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A Sulfone-Based Strategy for the Preparation of 2,4-Disubstituted Furan Derivatives

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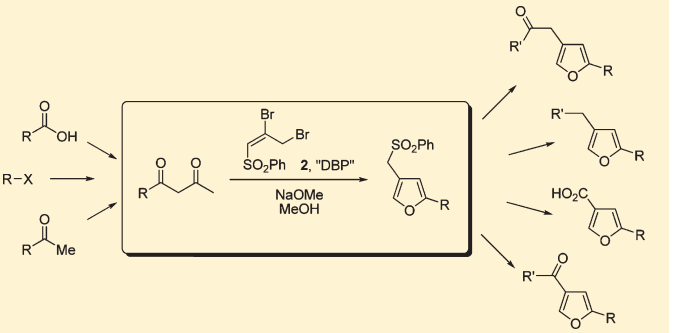
Supporting Information

ABSTRACT: 2,4-Disubstituted furans are prepared by treating 2,3-dibromo-1-phenylsulfonyl-1-propene (DBP, **2**) with 1,3-diketones under basic conditions. The furan-forming step involves a deacetylation, and the selectivity of this process depends upon the steric demand of the R group. The substituent in position 4 is elaborated by reaction of sulfonyl carbanions with alkyl halides, acyl halides, and aldehydes. Oxidative or reductive desulfonylation produces the 2,4-disubstituted furans in 60−92% yield. This strategy has been used to prepare rabdoketone A (**12**) and the naturally occurring nematotoxic furoic acid **13**.



The furan moiety enjoys wide-ranging eminence in the realm of organic synthesis.[1] Furans serve as the basis for many pharmacophores, and furan-containing natural products continue to captivate the imagination of synthetic chemists, as demonstrated by two recently reported independent syntheses of the marine alkaloid (−)-nakadomarin A.[2,3] Furans also serve as useful synthetic intermediates, finding utility as masked α,β-unsaturated esters[4] and precursors to hydroxypyranones[5] and polyoxygenated natural products,[6] as well as mono- and oligosaccharides.[7] The furan substructure is also an increasingly important motif in materials chemistry, providing promising plastics derived from renewable sources,[8] self-healing macromolecular materials,[9] conducting polymers,[10] and photovoltaics.[11] Consequently, the synthesis of furans has received considerable attention in the literature.[12]

One continuing challenge among existing preparative methods is general access to the 2,4-disubstituted derivatives, which are widely distributed in nature. Representatives of this class include methanofuran, a cofactor found in methanogenic microbes,[13] flufuran, an antifungal compound produced by *Aspergillus flavus*,[14] proximicins A−C, unusual DNA-binding oligomers isolated from a marine actinomycete,[15] several antiviral and anti-inflammatory metabolites from soft coral,[16] and elymniafuran, a scent component of the butterfly *Elymnias thryallis*.[17]

Previous routes to the 2,4-disubstituted furans[18] include the isomerization of alkynyl oxiranes (Figure 1, path a) using potassium *tert*-butoxide,[19] silver(I),[20] and gold(I)[21] catalysts; the *p*-toluenesulfonic acid mediated rearrangement of benzotriazolyl vinyl epoxides (path b)[18] or β-epoxyketones (path c),[22] the acid-catalyzed cyclization of hydroxyenals (path d),[23] the cycloisomerization of allenals (path e) using silver(I) or rhodium,;[24] the gold-catalyzed dimerization of allenones (path f),[25] the cyclization of

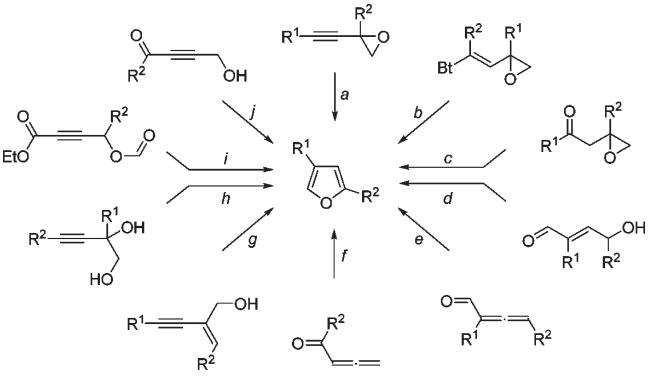


Figure 1. Synthetic approaches to 2,4-disubstituted furans.

2-alkynylallyl alcohols (path g) promoted by gold(I) catalysts bearing carbene ligands[26] or as intermediates in the Pd^{II}-mediated reaction between alkynes and alkynoates,[27] the gold-catalyzed dehydrative cyclization of 3-alkyne-1,2-diols (path h),[28] the phosphine-mediated reductive condensation of γ-acyloxy butynoates (path i),[29] and the cyclocondensation of γ-hydroxy ynones (path j) in the presence of sodium chloride and *p*-toluenesulfonic acid.[30] The cine substitution of 2-nitrofuran derivatives has also been used to access this architecture.[31] While these protocols represent stalwart advances in the preparation of 2,4-disubstituted furans, there are still opportunities to design methods with more easily accessible precursors and with greater

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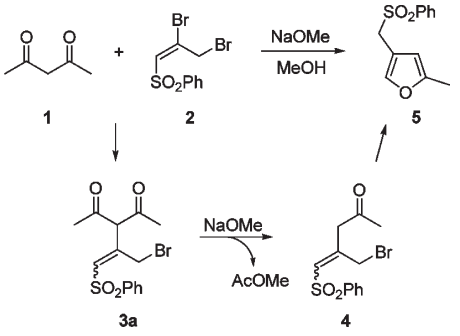
Scheme 1. Sulfone-Mediated Conversion of β-Diketone to Furan



flexibility in the range of substituents; thus, additional contributions are of general interest to the synthetic community.

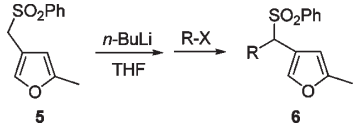
In connection with investigations into the unique reactivity of the crystalline, shelf-stable sulfone reagent 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP, **2**),[32] 2,4-pentanedione (**1**) was found to react with DBP under basic conditions to give the diketone **3a** via addition−elimination (Scheme 1). Under non-nucleophilic conditions, this adduct cyclizes to form a trisubstituted furan;[33] however, when sodium methoxide is used as a base, intermediate **3a** undergoes a sequence of deacetylation, O-alkylative ring closure, and double-bond migration to provide the 2,4-disubstituted sulfonyl furan **5**.[34] Since the formation of furans from β-diketones is unusual, we considered this novel result worthy of further investigation to develop the method into a general preparative route for 2,4-disubstituted furans.

We first turned our attention to the elaboration of the substituent at the 4-position. Since the alkylation of sulfonyl carbanions is well-established, we explored the reactivity of the sulfone-stabilized anion derived from furan **5**. Indeed, treatment of **5** with a slight excess of *n*-butyllithium at −78 °C led to smooth deprotonation, and the corresponding carbanion reacted with electrophiles to produce furan derivatives in fair to very good yields (Table 1). This procedure accommodates both alkyl halides (entries 1−8) and aldehydes (entries 9−11). Acyl chlorides can also be used (entries 12−14); however, it is necessary to generate the dianion of furan **5** in these cases.

Generality at the furan 2-position is a somewhat more subtle issue. Since this substituent is determined by the starting β-diketone, architectural flexibility at this location involves two key considerations: (a) access to the starting materials and (b) selectivity in the deacylation step (i.e., **3a** to **4**). For furan **5**, both considerations are trivial: 2,4-pentanedione is readily available and its symmetry renders the issue of deacylation selectivity moot. However, relying on symmetrical diketones is limiting at best, as few routes to symmetrical β-diketones exist; moreover, for complex substrates, discarding half of the hard-won substituent is inefficient. We therefore focused our efforts on non-symmetrical diketones, specifically methyl β-diketones.

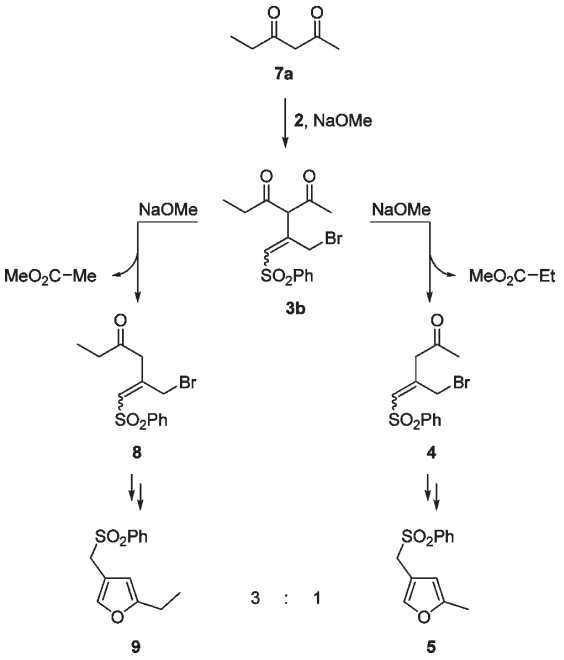
Access to methyl β-diketones can be achieved through a variety of methods, including the monoalkylation of 2,4-pentanedione,[35] the acetylation of methyl ketones,[36] and the acylation and subsequent Krapcho decarboxylation of ethyl acetoacetate.[37] The question remained as to the ability of methoxide to discriminate between the two carbonyls of the adduct, although similar selectivity in the cleavage of methyl β-diketones had been reported.[38]

Table 1. Elaboration of the Furan 4-Substituent



entry	electrophile	amt of nBuLi (equiv)	product	yield (%)
1	benzyl bromide	1.05	**6a**	81
2	allyl bromide	1.05	**6b**	54
3	3-chloro-2-methylpropene	1.05	**6c**	67
4	*tert*-butyl bromoacetate	1.05	**6d**	64
5	bromoethane	1.05	**6e**	70
6	1-bromo-2-methylpropane	1.05	**6f**	75
7	2-(bromoethyl)benzene	1.05	**6g**	71
8	2-bromopropane	1.05	**6h**	46
9	benzaldehyde	1.05	**6i**	53
10	pivaldehyde	1.05	**6j**	56
11	*trans*-crotonaldehyde	1.05	**6k**	54
12	trimethylacetyl chloride	2.05	**6l**	79
13	benzoyl chloride	2.05	**6m**	90
14	acetyl chloride	2.05	**6n**	58

Scheme 2. Selectivity in Deacetylation of Initial Adduct 3



We began with 2,4-hexanedione (**7a**), in which the symmetry has been broken by substituting an ethyl group for a methyl substituent. Encouragingly, treatment with DBP (**2**) under standard reaction conditions led to a 3:1 mixture of furans **9** and **5**, arising from intermediate loss of an acetyl group (via **8**) and a propionyl group (via **4**), respectively (Scheme 2). Although the selectivity in this example is somewhat modest, we considered such a level of discrimination promising in light of the similarity between the two substituents.

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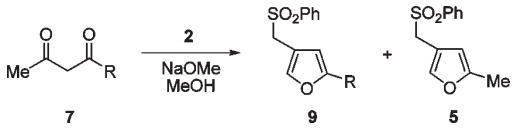
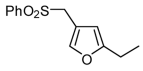
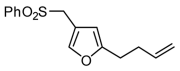
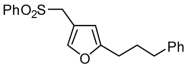
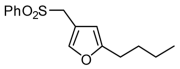
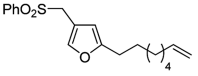
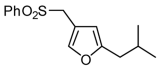
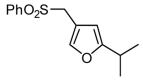
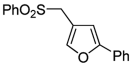
Table 2. Generality at the Furan 2-Position



7 9 5

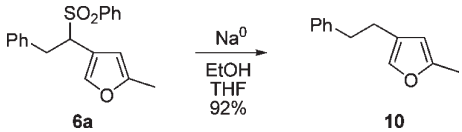
entry	diketone	product		9:5 ratio[a]	yield (%)
1	2,4-hexanedione (**7a**)		(**9a**)	3:1	55
2	7-octene-2,4-dione (**7b**)		(**9b**)	4:1	69
3	7-phenylheptane-2,4-dione (**7c**)		(**9c**)	5:1	36
4	octane-2,4-dione (**7d**)		(**9d**)	16:1	93
5	dodec-11-ene-2,4-dione (**7e**)		(**9e**)	11:1	41
6	6-methylheptane-2,4-dione (**7f**)		(**9f**)	21:1	88
7	5-methylhexane-2,4-dione (**7g**)		(**9g**)	38:1	95
8	benzoylacetone (**7h**)		(**9h**)	1.7:1	48

[a] Molar ratio determined from crude reaction mixture by ^{1}H NMR (see the Experimental Section)

We thus examined a series of substrates to explore the influence of substituent identity. We were gratified to observe that as the complexity of the R group increased, so too did the selectivity of deacylation, as shown in Table 2. Generally speaking, longer chains give higher selectivity (**9d** vs **9a**), although terminal unsaturation tends to diminish this effect (e.g., **9b**,**c**), presumably by privileging chain-extended conformers and thereby minimizing steric impact adjacent to the carbonyl. The most dramatic results are achieved by introducing branching, with a greater than 20:1 selectivity observed with a β-methyl group (i.e., **9f**) and an almost 40:1 ratio resulting from α-branching (i.e., **9g**). The procedure is tolerant to aromatic substituents, as demonstrated by benzoylacetone (entry 8).

The origin of this regioselectivity has not been established, but the results would indicate a steric bias in favor of nucleophilic attack at the methyl ketone moiety. Another potential factor could be the degree of enolization at each center. In similar Ad_N reactions involving α-diketones, Gewald and co-workers[39] invoked reaction at the less enolized ketone group. While this could also be operative in the present system, the constrained environment about the diketone locus in adducts of type **3** would be expected to inhibit the coplanarity required for enolization, an assumption supported by the observation that **3a** exhibits only one methyl signal in the ^{1}H NMR spectrum.[34] The electronic impact of the substituents may also come into play, modulating the inherent electrophilicity of the ketone moieties. This might contribute to the enhanced selectivity for isopropyl ketones (entry 7) and the marked decrease in selectivity for the benzoyl group (entry 8).

Scheme 3. Reductive Desulfonylation of Sulfonyl Furan



6a 10

To further demonstrate the potential of this methodology, we examined the desulfonylation of select substrates. For example, the benzyl derivative **6a** was reductively desulfonylated with sodium metal in a mixed medium of ethanol and THF[40] to provide 2-methyl-4-phenethylfuran (**10**) in excellent yield (Scheme 3).

With acylated furans, the sulfonyl group can be removed conveniently using samarium(II) iodide.[41] Thus, the combination of acetyl derivative **6n** with 2.6 equiv of SmI_2 in THF at −78 °C resulted in rapid desulfonylation to give 2-methyl-4-acetonylfuran (**11**) in 62% yield (Scheme 4).

Oxidative methods can also be used to advantage. For example, the isobutyl derivative **6f** was deprotonated with *n*-butyllithium and treated with dimethoxyboron chloride.[49] The resulting dimethylboronate intermediate was oxidized with *m*-chloroperbenzoic acid to give a labile α-hydroxysulfone, which rapidly decomposed with the ejection of phenylsulfinate anion, thus converting the sulfone moiety into a ketone.[42] This methodology proceeded in

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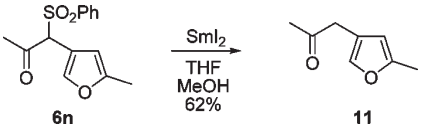
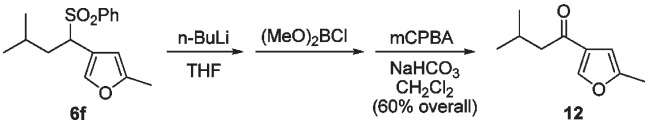
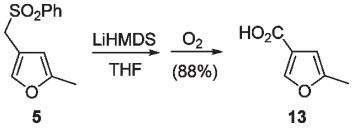
Scheme 4. Reductive Desulfonylation of α-Ketosulfonyl Furan



Scheme 5. Oxidative Desulfonylation to Furoketone; Synthesis of Rabdoketone A



Scheme 6. Oxidative Desulfonylation to Furoic Acid



60% overall yield to provide access to rabdoketone A (**12**), a component of *Rabdosia eriocalyx* extract used in traditional Chinese medicine for its antiedemic properties[43] (Scheme 5)

Finally, the unsubstituted phenylsulfonylmethyl group can be converted to a carboxylic acid moiety using an unprecedented aerobic oxidative desulfonylation technique. The method involves formation of the dianion using 2 equiv of lithium hexamethyldisilazide, followed by sparging with dry oxygen or air. The initial oxygen adduct spontaneously decomposes with the ejection of phenylsulfinate ion to yield the carboxylic acid, which is separated from the phenylsulfinate through pH-controlled extraction.[44] In this way, furan **5** was converted in 88% yield to the methylfuroic acid **13**, a natural product which has been shown to exhibit nematotoxic activity in the vegetative hyphae of *Coprinus comatus*[45] (Scheme 6)

In conclusion, we have developed a convenient methodology for the synthesis of 2,4-disubstituted furans which utilizes easily accessible alkane-2,4-diones as starting materials. The present protocol is quite flexible and complementary to existing methods.

EXPERIMENTAL SECTION

Conversion of 5 to 6 (General Procedure). 2-Methyl-4-[(phenylsulfonyl)methyl]furan (**5**[32]) in THF (5.5 mL/mmol **5**) was cooled to −78 °C and treated with 2.35 M *n*-butyllithium in hexanes (1.05 equiv). After the mixture was stirred for 15 min at −78 °C, the electrophile (1.05 equiv) was added dropwise. The mixture was stirred for 5 min at −78 °C, warmed to room temperature, and stirred another 12 h. Saturated aqueous ammonium chloride (3 mL) was added, and the THF was removed in vacuo. The residue was dissolved in dichloromethane (50 mL) and washed with water (50 mL). The aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic portions were dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography, except where noted otherwise.

*2-Methyl-4-(2-phenyl-1-(phenylsulfonyl)ethyl)furan (**6a**).* Prepared on a 6.2 mmol scale. Recrystallization (diethyl ether) gave **6a** (1.30 g, 64%) as a light yellow solid (mp 102−104 °C). Chromatography (20% EtOAc in hexane) of the supernatant provided additional product (335 mg, 17%), for a combined yield of 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.60 (t, *J* = 7.0 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.10−7.22 (m, 3H), 7.02 (d, *J* = 7.3 Hz, 2H), 6.75 (s, 1H), 6.05 (s, 1H), 4.13 (dd, *J* = 11.7, 2.6 Hz, 1H), 3.68 (dd, *J* = 13.7, 2.6 Hz, 1H), 3.09 (dd, *J* = 13.4, 11.9 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 141.2, 137.2, 136.9, 133.8, 129.2, 129.1, 128.8, 128.5, 126.9, 117.4, 106.4, 64.8, 33.8, 13.7. Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.9; H, 5.6. Found: C, 69.9; H, 5.5.

*2-Methyl-4-(1-(phenylsulfonyl)but-3-enyl)furan (**6b**).* Prepared on a 0.92 mmol scale. Chromatography (30% EtOAc in hexane) provided **6b** (137 mg, 54%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.68 (m, 3H), 7.43 (t, *J* = 7.9 Hz, 2H), 6.89 (s, 1H), 5.94 (s, 1H), 5.57 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.04 (ddt, *J* = 17.1, 1.5, 1.5 Hz, 1H), 4.98 (ddt, *J* = 10.2, 1.5, 1.1 Hz, 1H), 3.98 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.99 (dddt, *J* = 14.2, 7.0, 3.7, 1.1 Hz, 1H), 2.59 (dddt, *J* = 14.2, 11.6, 7.0, 1.1 Hz, 1H), 2.20 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 141.0, 137.0, 133.7, 133.1, 129.2, 128.8, 118.5, 117.5, 106.4, 62.8, 32.0, 13.6. HRMS: calcd for $C_{15}H_{16}O_3S$ 276.0820, found 276.0808.

*2-Methyl-4-(3-methyl-1-(phenylsulfonyl)but-3-enyl)furan (**6c**).* Prepared on a 1.28 mmol scale. Chromatography (25% EtOAc in hexane) provided **6c** (250 mg, 67%) as a white solid (mp 53−56 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.67 (m, 3H), 7.42 (t, *J* = 7.9 Hz, 2H), 6.88 (s, 1H), 5.92 (s, 1H), 4.70 (dt, *J* = 1.5, 1.1 Hz, 1H), 4.61 (s, 1H), 4.11 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.96 (d, *J* = 14.3 Hz, 1H), 2.55 (dd, *J* = 14.3, 12.1 Hz, 1H), 2.18 (d, *J* = 0.7 Hz, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 141.0, 140.1, 137.0, 133.7, 129.2, 128.8, 117.6, 114.1, 106.4, 61.8, 35.4, 22.1, 13.6. Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.2; H, 6.3. Found: C, 66.1; H, 6.3.

*tert-Butyl 3-(5-Methylfuran-3-yl)-3-(phenylsulfonyl)propanoate (**6d**).* Prepared on a 0.87 mmol scale. Chromatography (25% EtOAc in hexane) provided **6d** (195 mg, 64%) as a buff solid (mp 71−73 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.66 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 2H), 6.93 (s, 1H), 5.93 (s, 1H), 4.45 (dd, *J* = 10.5, 4.4 Hz, 1H), 3.14 (dd, *J* = 15.8, 4.4 Hz, 1H), 2.68 (dd, *J* = 15.8, 10.5 Hz, 1H), 2.18 (d, *J* = 0.7 Hz, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 153.1, 140.6, 136.5, 134.0, 129.3, 128.9, 117.6, 106.4, 81.8, 59.5, 34.7, 27.9, 13.6. Anal. Calcd for $C_{18}H_{22}O_5S$: C, 61.7; H, 6.3. Found: C, 61.3; H, 6.3.

*2-Methyl-4-(1-(phenylsulfonyl)propyl)furan (**6e**).* Prepared on a 0.84 mmol scale. Chromatography (20% EtOAc in hexane) provided **6e** (155 mg, 70%) as a buff solid (mp 58−60 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.69 (m, 5H), 6.92 (s, 1H), 5.95 (s, 1H), 3.82 (dd, *J* = 11.5, 3.5 Hz, 1H), 2.30 (dqd, *J* = 13.5, 7.4, 3.5 Hz, 1H), 2.23 (d, *J* = 0.7 Hz, 3H), 1.85 (ddq, *J* = 13.5, 11.5, 7.4 Hz, 1H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 141.0, 137.3, 133.6, 129.2, 128.7, 117.7, 106.2, 64.8, 21.0, 13.6, 11.6. Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.6; H, 6.1. Found: C, 63.3; H, 6.1.

*2-Methyl-4-(3-methyl-1-(phenylsulfonyl)butyl)furan (**6f**).* Prepared on a 1.5 mmol scale. Chromatography (25% EtOAc in hexane) provided **6f** (330 mg, 75%) as a light brown solid (mp 94−97 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.51 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.25 (s, 1H), 6.89 (s, 1H), 3.98 (dd, *J* = 11.35, 4.03 Hz, 1H), 2.23 (s, 3H), 1.84−1.99 (m, 2H), 1.43−1.56 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 140.8, 137.3, 133.5, 129.2, 128.7, 118.0, 106.3, 61.8, 35.7, 25.3, 23.6, 20.8, 13.6. Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.7; H, 6.9. Found: C, 65.8; H, 6.8.

*2-Methyl-4-(3-phenyl-1-(phenylsulfonyl)propyl)furan (**6g**).* Prepared on a 0.89 mmol scale. Chromatography (20% EtOAc in hexane) provided **6g** (215 mg, 71%) as a light yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.66 (m, 3H), 7.42 (t, J = 7.9 Hz, 2H), 7.15−7.29 (m, 3H), 7.07 (d, J = 7.0 Hz, 2H), 6.96 (s, 1H), 6.00 (s, 1H), 3.92 (dd, J = 11.4, 3.3 Hz, 1H), 2.73 (ddd, J = 13.1, 8.3, 4.7 Hz, 1H), 2.59 (dtd, J = 13.1, 8.1, 3.3 Hz, 1H), 2.48 (dt, J = 13.2, 8.1 Hz, 1H), 2.26 (s, 3H), 2.19 (dddd, J = 13.2, 11.4, 8.3, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 141.2, 140.1, 137.2, 133.7, 129.2, 128.8, 128.7, 128.5, 126.4, 117.7, 106.3, 62.3, 32.5, 29.0, 13.7. Anal. Calcd for $C_{20}H_{20}O_3S$: C, 70.6; H, 5.9. Found: C, 70.6; H, 6.0.

*2-Methyl-4-(2-methyl-1-(phenylsulfonyl)propyl)furan (**6h**).* Prepared on a 0.88 mmol scale. Chromatography (20% EtOAc in hexane) provided **6h** (113 mg, 46%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.68 (m, 3H), 7.40 (t, J = 7.9 Hz, 2H), 6.94 (s, 1H), 6.05 (s, 1H), 3.77 (d, J = 5.1 Hz, 1H), 2.76 (septd, J = 6.8, 5.1 Hz, 1H), 2.21 (s, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 141.3, 138.9, 133.3, 128.7, 128.6, 116.2, 107.7, 68.5, 27.5, 22.1, 19.3, 13.6. Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.7; H, 6.5. Found: C, 64.9; H, 6.6.

*2-(5-Methylfuran-3-yl)-1-phenyl-2-(phenylsulfonyl)ethanol (**6i**).* Prepared on a 3.7 mmol scale to give **6i** as a 2:1 mixture of diastereomers (determined by integration of ^{1}H NMR). Chromatography (33% EtOAc in hexane) provided the pure major isomer (674 mg, 53%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.72 (m, 5H), 7.15−7.24 (m, 5H), 6.62 (s, 1H), 5.77 (s, 1H), 5.49 (d, J = 9.5 Hz, 1H), 4.54 (br s, 1H), 4.31 (d, J = 9.5 Hz, 1H), 2.08 (d, 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 141.1, 139.8, 137.5, 134.1, 129.1, 128.9, 128.3, 128.2, 127.3, 116.0, 106.5, 73.6, 69.4, 13.4. Anal. Calcd for $C_{19}H_{18}O_4S$: C, 66.7; H, 5.3. Found: C, 66.5; H, 5.3.

*3,3-Dimethyl-1-(5-methylfuran-3-yl)-1-(phenylsulfonyl)butan-2-ol (**6j**).* Prepared on a 0.42 mmol scale to give **6j** as a 4:1 mixture of diastereomers (determined by integration of ^{1}H NMR). Chromatography (25% EtOAc in hexane) provided the pure major isomer (76 mg, 56%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 7.11 (s, 1H), 5.95 (s, 1H), 4.38 (d, J = 1.1 Hz, 1H), 4.12 (d, J = 1.1 Hz, 1H), 2.93 (br s, 1H), 2.16 (s, 3H), 0.80 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 142.0, 137.0, 133.8, 129.1, 128.8, 115.0, 108.6, 74.5, 64.6, 36.1, 26.7, 13.4. Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.3; H, 6.9. Found: C, 63.5; H, 6.7.

*(E)-1-(5-Methylfuran-3-yl)-1-(phenylsulfonyl)pent-3-en-2-ol (**6k**).* Prepared on a 0.42 mmol scale to give **6k** as a 4:1 mixture of diastereomers (determined by integration of ^{1}H NMR). Chromatography (25% EtOAc in hexane) provided the pure major isomer (70 mg, 54%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 7.0 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 6.84 (s, 1H), 5.83 (s, 1H), 5.73 (dqd, J = 15.0, 6.6, 1.1 Hz, 1H), 5.29 (ddq, J = 15.2, 6.6, 1.7 Hz, 1H), 4.89 (t, J = 7.7 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 3.94 (br s, 1H), 2.18 (s, 3H), 1.57 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 141.2, 137.4, 134.0, 129.7, 129.1, 129.0, 128.8, 115.9, 106.7, 70.8, 68.3, 17.8, 13.6. Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.7; H, 5.9. Found: C, 62.7; H, 6.0.

General Procedure for Reaction with Acyl Chlorides. A solution of 2-methyl-4-[(phenylsulfonyl)methyl]furan (0.95 mmol) in THF (7 mL) was cooled to −78 °C and treated dropwise with 2.26 M *n*-butyllithium in hexanes (0.84 mL, 1.89 mmol). Stirring was continued for 15 min at −78 °C, after which the acyl chloride (0.99 mmol) was added dropwise. The mixture was stirred for 5 min at −78 °C, warmed to room temperature, and stirred another 12 h. Saturated aqueous ammonium chloride (3 mL) was added, and the THF was removed in vacuo. The residue was taken up in dichloromethane (50 mL) and washed with water (50 mL). The aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic portions were dried over sodium sulfate and concentrated in vacuo to provide the crude product, which was purified by chromatography.

*3,3-Dimethyl-1-(5-methylfuran-3-yl)-1-(phenylsulfonyl)butan-2-one (**6l**).* The dianion of 2-methyl-4-[(phenylsulfonyl)methyl]furan was added to trimethylacetyl chloride using the general procedure. Chromatography (33% EtOAc in hexane) provided **6l** (239 mg, 79%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.67 (m, 3H), 7.42 (t, J = 7.7 Hz, 2H), 6.97 (s, 1H), 5.93 (s, 1H), 5.50 (s, 1H), 2.19 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0, 153.4, 141.5, 136.4, 134.0, 130.4, 128.3, 115.3, 106.9, 67.1, 46.0, 26.0, 13.6. Anal. Calcd for $C_{17}H_{20}O_4S$: C, 63.7; H, 6.3. Found: C, 63.5; H, 6.2.

*2-(5-Methylfuran-3-yl)-1-phenyl-2-(phenylsulfonyl)ethanone (**6m**).* The dianion of 2-methyl-4-[(phenylsulfonyl)methyl]furan was added to benzoyl chloride using the general procedure on a 2.1 mmol scale. Chromatography (33% EtOAc in hexane) provided **6m** (650 mg, 90%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 7.3 Hz, 2H), 7.69 (d, J = 7.3 Hz, 2H), 7.52−7.62 (m, 2H), 7.39−7.47 (m, 4H), 7.19 (s, 1H), 6.10 (s, 1H), 6.09 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 153.2, 142.0, 136.3, 136.1, 134.2, 130.3, 129.1, 129.0, 128.9, 128.5, 114.7, 107.3, 68.0, 13.6. HRMS: calcd for $C_{19}H_{16}O_4S$: 341.0848 (M + 1), found 341.0851.

*1-(5-Methylfuran-3-yl)-1-(phenylsulfonyl)propan-2-one (**6n**).* The dianion of 2-methyl-4-[(phenylsulfonyl)methyl]furan was added to acetyl chloride using the general procedure on a 1.5 mmol scale. Chromatography (25% EtOAc in hexane) provided **6n** (240 mg, 58%) as a buff solid (mp 65−67 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57−7.65 (m, 3H), 7.45 (t, J = 8.1 Hz, 2H), 7.12 (s, 1H), 6.03 (s, 1H), 5.11 (s, 1H), 2.43 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 153.2, 141.6, 136.1, 134.3, 129.8, 128.7, 113.9, 107.0, 73.2, 31.5, 13.5. Anal. Calcd for $C_{14}H_{14}O_4S$: C, 60.4; H, 5.1. Found: C, 60.0; H, 5.0.

General Procedure for Conversion of Alkane-2,4-diones into 2,4-Disubstituted Furans (9). The 1,3-diketone (0.74 mmol) was dissolved in anhydrous methanol (3.75 mL) and cooled to 0 °C. The solution was treated dropwise with 0.5 M methanolic sodium methoxide (1.76 mL, 0.88 mmol), warmed to room temperature, and stirred for 20 min. After the anion solution was cooled to 0 °C, (*E*)-2,3-dibromo-1-(phenylsulfonyl)-1-propene (250 mg, 0.74 mmol) was added in one portion. The reaction mixture was warmed to room temperature and stirred until TLC indicated the disappearance of starting material (4−7 h). The mixture was cooled to 0 °C and treated dropwise with 0.5 M methanolic sodium methoxide (2.06 mL, 1.03 mmol). After it was warmed to room temperature, the mixture was stirred for 12 h and quenched with saturated aqueous ammonium chloride (3 mL). Methanol was removed in vacuo, and the residue was partitioned between equal portions of water and dichloromethane (40 mL). The aqueous phase was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with water (30 mL), dried over sodium sulfate, and concentrated in vacuo to provide the crude product. Deacylation ratios were determined by comparing the integrals of the methyl group in **5** (2.23 ppm) with the corresponding protons in **9a**−**g**. For **9h**, the furan proton at 6.56 ppm was compared to the furan proton for **5** at 5.92 ppm. The desired product was separated from furan **5** using chromatography.

*2-Ethyl-4-(phenylsulfonylmethyl)furan (**9a**).* 2,4-Hexanedione[46] was converted on a 0.44 mmol scale. Chromatography was carried out twice (30% EtOAc in hexane) to provide **9a** (60 mg, 55%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.4 Hz, 2H), 7.62 (t, J = 7.0 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.05 (s, 1H), 5.89 (s, 1H), 4.12 (s, 2H), 2.57 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 141.0, 133.8, 129.1, 129.0, 128.7, 113.0, 106.1, 53.8, 21.4, 12.1. HRMS: calcd for $C_{13}H_{14}O_3S$ 250.0664, found 250.0658.

*2-(But-3-enyl)-4-(phenylsulfonylmethyl)furan (**9b**).* 7-Octene-2,4-dione[47] was converted as described in the general procedure. Chromatography (20% EtOAc in hexane) provided **9b** (140 mg, 69%) as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.3 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.9 Hz, 2H), 7.04 (s, 1H), 5.91 (s, 1H), 5.78 (ddt, J = 17.2, 10.3, 6.6 Hz, 1H), 5.02 (ddt, J = 17.2, 1.8, 1.5 Hz, 1H), 4.98 (ddt, J = 10.3, 1.5, 1.5 Hz, 1H), 4.12 (s, 2H), 2.64 (t, J = 7.5 Hz,

2H), 2.33 (q, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 141.2, 137.2, 133.8, 129.0, 128.7, 115.5, 113.1, 107.2, 100.0, 53.7, 31.9, 27.5. HRMS: calcd for $C_{15}H_{16}O_3S$ 276.0820, found 276.0824.

*2-(3-Phenylpropyl)-4-(phenylsulfonylmethyl)furan (**9c**).* 7-Phenylheptane-2,4-dione[38] was converted on a 0.93 mmol scale. Chromatography (20% EtOAc in hexane) provided **9c** (112 mg, 36%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.6 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.9 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.13−7.22 (m, 3H), 7.06 (s, 1H), 5.92 (d, J = 0.7 Hz, 1H), 4.13 (s, 2H), 2.60 (t, J = 7.7 Hz, 2H), 2.57 (t, J = 7.7 Hz, 2H), 1.91 (t, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 141.8, 141.2, 138.0, 133.8, 129.0, 128.7, 128.5, 128.4, 126.0, 113.1, 107.1, 53.7, 35.1, 29.5, 27.4. Anal. Calcd for $C_{20}H_{20}O_3S$: C, 70.6; H, 5.9. Found: C, 70.2; H, 5.9.

*2-Butyl-4-(phenylsulfonylmethyl)furan (**9d**).* Octane-2,4-dione was converted on a 0.88 mmol scale. Chromatography (20% EtOAc in hexane) provided **9d** (220 mg, 93%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.04 (s, 1H), 5.88 (s, 1H), 4.12 (s, 2H), 2.54 (t, J = 7.5 Hz, 2H), 1.55 (quint, J = 7.4 Hz, 2H), 1.30 (sext, J = 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 141.0, 138.0, 133.8, 129.0, 128.7, 113.0, 106.8, 53.8, 30.0, 27.6, 22.2, 13.9. Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.7; H, 6.5. Found: C, 64.9; H, 6.5.

*2-(Oct-7-enyl)-4-(phenylsulfonylmethyl)furan (**9e**).* Dodec-11-ene-2,4-dione[38] was converted as described in the general procedure. Chromatography (20% EtOAc in hexane) provided **9e** (100 mg, 41%) as a light yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.04 (s, 1H), 5.88 (s, 1H), 5.80 (ddt, J = 17.2, 10.3, 6.6 Hz, 1H), 4.99 (ddt, J = 17.2, 2.2, 1.5 Hz, 1H), 4.93 (ddt, J = 10.3, 2.2, 1.1 Hz, 1H), 4.12 (s, 2H), 2.53 (t, J = 7.5 Hz, 2H), 2.03 (m, 2H), 1.56 (quint, J = 7.3 Hz, 2H), 1.22−1.42 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 141.0, 139.1, 138.0, 133.8, 129.0, 128.7, 114.3, 113.0, 106.8, 100.0, 53.8, 33.8, 28.9, 28.8, 27.9, 27.8. Anal. Calcd for $C_{19}H_{24}O_3S$: C, 68.6; H, 7.3. Found: C, 68.8; H, 7.3.

*2-Isobutyl-4-(phenylsulfonylmethyl)furan (**9f**).* 6-Methylheptane-2,4-dione was converted as described in the general procedure. Chromatography (25% EtOAc in hexane) provided **9f** (180 mg, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.7 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.9 Hz, 2H), 7.04 (s, 1H), 5.86 (s, 1H), 4.13 (s, 2H), 2.40 (d, J = 7.0 Hz, 2H), 1.89 (nont, J = 6.8 Hz, 1H), 0.87 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 141.1, 137.9, 133.8, 129.0, 128.7, 113.1, 107.7, 53.8, 37.1, 27.9, 22.3. Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.7; H, 6.5. Found: C, 64.7; H, 6.5.

*2-Isopropyl-4-(phenylsulfonylmethyl)furan (**9g**).* 5-Methylhexane-2,4-dione[48] was converted as described in the general procedure. Chromatography (25% EtOAc in hexane) provided **9g** (185 mg, 95%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 7.3 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.06 (s, 1H), 5.84 (s, 1H), 4.12 (s, 2H), 2.85 (sept, J = 7.0 Hz, 1H), 1.17 (d, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 141.0, 138.1, 133.8, 129.0, 128.7, 112.8, 104.8, 53.8, 27.8, 21.0. Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.6; H, 6.1. Found: C, 63.8; H, 6.1.

*2-Phenyl-4-(phenylsulfonylmethyl)furan (**9h**).* Benzoylacetone was converted on a 0.59 mmol scale. Chromatography (dichloromethane) provided **9h** (85 mg, 48%) as a white solid (mp 117−118 °C) with spectroscopic properties in agreement with those reported in the literature.[34] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.3 Hz, 2H), 7.56−7.66 (m, 3H), 7.50 (t, J = 7.9 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.9 Hz, 1H), 7.20 (s, 1H), 6.56 (s, 1H), 4.20 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 142.1, 137.8, 134.0, 130.2, 129.1, 128.8, 128.7, 128.0, 124.0, 114.7, 106.6, 53.6.

2-Methyl-4-(2-phenylethyl)furan (10). 2-Methyl-4-(2-phenyl-1-(phenylsulfonyl)ethyl)furan (**6a**; 251 mg, 0.77 mmol) was dissolved in THF (20 mL) and absolute ethanol (0.9 mL). The resulting solution was cooled to −20 °C and treated with sodium metal (368 mg, 16.0 mmol). Stirring was continued at −20 °C until TLC indicated the consumption of starting material (2.5 h). The reaction was quenched with a mixture of methanol (2 mL) and saturated aqueous ammonium chloride (2 mL). The mixture was diluted with diethyl ether (40 mL) and washed sequentially with saturated aqueous ammonium chloride (20 mL) and brine (20 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo to yield a crude oil, which was purified by chromatography (dichloromethane) to give **10** (132 mg, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, J = 7.5 Hz, 2H), 7.20−7.27 (m, 3H), 7.08 (s, 1H), 5.90 (s, 1H), 2.88 (t, J = 8.0 Hz, 2H), 2.71 (t, J = 8.0 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 142.0, 137.2, 128.5, 128.4, 126.1, 125.6, 107.2, 36.5, 27.1, 13.7. Anal. Calcd for $C_{13}H_{14}O$: C, 83.8; H, 7.6. Found: C, 84.0; H, 7.4.

1-(5-Methylfuran-3-yl)propan-2-one (11). To a 15 mL round-bottom flask containing samarium(II) iodide in THF (0.1 M, 4.9 mL, 0.49 mmol) at −78 °C was added dropwise a solution of 1-(5-methylfuran-3-yl)-1-(phenylsulfonyl)propan-2-one (53.5 mg, 0.19 mmol) in a mixture of methanol (0.14 mL) and THF (0.42 mL). The combined contents were stirred for 10 min at −78 °C, warmed to room temperature, and stirred for a further 15 min. The reaction mixture was partitioned between diethyl ether (40 mL) and saturated aqueous potassium carbonate (40 mL). The aqueous phase was extracted with diethyl ether (20 mL). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated in vacuo, and subjected to chromatography (diethyl ether) to give **11** (16.4 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 5.89 (s, 1H), 3.45 (s, 2H), 2.25 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 152.9, 138.7, 118.3, 107.5, 40.4, 29.2, 13.6. Anal. Calcd for $C_8H_{10}O_2$: C, 69.5; H, 7.3. Found: C, 69.5; H, 7.5.

3-Methyl-1-(5-methylfuran-3-yl)butan-1-one (Rabdoketone A, 12). 2-Methyl-4-(3-methyl-1-(phenylsulfonyl)butyl)furan (146 mg, 0.50 mmol) was dissolved in THF (1.0 mL). The solution was cooled to −78 °C and treated with a solution of *n*-butyllithium in hexane (2.5 M, 0.22 mL, 0.55 mmol). The mixture was stirred for 5 min at −78 °C, warmed to −20 °C, and treated with a solution of dimethoxyboron chloride in hexanes[49] (1.5 M, 0.42 mL, 0.63 mmol). Stirring was continued at −20 °C for 15 min and then at room temperature for 2 h, after which time the solvent was removed by rotary evaporation. The residue was taken up in dichloromethane (1.25 mL) and added to a mixture of *m*-chloroperbenzoic acid (75 wt %, 144 mg, 0.62 mmol) and sodium bicarbonate (106 mg, 1.26 mmol) in dichloromethane (3.75 mL) at −20 °C. The mixture was stirred for 1 h at −20 °C and then partitioned between dichloromethane (40 mL) and a 1:1 mixture of saturated sodium carbonate and brine (40 mL). The organic layer was dried over sodium sulfate, concentrated in vacuo, and subjected to chromatography (15% EtOAc in hexane) to give **12** (50 mg, 60%) as a straw-colored oil with spectroscopic properties in agreement with those reported in the literature.[43] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 6.33 (s, 1H), 2.54 (d, J = 7.0 Hz, 2H), 2.29 (s, 3H), 2.15−2.28 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 154.2, 145.8, 129.3, 104.5, 49.3, 25.6, 22.8, 13.5.

5-Methylfuran-3-carboxylic Acid (13). An oven-dried 25 mL round-bottom flask was charged with 2-methyl-4-(phenylsulfonylmethyl)-furan[32] (99 mg, 0.42 mmol), sealed, and flushed with nitrogen, after which anhydrous THF (5 mL) was added. The resulting solution was cooled to −78 °C and treated dropwise with 0.5 M potassium hexamethyldisilazide in toluene (2.1 mL, 1.05 mmol, 2.5 equiv). After stirring for 30 min, dry oxygen was sparged through the stirred mixture at −78 °C via a 22 gauge needle until the disappearance of starting material (30−60 min).

After warming to room temperature, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (5 mL) and saturated aqueous sodium carbonate (5 mL). The contents were

transferred to a separatory funnel with deionized water. The aqueous mixture was extracted with ethyl ether (2 × 30 mL) to remove traces of starting material and then carefully acidified with 1 M hydrochloric acid (ca. 30 mL) to pH 1.2.

The acidic aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed successively with pH 2 bisulfate buffer (20 mL), 1 M sodium metabisulfite solution at pH 2 (2 × 20 mL), and brine at pH 1 (20 mL). Drying over sodium sulfate and removal of solvent in vacuo afforded **13** (47 mg, 88%) as a white solid (mp 110−112 °C) with spectroscopic properties in agreement with those reported in the literature.[50] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 6.33 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.58, 119.76, 105.54, 154.01, 168.39, 13.33.

■ ASSOCIATED CONTENT

Supporting Information. Text giving general experimental details and figures giving ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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