


Scheme 3

Other examples for the synthesis of γ-substituted γ-butenolides **25** are summarized in Table 3. The procedure carried out with allyl iodide is shown in entry 1. Although the yield was moderate, α,γ-disubstituted γ-butenolide, bearing an allyl group at the γ-position **25a**, was obtained. Entries 2 and 3 show the synthesis of β,γ-disubstituted γ-butenolides. Again, the yield for the β,γ-disubstituted γ-butenolide, bearing a furyl group at the γ-position, was found to be low (entry 3).

Finally, the procedure described above was extended to the synthesis of α-amino-substituted γ-butenolides **28**. The complete sequence is shown in Table 4. At first, 1-chlorovinyl *p*-tolyl sulfoxide **3** was treated with the lithium enolate of *N*,*N*-dibenzylglycine *tert*-butyl ester (7.5 equiv) in tetrahydrofuran at –45 °C for one hour to give adduct **26** in almost quantitative yield as a mixture of two diastereomers with respect to the carbon bearing the R^2 group.[7] Adduct **26** was treated with TFAA/NaI under the aforementioned conditions to give γ-sulfanyl γ-lactones, bearing a dibenzylamino group at the α-position **27**, in up to 85% yield. Finally, oxidation with MCPBA followed by thermal *syn*-elimination of **27** resulted in the formation of the desired α-amino-substituted γ-butenolides **28** in up to 67% yield.

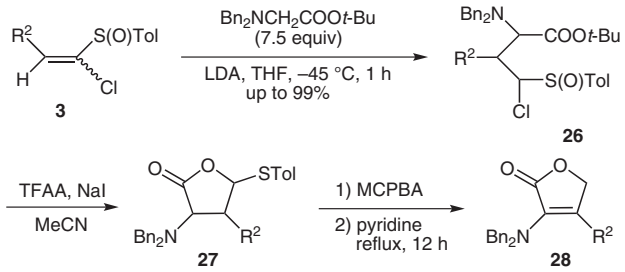
Table 3 Synthesis of α,γ- and β,γ-Disubstituted γ-Butenolides **25** from **24**



Entry	**24**			**25**	Yield (%)[a]
	R^1	R^2	R^3		
1	$PhCH_2CH_2$	H	$CH_2CH{=}CH_2$	**25a**	44
2	H	2-thienyl	Me (*trans*/*cis* = 1:1)	**25b**	48
3	H	2-furyl	Me (*trans*/*cis* = 1:1)	**25c**	20

[a] Isolated yield.

Table 4 Synthesis of γ-Butenolides **28** Bearing a Dibenzylamino Group at the α-Position



Entry	**27**	R^2	Yield (%)[a,b]	**28**	Yield (%)[a,c]
1	**27a**	H	33	**28a**	50
2	**27b**	$PhCH_2CH_2$	85[d]	**28b**	67
3	**27c**	2-thienyl	81[e]	**28c**	59
4	**27d**	2-furyl	71[f]	**28d**	33

[a] Isolated yield.
[b] Yield from **26**.
[c] Two-step overall yield from **27**.
[d] Ratio *trans*/*cis* not determined.
[e] Ratio *trans*/*cis* = 7:1.
[f] Ratio *trans*/*cis* = 3:1.

In conclusion, a method for the synthesis of multisubstituted γ-butenolides was realized by Pummerer-type cyclization of 4-chloro-4-(*p*-tolylsulfinyl)butyric acid esters, which were synthesized from aldehydes, with TFAA/NaI as the key reaction. Although a synthesis of fully substituted γ-butenolides could not be achieved, the procedure presented in this paper would contribute to the synthesis of several γ-butenolides.

All melting points were measured with a Yanaco MP-S3 apparatus and are uncorrected. ^{1}H NMR spectra were measured from samples dissolved in $CDCl_3$ with JEOL JNM-LA 300, 500, Bruker DPX

400, or AV 600 spectrometers. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion with a HITACHI M-80B mass spectrometer. IR spectra were recorded with a Perkin–Elmer Spectrum One FTIR instrument. Silica gel 60 N (Kanto Chemical) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography; products with UV absorption were detected by UV irradiation. In experiments requiring anhydrous solvents and reagents, THF was distilled from diphenyl ketyl. Diisopropylamine, pyridine, toluene, DMF and DMSO were distilled from CaH_2. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware that was flame-dried under a positive pressure of argon. Compounds 3-phenyl-5*H*-furan-2-one (**17b**),[8] 4-phenyl-5*H*-furan-2-one (**17c**),[9] 4-thiophen-2-yl-5*H*-furan-2-one (**17d**),[9] 2′*H*-[2,3′]bifuranyl-5′-one (**17e**)[10] are all known in the literature.

tert-Butyl 3-[Chloro(*p*-tolylsulfinyl)methyl]-5-phenylpentanoate (11)

tert-Butyl acetate (3.4 mL, 25 mmol) was added to a solution of LDA (25 mmol) in anhydrous THF (62.5 mL) at –78 °C with stirring. The solution was stirred for 15 min, then a solution of **10** (1.52 g, 5 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 10 min at –78 °C, and the reaction was quenched by adding sat. aq NH_4Cl (50 mL). The mixture was extracted with $CHCl_3$ (2 × 50 mL) and the product was purified by silica gel column chromatography (hexane–EtOAc) to afford **11**[3d] (2.1 g, 99%) as a colorless oil.

4-(2-Phenylethyl)-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (12)

A solution of NaI (3.75 g, 25 mmol) in MeCN (90 mL) was stirred for 15 min at –40 °C. TFAA (3.47 mL, 25 mmol) was added dropwise with stirring at –40 °C and the solution was stirred for 15 min. Ester **11** (2.1 g, 5 mmol) in MeCN (5 mL) was added dropwise at –40 °C with stirring and the reaction mixture was stirred for 10 min. The reaction was quenched by adding sat. aq $NaHCO_3$ (25 mL) followed by sat. aq Na_2SO_3 (25 mL). The mixture was extracted with $CHCl_3$ (2 × 50 mL), the organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **12**.

Yield: 1.45 g (93%); colorless oil; ca. 10:1 mixture of two diastereomers.

IR (neat): 2923, 1789 (CO), 1494, 1454, 1205, 1144, 957, 813, 751, 701, 457 cm^{-1}.

^1H NMR (500 MHz): δ = 1.66–1.82 (m, 1 H), 2.01–2.16 (m, 1 H), 2.17–2.30 (m, 1 H), 2.31–2.46 (m, 1 H), 2.34 (s, 3 H), 2.51–2.8 (m, 3 H), 5.34 (d, *J* = 6.36 Hz, 0.91 H), 5.78 (d, *J* = 6.93 Hz, 0.09 H), 7.07–7.47 (m, 9 H).

MS: *m*/*z* (%) = 312 (8) $[M]^+$, 189 (20), 143 (16), 129 (100), 124 (35), 117 (12), 91 (64).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{20}O_2S$: 312.1183; found: 312.1182.

4-(2-Phenylethyl)-5*H*-furan-2-one (15)

MCPBA (85.1 mg, 0.37 mmol) was added to a solution of **12** (103 mg, 0.33 mmol) in $CHCl_3$ (6 mL) at 0 °C with stirring. The solution was stirred for 30 min, and the reaction was quenched by adding sat. aq Na_2SO_3 (5 mL) and sat. aq $NaHCO_3$ (5 mL). The mixture was extracted with $CHCl_3$ (2 × 20 mL) and the organic layer was washed with 5% aq NaOH (10 mL) and dried over $MgSO_4$. The product was purified by silica gel column chromatography (hexane–EtOAc) to give **13**[4b] (98.5 mg, 90%) as a colorless oil. A solution of γ-sulfinyl γ-lactone **13** (98.5 mg, 0.3 mmol) in distilled pyridine (6 mL) was heated at reflux for 12 h. Toluene (6 mL) was added and the mixture was evaporated three times. The residue was purified by silica gel column chromatography (hexane–EtOAc) to afford **15**.

Yield: 42.7 mg (76%); colorless crystals; mp 52.5–53 °C (hexane–EtOAc).

IR (KBr): 2948, 1784, 1733 (CO), 1635, 1173, 1130, 1038, 998, 892, 846, 757, 716, 704 cm^{-1}.

^1H NMR (500 MHz): δ = 2.7–2.79 (m, 2 H), 2.88–2.97 (m, 2 H), 4.65–4.69 (m, 2 H), 5.84–5.89 (m, 1 H), 7.15–7.35 (m, 5 H).

MS: *m*/*z* (%) = 188 (30) $[M]^+$, 97 (21), 91 (100).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}O_2$: 188.0834; found: 188.0837.

3-(2-Phenylethyl)-5*H*-furan-2-one (17a)

Colorless oil.

IR (neat): 2929, 1747 (CO), 1497, 1454, 1348, 1203, 1082, 1069, 1050, 831, 751, 700 cm^{-1}.

^1H NMR (400 MHz): δ = 2.59–2.71 (m, 2 H), 2.85–2.98 (m, 2 H), 4.71–4.78 (m, 2 H), 6.98–7.06 (m, 1 H), 7.14–7.35 (m, 5 H).

MS: *m*/*z* (%) = 188 (33) $[M]^+$, 91 (100).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}O_2$: 188.0834; found: 188.0831.

3,4-Di(2-phenylethyl)-5*H*-furan-2-one (17f)

Colorless oil.

IR (neat): 2927, 1747 (CO), 1671, 1496, 1454, 1081, 1068, 1030, 752, 701 cm^{-1}.

^1H NMR (400 MHz): δ = 2.37–2.57 (m, 6 H), 2.71–2.81 (m, 2 H), 4.48 (s, 2 H), 7.00–7.08 (m, 2 H), 7.10–7.34 (m, 8 H).

MS: *m*/*z* (%) = 292 (57) $[M]^+$, 91 (100).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{20}O_2$: 292.1462; found: 292.1461.

3-(2-Phenylethyl)-4-thiophen-2-yl-5*H*-furan-2-one (17g)

Colorless crystals; mp 101–101.5 °C (hexane–EtOAc).

IR (KBr): 2934, 1744 (CO), 1732 (CO), 1641, 1451, 1423, 1351, 1082, 1038, 723, 701 cm^{-1}.

^1H NMR (400 MHz): δ = 2.91 (m, 4 H), 5.09 (s, 2 H), 7.16 (dd, *J* = 3.7, 5.1 Hz, 1 H), 7.19–7.24 (m, 2 H), 7.28–7.33 (m, 4 H), 7.60 (dd, *J* = 1.1, 5.1 Hz, 1 H).

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 70.98; H, 5.19; S, 11.83.

4′-(2-Phenylethyl)-2′*H*-[2,3′]bifuranyl-5′-one (17h)

Colorless crystals; mp 61.5–62 °C (hexane–EtOAc).

IR (KBr): 2934, 1731 (CO), 1659, 1342, 1172, 1065, 1040, 1022, 928, 770, 760, 697 cm^{-1}.

^1H NMR (400 MHz): δ = 2.82–2.97 (m, 4 H), 5.01 (s, 2 H), 6.55 (dd, *J* = 1.8, 3.5 Hz, 1 H), 6.65 (d, *J* = 3.5 Hz, 1 H), 7.12–7.39 (m, 5 H), 7.59 (d, *J* = 1.8 Hz, 1 H).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.25; H, 5.44.

tert-Butyl 4-Chloro-2-(2-phenylethyl)-4-(*p*-tolylsulfinyl)pentanoate (20)

tert-Butyl 4-phenylbutyrate (440 mg, 2 mmol) was added to a solution of LDA in anhydrous THF (12 mL) at –78 °C with stirring. The mixture was stirred for 15 min, then a solution of **18** (100 mg, 0.5 mmol) in anhydrous THF (1 mL) was added. After stirring the mixture for 5 min at –78 °C, MeI (354 mg, 2.5 mmol) was added and the mixture was stirred for 5 min. The reaction was quenched by addition of sat. aq NH_4Cl (30 mL) and the mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was evaporated to give a residue, which was purified by silica gel column chromatography (hexane–EtOAc) to afford methylated adduct **20**.[4b]

Yield: 208 mg (99%); colorless crystals.

5-Methyl-3-(2-phenylethyl)-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (22)
Trifluoroacetic acid (TFA, 0.56 mL, 7.5 mmol) was added to a solution of **20** (208 mg, 0.5 mmol) in $CHCl_3$ (10 mL) at r.t. The reaction mixture was stirred for 1 d and the reaction was quenched by addition of sat. aq $NaHCO_3$ (20 mL). The mixture was extracted with $CHCl_3$ (3 × 20 mL) and the aqueous layer was separated. The aqueous layer was acidified with aq 10% HCl and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were evaporated to give carboxylic acid **21** (172 mg, 91%) as colorless crystals.

A solution of NaI (0.67 g, 4.5 mmol) in MeCN (16.2 mL) was stirred for 15 min at –40 °C then TFAA (0.62 mL, 4.5 mmol) was added dropwise with stirring at –40 °C and the solution was stirred for 15 min. Carboxylic acid **21** (172 mg, 0.45 mmol) in MeCN (1 mL) was added dropwise at –40 °C with stirring and the reaction mixture was stirred for 10 min. The reaction was quenched by addition of sat. aq $NaHCO_3$ (15 mL) followed by sat. aq Na_2SO_3 (15 mL). The mixture was extracted with $CHCl_3$ (2 × 30 mL) and the organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane–EtOAc) to give **22**[4b] (112 mg, 73%) as colorless crystals.

5-Methyl-3-(2-phenethyl)-5*H*-furan-2-one (23)
MCPBA (80.5 mg, 0.35 mmol) was added to a solution of **22** (112 mg, 0.32 mmol) in $CHCl_3$ (4 mL) at 0 °C with stirring. The solution was stirred for 30 min, and the reaction was quenched by addition of sat. aq Na_2SO_3 (3 mL) and sat. aq $NaHCO_3$ (3 mL). The mixture was extracted with $CHCl_3$ (3 × 20 mL) and the organic layer was washed with 5% aq NaOH (5 mL) and dried over $MgSO_4$. The product was purified by silica gel column chromatography (hexane–EtOAc) to give γ-sulfinyl γ-lactone (113 mg, 99%) as colorless crystals.

The γ-sulfinyl γ-lactone (113 mg, 0.32 mmol) was heated at reflux in distilled pyridine (6 mL) for 12 h. To the solution was added toluene (6 mL) and the mixture was evaporated three times. The residue was purified by silica gel column chromatography (hexane–EtOAc) to afford **23**.

Yield: 38.2 mg (59%); colorless oil.

IR (neat): 2932, 1748 (CO), 1497, 1455, 1320, 1119, 1095, 1082, 1029, 1013, 751, 701 cm^{-1}.

^1H NMR (400 MHz): δ = 1.35 (d, *J* = 7.0 Hz, 3 H), 2.54–2.66 (m, 2 H), 2.83–2.93 (m, 2 H), 4.89–4.99 (m, 1 H), 6.83–6.88 (m, 1 H), 7.12–7.23 (m, 3 H), 7.24–7.32 (m, 2 H).

MS: *m*/*z* (%) = 202 (39) $[M]^+$, 173 (9), 157 (25), 65 (12).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}O_2$: 202.0995; found: 202.0996.

5-Allyl-3-(2-phenylethyl)-5*H*-furan-2-one (25a)
Colorless oil.

IR (neat): 2924, 1752 (CO), 1497, 1455, 1335, 1087, 1060, 1032, 997, 924, 749, 701 cm^{-1}.

^1H NMR (400 MHz): δ = 2.28–2.51 (m, 2 H), 2.56–2.72 (m, 2 H), 2.83–2.94 (m, 2 H), 4.83–4.94 (m, 1 H), 5.07–5.13 (m, 1 H), 5.14–5.17 (m, 1 H), 5.59–5.76 (m, 1 H), 6.84–6.90 (m, 1 H), 7.13–7.24 (m, 3 H), 7.26–7.34 (m, 2 H).

MS: *m*/*z* (%) = 228 (36) $[M]^+$, 187 (20), 169 (8), 141 (9), 129 (8), 65 (8).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{16}O_2$: 228.1150; found: 228.1150.

5-Methyl-4-thiophen-2-yl-5*H*-furan-2-one (25b)
Colorless oil.

IR (neat): 3101, 1748 (CO), 1615, 1423, 1320, 1168, 1056, 961, 845 cm^{-1}.

^1H NMR (400 MHz): δ = 1.65 (d, *J* = 6.6 Hz, 3 H), 5.42 (dq, *J* = 1.3, 6.6 Hz, 1 H), 6.14 (d, *J* = 1.3 Hz, 1 H), 7.16 (dd, *J* = 3.8, 5.1 Hz, 1 H), 7.30 (dd, *J* = 1.0, 3.8 Hz, 1 H), 7.57 (dd, *J* = 1.0, 5.1 Hz, 1 H).

MS: *m*/*z* (%) = 180 (95) $[M]^+$, 165 (13), 137 (88), 108 (100), 69 (12), 65 (10), 63 (10).

HRMS: *m*/*z* $[M]^+$ calcd for $C_9H_8O_2S$: 180.0245; found: 180.0245.

2′-Methyl-2′*H*-[2,3′]bifuranyl-5′-one (25c)
Colorless oil.

IR (neat): 3125, 1748 (CO), 1634, 1321, 1214, 1169, 1085, 1054, 1026, 987, 757 cm^{-1}.

^1H NMR (400 MHz): δ = 1.63 (d, *J* = 6.7 Hz, 3 H), 5.36 (dq, *J* = 1.4, 6.7 Hz, 1 H), 6.17 (d, *J* = 1.4 Hz, 1 H), 6.57 (dd, *J* = 1.8, 3.6 Hz, 1 H), 6.76 (d, *J* = 3.6 Hz, 1 H), 7.61 (d, *J* = 1.8 Hz, 1 H).

MS: *m*/*z* (%) = 164 (93) $[M]^+$, 149 (27), 121 (100), 92 (66), 63 (21).

HRMS: *m*/*z* $[M]^+$ calcd for $C_9H_8O_3$: 164.0472; found: 164.0471.

3-Dibenzylamino-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (27a)
A solution of *N*,*N*-dibenzylglycine *tert*-butyl ester (1.17 g, 3.75 mmol) in THF (5 mL) was added to a solution of LDA (3.75 mmol) in anhydrous THF (18 mL) at –45 °C with stirring. The solution was stirred for 15 min, then **18** (0.1 g, 0.5 mmol) was added. The solution was stirred for 1 h at –45 °C, and the reaction was quenched by adding sat. aq NH_4Cl (20 mL). The mixture was extracted with $CHCl_3$ (2 × 20 mL) and the organic layer was washed with sat. aq NH_4Cl (2 × 20 mL). The product was purified by silica gel column chromatography (hexane–EtOAc) to afford the adduct (0.189 g, 74%) as colorless crystals.

A solution of NaI (0.277 g, 1.85 mmol) in MeCN (6.7 mL) was stirred for 15 min at –40 °C, TFAA (0.257 mL, 1.85 mmol) was added dropwise with stirring at –40 °C and the solution was stirred for 15 min. The adduct (0.189 g, 0.37 mmol) in MeCN (3 mL) was added dropwise to the solution of NaI and TFAA at –40 °C dropwise with stirring and the reaction mixture was stirred for 10 min. The reaction was quenched by addition of sat. aq $NaHCO_3$ (5 mL) followed by sat. aq Na_2SO_3 (5 mL). The mixture was extracted with $CHCl_3$ (2 × 10 mL), the organic layer was dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc) to give **27a**[7] (49.8 mg, 33%).

3-Dibenzylamino-5*H*-furan-2-one (28a)
MCPBA (31.1 mg, 0.135 mmol) was added to a solution of **27a** (49.8 mg, 0.123 mmol) in $CHCl_3$ (4 mL) at 0 °C with stirring. The solution was stirred for 30 min, and the reaction was quenched by addition of sat. aq Na_2SO_3 (3 mL) and sat. aq $NaHCO_3$ (3 mL). The mixture was extracted with $CHCl_3$ (3 × 10 mL), and the organic layer was washed with 5% aq NaOH (6 mL) and dried over $MgSO_4$. The product was purified by silica gel column chromatography (hexane–EtOAc) to give the γ-sulfinyl γ-lactone (36.6 mg, 71%). The γ-sulfinyl γ-lactone (36.6 mg, 0.087 mmol) in distilled pyridine (6 mL) was heated at reflux for 12 h, then toluene (6 mL) was added and the mixture was evaporated three times. The residue was purified by silica gel column chromatography (hexane–EtOAc) to afford **28a**.

Yield: 17 mg (70%); colorless oil.

IR (neat): 3030, 1748 (CO), 1634, 1495, 1455, 1351, 1120, 1079, 1057, 1017, 773, 747, 699 cm^{-1}.

^1H NMR (500 MHz): δ = 4.49 (s, 4 H), 4.68 (d, *J* = 2.3 Hz, 2 H), 5.71 (t, *J* = 2.3 Hz, 1 H), 7.18–7.37 (m, 10 H).

MS: *m/z* (%) = 279 (39) [M]$^+$, 188 (100), 91 (88), 65 (13).

HRMS: *m/z* [M]$^+$ calcd for $C_{18}H_{17}NO_2$: 279.1260; found: 279.1261.

3-Dibenzylamino-4-(2-phenylethyl)-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (27b)
Colorless oil.

IR (neat): 3028, 1771 (CO), 1494, 1455, 1216, 1139, 960, 753, 699 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.67–1.9 (m, 2 H), 2.20 (s, 3 H), 2.28–2.41 (m, 1 H), 2.45–2.68 (m, 2 H), 3.44–3.59 (m, 3 H), 3.8 (d, *J* = 13.6 Hz, 2 H), 5.11 (d, *J* = 9.2 Hz, 1 H), 7.02–7.12 (m, 4 H), 7.17–7.40 (m, 15 H).

MS: *m/z* (%) = 507 (10) [M]$^+$, 356 (17), 340 (100), 91 (81).

HRMS: *m/z* [M]$^+$ calcd for $C_{33}H_{33}NO_2S$: 507.2248; found: 507.2264.

3-Dibenzylamino-4-(2-phenylethyl)-5*H*-furan-2-one (28b)
Colorless oil.

IR (neat): 3028, 1749 (CO), 1495, 1454, 1128, 1110, 1076, 1029, 750, 700 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.26–2.46 (m, 4 H), 4.20 (s, 4 H), 4.35 (s, 2 H), 6.9–7.0 (m, 2 H), 7.14–7.36 (m, 13 H).

MS: *m/z* (%) = 383 (4) [M]$^+$, 292 (88), 91 (100).

HRMS: *m/z* [M]$^+$ calcd for $C_{26}H_{25}NO_2$: 383.1878; found: 383.1871.

3-Dibenzylamino-4-thiophen-2-yl-5-(*p*-tolylsulfanyl)dihydrofuran-2-one (27c)
Colorless oil (ca. 7:1 mixture of two diastereomers).

IR (neat): 3028, 1779 (CO), 1494, 1455, 1215, 1135, 959, 815, 751, 698 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.22 (s, 2.62 H), 2.32 (s, 0.38 H), 3.47 (d, *J* = 13.8 Hz, 1.75 H), 3.67 (dd, *J* = 9.8, 11.3 Hz, 0.87 H), 3.77 (d, *J* = 13.8 Hz, 1.75 H), 3.85 (d, *J* = 13.8 Hz, 0.25 H), 3.91 (d, *J* = 11.3 Hz, 0.87 H), 3.99 (d, *J* = 13.8 Hz, 0.25 H), 4.25–4.3 (m, 0.25 H), 5.34 (d, *J* = 9.8 Hz, 0.87 H), 5.81–5.85 (m, 0.13 H), 6.40–6.44 (m, 0.13 H), 6.68–6.73 (m, 0.87 H), 6.93 (dd, *J* = 3.6, 5.1 Hz, 0.13 H), 6.97 (dd, *J* = 3.6, 5.1 Hz, 0.87 H), 7.06–7.32 (m, 13.26 H), 7.38–7.46 (m, 1.75 H).

MS: *m/z* (%) = 485 (9) [M]$^+$, 318 (52), 232 (62), 208 (15), 91 (100).

HRMS: *m/z* [M]$^+$ calcd for $C_{29}H_{27}NO_2S_2$: 485.1484; found: 485.1485.

3-Dibenzylamino-4-thiophen-2-yl-5*H*-furan-2-one (28c)
Colorless oil.

IR (neat): 3029, 1748 (CO), 1634, 1495, 1455, 1427, 1350, 1122, 1067, 1043, 751, 699 cm^{-1}.

^{1}H NMR (500 MHz): δ = 4.27 (s, 4 H), 4.98 (s, 2 H), 6.97 (dd, *J* = 1.1, 3.7 Hz, 1 H), 7.06 (dd, *J* = 3.7, 5.1 Hz, 1 H), 7.19–7.37 (m, 10 H), 7.52 (dd, *J* = 1.1, 5.1 Hz, 1 H).

MS: *m/z* (%) = 361 (54) [M]$^+$, 270 (100), 226 (27), 91 (95).

HRMS: *m/z* [M]$^+$ calcd for $C_{22}H_{19}NO_2S$: 361.1143; found: 361.1149.

4′-Dibenzylamino-2′-(*p*-tolylsulfanyl)-3′,4′-dihydro-2′*H*-[2,3′]bifuranyl-5′-one (27d)
Colorless oil (ca. 3:1 mixture of two diastereomers).

IR (neat): 3028, 1779 (CO), 1494, 1455, 1211, 1135, 1012, 960, 813, 741, 699 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.23 (s, 2.25 H), 2.32 (s, 0.75 H), 3.40 (d, *J* = 13.9 Hz, 1.5 H), 3.53 (dd, *J* = 9.8, 11.2 Hz, 0.75 H), 3.69–3.83 (m, 2 H), 3.96 (d, *J* = 13.7 Hz, 0.5 H), 4.04 (d, *J* = 11.2 Hz, 0.75 H), 4.17 (dd, *J* = 7.6, 12 Hz, 0.25 H), 4.27 (d, *J* = 12 Hz, 0.25 H), 5.46 (d, *J* = 9.8 Hz, 0.75 H), 5.76 (d, *J* = 3.3 Hz, 0.25 H), 5.87 (d, *J* = 7.6 Hz, 0.25 H), 6.17–6.22 (m, 0.75 H), 6.33 (dd, *J* = 1.9, 3.3 Hz, 0.25 H), 6.39 (dd, *J* = 1.9, 3.2 Hz, 0.75 H), 7.06–7.44 (m, 15 H).

MS: *m/z* (%) = 469 (8) [M]$^+$, 302 (39), 216 (68), 91 (100).

HRMS: *m/z* [M]$^+$ calcd for $C_{29}H_{27}NO_3S$: 469.1714; found: 469.1716.

4′-Dibenzylamino-2′*H*-[2,3′]bifuranyl-5′-one (28d)
Colorless oil.

IR (neat): 3029, 1748 (CO), 1638, 1494, 1454, 1350, 1090, 1079, 1067, 1042 cm^{-1}.

^{1}H NMR (500 MHz): δ = 4.35 (s, 4 H), 4.98 (s, 2 H), 6.41–6.46 (m, 1 H), 6.48–6.52 (dd, *J* = 1.8, 3.4 Hz, 1 H), 7.20–7.34 (m, 10 H), 7.45–7.5 (m, 1 H).

MS: *m/z* (%) = 345 (58) [M]$^+$, 254 (72), 210 (15), 107 (13), 91 (100), 65 (13).

HRMS: *m/z* [M]$^+$ calcd for $C_{22}H_{19}NO_3$: 345.1368; found: 345.1371.

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